PSYCHOLOGICAL IMPACT OF TESTING POSITIVE
FOR HUMAN PAPILLOMAVIRUS AT
CERVICAL CANCER SCREENING

Emily Patricia McBride

A thesis submitted for the degree of Doctor of Philosophy

University College London
DECLARATION

I, Emily Patricia McBride, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated.
ACKNOWLEDGEMENTS

Firstly, thank you to my wonderfully insightful supervisors, Dr Jo Waller and Dr Laura Marlow, who have acted as pillars of support throughout this process. Jo has fostered my academic thinking, and I would not have gained as much from this experience without her. Laura has helped to focus my attention to detail and provided me with much needed motivational support. I have been incredibly lucky to work with, and learn from, such intelligent and lovely people.

I would also like to thank many of my colleagues within the Department of Behavioural Science and Health at UCL for their guidance, advice, and coffee conversations during my studies, including Professor Andrew Steptoe, Dr Alice Forster, Dr Robert Kerrison, Dr Andrea Smith, Dr Samantha Quaife, and Dr Christian Von Wagner. I would like to provide a special acknowledgement to five people who originally started with me at UCL before going off to forge their own career paths: Lauren Rockliffe, Hanna Skrobanski, William Goodman, Stephanie Philpot, and Madeleine Freeman. These five began as my lunch colleagues and will now remain friends for life. They have all, in their own individual way, motivated me to persevere, and inspired me to ride the inevitable highs and lows of the PhD process.

I would also like to thank the NHS clinical laboratory managers and staff who helped to recruit participants for my research. Thank you to Ruth Stubbs and Karen Denton at Public Health England for their design input and facilitation of HRA approvals. Thanks also to my inspiring colleagues and collaborators from other institutions who generously offered their time and support to enhance my development: Dr Zeev Rosberger, Dr Ovidiu Tatar, Professor Rona Moss-Morris, and Dr Joseph Chilcot. I am very grateful to my examiners, Dr Katie Robb and Professor John Weinman, for taking the time to appraise my thesis and perform my viva. Also, to Professor Rob Horne for examining my upgrade. Importantly, thank you to the women who kindly gave up their time to take part in my research; and to the Patient and Public Representatives who co-developed materials.

Lastly, I am eternally grateful to my amazing family, supportive partner, and brilliant friends for their unconditional love and encouragement. They will forever keep me grounded in the vibrant world outside of academia. In the words of my gran: “Emily, I’m not trying to be funny, and I know you’ve told me this before, but what is it that you actually do?”
ABSTRACT

In the UK and elsewhere, cervical cancer screening has changed to incorporate primary human papillomavirus (HPV) testing. This means all women who attend screening are told whether they test positive or negative for high-risk HPV. Testing positive for HPV has been associated with elevated anxiety and distress; and can also carry a negative label due to its sexually transmitted nature. Prior to this PhD, there had been no major studies assessing the psychological impact of routine HPV primary screening, or the impact of testing HPV-positive with normal cytology, a result unique to these screening methods. Four studies were conducted: 1) mixed-method systematic review to synthesise emotional response to testing HPV-positive at cervical cancer screening (33 studies); 2) cross-sectional survey comparing anxiety and distress between different test result groups at routine HPV primary screening (n=1127); 3) cross-sectional survey exploring illness representation profiles and anxiety in women testing HPV-positive with normal cytology (n=646); and 4) comparative qualitative interview study to explore reasons for variations in anxiety in women testing HPV-positive with normal cytology (n=30). Overall, testing HPV-positive at cervical screening was sometimes associated with adverse emotional, cognitive, behavioural, and physiological sequelae. These impacts appeared to differentially affect subgroups of the population in terms of intensity, duration, and clinical significance. For women testing HPV-positive with normal cytology, maladaptive illness representations may partially account for clinically significant anxiety. Highly anxious women primarily expressed fear of developing cervical cancer and had concerns about potential relationship infidelity and fertility issues. Cognitive Behavioural Theory and Leventhal’s Common-Sense Model of Self-Regulation were used to formulate overarching findings, providing a preliminary theoretical literature in an otherwise atheoretical domain. The findings of this PhD begin to develop an evidence-base for specific messages which could be used by policymakers in routine patient communication materials, to alleviate unnecessary anxiety at HPV primary screening.
IMPACT STATEMENT

Human papillomavirus (HPV) is a common sexually transmitted inflection responsible for virtually all cervical cancers. In England, recently implemented cervical cancer screening methods, called HPV primary testing, mean that all screened women get tested for HPV and receive an HPV-positive or HPV-negative result. To complement the English national implementation of HPV primary screening, the research outlined in this thesis provides a comprehensive in-depth account of the psychological impacts associated with receiving an HPV-positive result at routine screening. Taken independently and together, the four studies embedded showcase original research contributions and provide novel insights which both advance the academic literature and have external implications for health policy and third sector organisations. Prior to this PhD, there had been no systematic review assessing emotional response to HPV at cervical screening, despite a relatively comprehensive existing published literature. Internationally, there had been no major psychological evaluation assessing short-term anxiety and distress at routine HPV primary screening. Linked to this, there had been no research exploring reasons for anxiety in a new (and common) group of women receiving HPV-positive with normal cytology results at HPV primary screening. Further, this body of work was the first to add a theoretical lens to the psychological literature in this domain, and appraise findings on the basis of clinical significance. Evidencing academic impact to date, three out of four studies in this thesis have been published in peer-reviewed journals (with the fourth study under review), as well as disseminated at national and international conferences. In terms of policy impact, the findings have contributed to the wording used in, and provision of, routine communication materials sent to >400,000 women each year who attend HPV primary screening in England. Some of the work has been presented at national policy meetings and formed the basis of internal policy reports. Overall, several conceptual and pragmatic suggestions are outlined which are relevant for academics, policymakers, and third sector organisations working within the field HPV and cervical cancer screening. This thesis provides a preliminary evidence base for the development and testing of targeted communication materials, which can help to minimise unnecessary psychological burden at routine cervical cancer screening.
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARATION</td>
<td>2</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>3</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>4</td>
</tr>
<tr>
<td>IMPACT STATEMENT</td>
<td>5</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>12</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>14</td>
</tr>
<tr>
<td>LIST OF APPENDICES</td>
<td>16</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>17</td>
</tr>
<tr>
<td>CHAPTER 1: BACKGROUND</td>
<td>20</td>
</tr>
<tr>
<td>CERVICAL CANCER PREVENTION</td>
<td>23</td>
</tr>
<tr>
<td>Primary Prevention: HPV Vaccination</td>
<td>23</td>
</tr>
<tr>
<td>Secondary Prevention: Cervical Cancer Screening</td>
<td>24</td>
</tr>
<tr>
<td>Conventional cytology (The Pap Smear)</td>
<td>24</td>
</tr>
<tr>
<td>Trends in Cervical Screening</td>
<td>25</td>
</tr>
<tr>
<td>Transition to HPV Testing in Cervical Screening</td>
<td>27</td>
</tr>
<tr>
<td>Cervical Cancer Screening in England</td>
<td>28</td>
</tr>
<tr>
<td>Establishment of the NHSCSP</td>
<td>28</td>
</tr>
<tr>
<td>Implementation of HPV Primary Screening</td>
<td>29</td>
</tr>
<tr>
<td>PSYCHOLOGICAL CONSIDERATIONS AT CERVICAL SCREENING</td>
<td>33</td>
</tr>
<tr>
<td>Psychological Response to Cervical Screening Results</td>
<td>33</td>
</tr>
<tr>
<td>Psychological Response and the Integration of HPV testing</td>
<td>34</td>
</tr>
<tr>
<td>HPV Knowledge and Understanding</td>
<td>35</td>
</tr>
<tr>
<td>HPV awareness</td>
<td>35</td>
</tr>
<tr>
<td>Importance of Knowledge in the Context of HPV Primary Screening</td>
<td>36</td>
</tr>
<tr>
<td>Information Provision at HPV Primary Screening</td>
<td>37</td>
</tr>
<tr>
<td>HPV Positive with Normal Cytology: The New Result Group</td>
<td>39</td>
</tr>
<tr>
<td>Chapter/Section</td>
<td>Page</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Re-Attendance at 12-Month Recall</td>
<td>42</td>
</tr>
<tr>
<td>THEORETICAL APPROACH</td>
<td>43</td>
</tr>
<tr>
<td>Cognitive Behavioural Theory</td>
<td>44</td>
</tr>
<tr>
<td>Leventhal’s Common Sense Model of Self-Regulation</td>
<td>46</td>
</tr>
<tr>
<td>AIMS OF THE PHD</td>
<td>49</td>
</tr>
<tr>
<td>Aim</td>
<td>49</td>
</tr>
<tr>
<td>Objectives</td>
<td>49</td>
</tr>
<tr>
<td>Policy Impact</td>
<td>50</td>
</tr>
<tr>
<td>SUMMARY OF METHODOLOGY</td>
<td>51</td>
</tr>
<tr>
<td>Overarching Design</td>
<td>51</td>
</tr>
<tr>
<td>Data Source and Population</td>
<td>51</td>
</tr>
<tr>
<td>Psychological Impact of HPV Primary Screening (PIPS)</td>
<td>51</td>
</tr>
<tr>
<td>Using Behavioural Science to Understand Anxiety at Cervical Cancer Screening</td>
<td>52</td>
</tr>
<tr>
<td>Overview of Studies</td>
<td>52</td>
</tr>
<tr>
<td>Definitions</td>
<td>53</td>
</tr>
<tr>
<td>CHAPTER 2: STUDY 1</td>
<td>55</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>57</td>
</tr>
<tr>
<td>METHODS</td>
<td>59</td>
</tr>
<tr>
<td>Search Strategy</td>
<td>59</td>
</tr>
<tr>
<td>Design</td>
<td>59</td>
</tr>
<tr>
<td>Eligibility</td>
<td>61</td>
</tr>
<tr>
<td>Definition of Emotion</td>
<td>61</td>
</tr>
<tr>
<td>Selection Process</td>
<td>62</td>
</tr>
<tr>
<td>Data Extraction</td>
<td>62</td>
</tr>
<tr>
<td>Data Synthesis and Meta-Analysis</td>
<td>62</td>
</tr>
<tr>
<td>Cognitive Behavioural Framework – Mapping Interacting Constructs</td>
<td>64</td>
</tr>
<tr>
<td>Quality Assessment (Risk of Bias)</td>
<td>64</td>
</tr>
<tr>
<td>Rigour</td>
<td>65</td>
</tr>
<tr>
<td>RESULTS</td>
<td>66</td>
</tr>
<tr>
<td>Search Results</td>
<td>66</td>
</tr>
<tr>
<td>Study Characteristics</td>
<td>67</td>
</tr>
<tr>
<td>Anxiety</td>
<td>102</td>
</tr>
<tr>
<td>Quantitative (anxiety)</td>
<td>102</td>
</tr>
<tr>
<td>Qualitative (anxiety)</td>
<td>106</td>
</tr>
</tbody>
</table>
Distress ................................................................. 106
  Quantitative (distress) ........................................... 106
  Qualitative (distress) .......................................... 111
Fear........................................................................... 111
  Quantitative (fear) .............................................. 111
  Qualitative (fear) ............................................... 112
Disgust and Shame .................................................. 112
  Quantitative (disgust and shame) ........................... 112
  Qualitative (disgust and shame) ............................ 112
Surprise (and Confusion) ......................................... 113
Sadness .................................................................... 113
  Quantitative (sadness) ........................................ 113
  Qualitative (sadness) .......................................... 113
Positive Affect (relief, acceptance) .......................... 114
Apathy ................................................................. 114
  Quantitative (apathy) ........................................ 114
  Qualitative (apathy) .......................................... 114
Cognitive Behavioural Framework – Interacting Constructs ........................................ 115
  Cognitions Related to Emotional Response .............. 115
  Behaviours Related to Emotional Response .......... 115
DISCUSSION .................................................................. 118
  Main Findings ...................................................... 118
  Methodological Considerations ......................... 121
  Limitations ........................................................ 122
  Implications for Policy and Practice ................. 123
  Conclusion ........................................................ 124

CHAPTER 3: STUDY 2 ...................................................... 125

INTRODUCTION ................................................................ 127
  Overview ............................................................ 127
  Background ........................................................ 127
METHODS .................................................................... 128
  Design ................................................................. 128
  Participants ........................................................ 128
  Procedures and Clinical Management .............. 130
  Outcome Measures ............................................ 131
Sample Size and Response Rate ................................................................. 134
Data Analysis .......................................................................................... 134
Patient and Public Involvement (PPI) ....................................................... 137
RESULTS .................................................................................................... 137
Demographics .......................................................................................... 137
Primary outcomes .................................................................................... 137
    Anxiety (S-STAI-6) .............................................................................. 137
    General Distress (GHQ-12) ................................................................. 138
Secondary Outcomes .............................................................................. 143
    Very High Anxiety and Case-level General Distress ............................ 143
    Worry about Developing Cervical Cancer .......................................... 143
    Concern and Reassurance Related to Results ..................................... 143
DISCUSSION ............................................................................................ 144
   Main Findings ....................................................................................... 144
   Strengths and Limitations ................................................................... 146
   Implications .......................................................................................... 147
   Conclusion ........................................................................................... 147

CHAPTER 4: STUDY 3 .............................................................................. 149
INTRODUCTION ....................................................................................... 151
   Overview .............................................................................................. 151
   Background .......................................................................................... 151
METHOD ................................................................................................. 154
   Participants and Design ....................................................................... 154
   Sample Size ......................................................................................... 154
   Procedures ............................................................................................ 154
   Measures ............................................................................................. 155
       Anxiety (S-STAI-6) ........................................................................... 155
       Illness Perceptions (BIPQ) ................................................................. 155
       HPV-related Symptom Attributions (IPQ-R subscale) ...................... 156
       Demographics .................................................................................. 156
       Clinical characteristics ..................................................................... 157
   Analysis ............................................................................................... 157
   Patient and Public Involvement (PPI) ................................................... 159
RESULTS ................................................................................................. 160
   Demographics and Sample Characteristics ......................................... 160
Identifying Illness Representations ................................................................. 160
Associations Between Anxiety and Illness Representations .......................... 172
DISCUSSION .................................................................................................. 175
Main Findings ............................................................................................... 175
Interpretation of Illness Representation Profiles and Anxiety .......................... 175
Limitations ...................................................................................................... 179
Conclusion ...................................................................................................... 180

CHAPTER 5: STUDY 4 .................................................................................. 182
INTRODUCTION ............................................................................................ 183
Overview ........................................................................................................ 183
METHODS ...................................................................................................... 184
Participants and Design .................................................................................. 184
Procedures ..................................................................................................... 184
Analysis .......................................................................................................... 185
Rigour ............................................................................................................. 186
RESULTS ....................................................................................................... 187
Summary of Themes ....................................................................................... 189
Emotional Response ....................................................................................... 191
Cognitions About HPV .................................................................................... 192
Understanding of Result .................................................................................. 192
Cervical Cancer and the Aetiology of HPV ...................................................... 193
12-month screening interval .......................................................................... 195
Sexual Impact .................................................................................................. 197
Symptom Attributions ..................................................................................... 199
Other HPV-related Cognitions ....................................................................... 199
Behaviours ..................................................................................................... 200
Disclosure of Result and Social Influence ......................................................... 201
Physiological Response ................................................................................... 202
Interactions of Stressful Life Events or Health Conditions ............................. 203
DISCUSSION ................................................................................................. 203
Main findings .................................................................................................. 203
Strengths and Limitations ............................................................................. 206
Implications ..................................................................................................... 207
Conclusion ...................................................................................................... 207
## Novel Contributions

- High-Risk Groups and Adverse Psychological Impacts
- Anxiety, Fear, and Worry Associated with HPV: Are They Distinct Or All One And The Same?
- What Constitutes Adverse Psychological Impact And Where Does The Ethical Threshold Lie?
- HPV Positivity and Psychological Impact: Correlation, Causation, or Interaction?
- HPV and Psychological Stress, Sexual Distress, and Pre-Existing Conditions

### IMPLICATIONS FOR PSYCHOLOGY THEORY

- The Utility of the CSM and CBT
- Alternative Theoretical Formulations and Relevant Constructs
  - Williams’ Affect and Behavioural Framework
  - Intolerance of Uncertainty
- Health Psychology and the Role of Affect Regulation
- Affect Regulation and Behavioural Response to Testing HPV-Positive

### IMPLICATIONS FOR POLICY AND PRACTICE

- Tailoring Information to Reach High-Risk Subgroups
- Pragmatic Policy Suggestions
- Testing of Materials and Brief Intervention Development
- Other Health Services and Unknown Policy Impacts
- Policy Impact of the Research in this PhD
- Stakeholder Engagement

### STRENGTHS AND LIMITATIONS

### CONCLUSION

### REFERENCES
LIST OF TABLES

Table 1.1 - Cochrane and Holland (1971) recommended criteria........................................25
Table 1.2 - Overview of the main cervical screening methods adopted since 1930s. ....26
Table 1.3 – Estimated numbers receiving results at cervical screening in England......31
Table 1.4 – Key definitions for interpreting this thesis.........................................................53
Table 2.1 - Descriptive characteristics of quantitative studies...........................................69
Table 2.2 - Descriptive characteristics of qualitative studies.............................................74
Table 2.3 - Quality assessment using the Mixed Methods Appraisal Tool (MMAT). ...80
Table 2.4 – Definition of each of the emotions identified as themes.................................82
Table 2.5 - Results of quantitative studies (or mixed-methods quantitative components)
included in the review........................................................................................................83
Table 2.6 - Results of qualitative studies (or mixed-methods qualitative components)
included in the review.......................................................................................................95
Table 2.7 – Integration matrix of the themes of emotion generated from the quantitative
and qualitative syntheses.................................................................................................99
Table 3.1 - HPV and cytology results for the six groups included in study 2 ............129
Table 3.2 - Summary of the primary and secondary outcomes measures.................131
Table 3.3 – Descriptive outcome measures..........................................................................133
Table 3.4 - Demographic characteristics of non-responders vs. responders (no weights
or adjustments applied).................................................................................................136
Table 3.5 - Demographic characteristics of the whole sample (n=1127) and by results
group (no weights or adjustments applied)......................................................................139
Table 3.6 - Descriptive characteristics for primary and secondary outcomes by results
group (no weights or adjustments applied).....................................................................141
Table 3.7 - Results for primary and secondary outcomes by test result groups (weighted
and adjusted).....................................................................................................................142
Table 4.1 - Demographic and clinical characteristics .........................................................162
Table 4.2 - List of individual HPV-related symptom attributions. .................................164
Table 4.3 – Model fit statistics for latent profile analysis of illness perceptions..........165
Table 4.4 – Estimated means (95% confidence intervals) of illness perceptions for the 3-
profile LPA solution.........................................................................................................166
Table 4.5 – Illness perceptions by latent profile.................................................................168
Table 4.6 – HPV-related symptom attributions by the latent profile ......................... 169
Table 4.7 – Descriptive and clinical characteristics by latent profile. ....................... 170
Table 4.8 – Univariate analysis of demographics and outcomes variables for anxiety (N=646) ........................................................................................................ 173
Table 4.9 - Multiple hierarchical linear regression for anxiety .............................. 174
Table 5.1 – Participant characteristics and demographics overall and by anxiety group for study 4. ........................................................................................................ 188
LIST OF FIGURES

Figure 1.1 - An overview of the relationship between HPV and cervical cancer. ...........22
Figure 1.2 - HPV primary screening management algorithm in England. ......................32
Figure 1.3 - HPV primary screening invitation letter. ....................................................38
Figure 1.4 - Cover of the helping you decide leaflet posted to patients through the
NHSCSP in England. ........................................................................................................39
Figure 1.5 - Result letter sent to women testing HPV-positive with normal cytology in
the English HPV primary screening pilot. .................................................................41
Figure 1.6 - An overview of the Cognitive Behavioural Model. .................................45
Figure 1.7 - An overview of the CSM ........................................................................48
Figure 2.1 - Overview of the results-based convergent synthesis design. ..............60
Figure 2.2 - Prisma Flowchart: overview of searches and selection process ..........66
Figure 2.3 - Forest plot comparing short-term anxiety (result notification ≤ 2 months)
between those testing positive for HPV with abnormal cytology and control groups..104
Figure 2.4 - Forest plot comparing short-term anxiety (result notification ≤ 2 months)
between those testing positive for HPV with normal cytology and control groups.....104
Figure 2.5 - Forest plot comparing long-term anxiety (>2 months) between those testing
positive for HPV with abnormal cytology and control groups .............................105
Figure 2.6 – Forest plot comparing short-term distress (result notification ≤ 2 months)
between those testing positive for HPV with abnormal cytology and control groups.109
Figure 2.7 - Forest plot comparing long-term distress (>2 months) between those testing
positive for HPV with normal cytology and control groups ....................................109
Figure 2.8 - Forest plot comparing long-term distress (>2 months) between those testing
positive for HPV with abnormal cytology and control groups ............................110
Figure 2.9 - Emotional response to testing positive for HPV from all studies mapped on
to a cognitive behavioural framework ......................................................................117
Figure 3.1 - Overview of recruitment and response ..................................................138
Figure 4.1 - Thematic comparisons between women with low vs. high anxiety. .......190
Figure 5.1 - Overarching findings formulated using Leventhal’s Common Sense Model
of Self-Regulation .......................................................................................................225
Figure 5.2 - New test result letter for women who test HPV-positive with normal
cytology at NHSCSP HPV primary screening in England. ....................................238
Figure 5.3 – Frequently Asked Questions found on the flip-side of HPV-positive with normal cytology result letters..............................................................................239
LIST OF APPENDICES

Appendix 1.1 - HPV primary screening information sent alongside screening invite letters in the NHSCSP pilot sites.................................................................273
Appendix 1.2 – The NHSCSP ‘Helping You Decide’ leaflet sent alongside screening invitation letters...........................................................................................................275
Appendix 2.1 – Published paper in Health Psychology Review for Study 1..............283
Appendix 2.2 - Search Strategy for Systematic Review ...........................................318
Appendix 2.3 – Table containing raw data used for the meta-analyses..................321
Appendix 3.1 - Published paper for Study 2 in International Journal of Cancer ........325
Appendix 3.2 - Published protocol paper for Study 2 in BMJ Open.....................335
Appendix 3.3 - HRA Approval Letter for Study 2..................................................341
Appendix 3.4 – Questionnaire and consent form used for Study 2 .......................343
Appendix 3.5 – Results of univariate analysis for primary and secondary outcomes by result group (unweighted & using raw data only) for Study 2..........................348
Appendix 4.1 - HRA approval letter for Studies 3 and 4.......................................350
Appendix 4.2 - Questionnaire used for Study 3....................................................353
Appendix 4.3 - Participant Information Sheet for Study 3.................................359
Appendix 5.1 - Published Paper for Study 4 in Psycho-Oncology.....................360
Appendix 5.2 – Topic Guide used for Study 4. ....................................................369
Appendix 5.3 - Participant Information Sheet for Study 4. ...............................371
Appendix 5.4 – Consent form used for Study 4....................................................372
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABIC</td>
<td>Adjusted Bayesian Information Criterion</td>
</tr>
<tr>
<td>AIC</td>
<td>Akaike Information Criterion</td>
</tr>
<tr>
<td>ALMR LR TEST</td>
<td>Adjusted Lo-Mendell-Rubin likelihood ratio test</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis Of Variance</td>
</tr>
<tr>
<td>ASCUS</td>
<td>Atypical Squamous Cells of Undetermined Significance</td>
</tr>
<tr>
<td>BAI</td>
<td>Beck Anxiety Inventory</td>
</tr>
<tr>
<td>BIC</td>
<td>Bayesian Information Criterion</td>
</tr>
<tr>
<td>BIPQ</td>
<td>Brief Illness Perception Questionnaire</td>
</tr>
<tr>
<td>BISF-W</td>
<td>Brief Index of Sexual Functioning for Women</td>
</tr>
<tr>
<td>BLR-TEST</td>
<td>Bootstrapped Likelihood Ratio Test</td>
</tr>
<tr>
<td>BPS</td>
<td>British Psychological Society</td>
</tr>
<tr>
<td>CAG</td>
<td>Confidentiality Advisory Group</td>
</tr>
<tr>
<td>CBA</td>
<td>Cognitive Behavioural Assessment</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavioural Theory</td>
</tr>
<tr>
<td>COM-B</td>
<td>Capability Opportunity Motivation - Behaviour</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus; SARS-CoV-2, 2019</td>
</tr>
<tr>
<td>CSM</td>
<td>Common Sense Model of Self-Regulation</td>
</tr>
<tr>
<td>CSQ</td>
<td>Cervical Screening Questionnaire</td>
</tr>
<tr>
<td>DHSC</td>
<td>Department of Health and Social Care</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>F</td>
<td>F-Test</td>
</tr>
<tr>
<td>FAQ</td>
<td>Frequently Asked Questions</td>
</tr>
<tr>
<td>FOP-Q</td>
<td>Fear of Progression Questionnaire</td>
</tr>
<tr>
<td>FSFI</td>
<td>Female Sexual Function Index</td>
</tr>
<tr>
<td>GHQ-12</td>
<td>General Health Questionnaire</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>HA</td>
<td>High Anxiety</td>
</tr>
<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
</tr>
<tr>
<td>HIC</td>
<td>High Income Country</td>
</tr>
</tbody>
</table>
HIP: HPV Impact profile
HPV: Human Papillomavirus
HPV+: HPV Positive
HPV+/normal: HPV Positive with Normal Cytology
HPV-: HPV Negative
HRA: Health Research Authority
IMD: Index of Multiple Deprivation
IPQ-R: Illness Perceptions Questionnaire - Revised
LA: Low Anxiety
LEEP: Loop Electrosurgical Excision Procedure
LIC: Low Income Country
LMRLR TEST: Lo-Mendell-Rubin likelihood ratio test
LPA: Latent Profile Analysis
MANOVA: Multiple Analysis of Variance
MD: Mean Difference
MINDSPACE: Messenger; Incentives; Norms; Default; Salient; Priming; Affect; Commitment; Ego
MMAT: Mixed Methods Appraisal Tool
N: Number
N/A: Not Applicable
NHSCSP: National Health Service Cervical Screening Programme
NHS: National Health Service
NIHR: National Institute for Health Research
OR: Odds Ratio
P: Probability Value
PAIS-SR: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PEAPS-Q: Psychosocial Effects of Abnormal Pap Smears Questionnaire
PHE: Public Health England
PHQ-4: Patient Health Questionnaire
PIPS: Psychological Impact of Primary Screening for HPV
PPI: Patient and Public Involvement
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT: Randomised Controlled Trial
SAT-P: Satisfactory Profile
SD: Standard Deviation
SE: Standard Error
SMD: Standardised Mean Difference
SPSS: Statistical Package for Social Scientists
S-STA1-6: State-Trait Anxiety Inventory, Short-form
STA1: State-Trait Anxiety Inventory
STI: Sexually Transmitted Infection
TOMBOLA: Trial of management of borderline and other low-grade abnormal smears
UCL: University College London
UK: United Kingdom
UMIC: Upper Middle Income Country
US: United States
USA: United States of America
CHAPTER 1: BACKGROUND

EPIDEMIOLOGY OF CERVICAL CANCER AND HPV

Global Burden

Cervical cancer is one of the leading causes of death in women worldwide. Over 570,000 new cases of cervical cancer are diagnosed annually, making it the fourth most common female cancer responsible for around 7.5% of all-cause female mortality (1). The last four decades have seen tremendous gains in understanding the biological, environmental, behavioural, and psychosocial mechanisms of cervical cancers. Since 1970s, invasive cervical cancer incidence and mortality have declined starkly in most high-income-countries (HIC) due to advances in evidence-based interventions for prevention, early detection, and treatment. Cervical cancer mortality in the United Kingdom (UK), for example, decreased by 75% between 1971 and 2017 (2). Large global inequalities remain, however, with over 85% of cervical cancer age-standardised deaths occurring in low-and-middle-income countries (LMIC) (3, 4). Mortality rates have remained unchanged or risen in many LMIC (5); and without intervention are predicted to rise further by 2030 (6).

In HIC and upper-middle-income countries (UMIC), although mortality rates have fallen overall, sociodemographic inequities persist. Cervical cancer incidence and burden disproportionately affects low socioeconomic and ethnic minority groups (7-12). These inequalities have been observed across most HIC, but tend to be greatest in countries utilising opportunistic (ad-hoc) screening compared with organised screening programmes (13).

In 2018 globally, the average age of cervical cancer diagnosis was 53 years, and the average age of mortality was 59 years. Cervical cancer incidence rate usually peaks between ages 50–54 years; however, this varies between countries depending on the prevention methods employed. The UK displays the earliest worldwide peak at 30–34 years (14).
Aetiology of Cervical Cancer and HPV

Over 99% of cervical cancers are caused by persistent infection with a carcinogenic type of human papillomavirus (HPV) (15, 16). HPV is an asymptomatic, sexually transmitted infection (STI) passed on through skin-to-skin genital contact including non-penetrative sex.

Virologist Harold zur Hausen established the causal role of HPV in cervical cancer in the early 1980s, going on to win the Nobel Prize for his discovery in 2008 (17-19). Since then, over 100 types of HPV have been identified. The International Agency for Research on Cancer classified 12 high-risk types as carcinogenic (20). HPV types 16 and 18 are the most common carcinogenic (often referred to as ‘high-risk’) types, together, responsible for around 70% of cervical cancers worldwide (21). HPV type 16 has been detected in about 24% of HPV infections, and type 18 in about 9% (22). Low-risk HPV types also exist which rarely lead to cancer but can cause genital warts; HPV types 6 and 11 account for 90% of genital warts (23). Figure 1.1 depicts an overview of the main HPV types and their relationship with cervical cancer.

Further, HPV is an incredibly common infection. Around 80% of women and 70% of men have been infected with at least one HPV type by the age of 45 (16, 24). Estimates indicate that 10.4% of the female population worldwide, or approximately 291 million women, are infected with HPV at any given time (22). Factors that increase the risk of HPV infection include a higher number of sexual partners and engaging in sexual intercourse at an early age (25, 26). For these reasons, HPV prevalence is strongly associated with age; the highest HPV incidence rates are usually observed in late adolescence and women in their 20s (27).

Often, HPV is transient and can lie dormant for several years before presenting as an active, detectable viral infection. When HPV is active, the body’s immune system usually clears the infection without causing problems; 65% of cases clear naturally within 18 months, and 90% within 24 months (28). However, if the immune system is unable to clear HPV, and it persists as a chronic infection, this can act as the precursor to the development of cervical cell abnormalities which can ultimately lead to cervical cancer.
Figure 1.1 - An overview of the relationship between HPV and cervical cancer.

Cervical Cell Abnormalities

Cervical abnormalities occur when cells in the cervix form precancerous lesions, and can worsen over time. These abnormalities are usually detected using ‘cytology’ testing which involves microscopic inspection of cells scraped from the cervix. Classification of cell abnormality is based on the severity of cellular changes, ranging from low grade abnormal changes (mild-borderline changes; cervical intra-epithelial neoplasia 1; low-grade dyskaryosis) to high-grade changes (cervical intra-epithelial neoplasia 2 or 3; moderate or severe dyskaryosis), before developing into cervical cancer. In HIC, receiving abnormal results from cytology testing often leads to referral for colposcopy. Colposcopy is a diagnostic procedure performed by a trained medical professional (usually known as a ‘colposcopist’) to visually detect changes in the cervix and guide biopsies to obtain a histological diagnosis (i.e. examination of cervical tissue).

It usually takes between 10 and 20 years for low-grade cervical cellular changes to progress to cervical cancer (29). Factors that increase the risk of cell abnormalities and cancer include higher parity (number of times a woman gives birth), young age at first child birth, coinfection with another STI, a weakened immune system, and tobacco smoking (1).
Treatment of Cervical Cell Abnormalities

Unlike HPV which has no cure, abnormalities in cervical cells can be treated to prevent the majority of cervical cancers. Before 1970s, treatment for these abnormalities mainly included cervical conisation (i.e. excision of tissue from the mucous membrane of the cervix) and hysterectomy (i.e. surgical removal of the uterus). Over time, more conservative treatment methods have been adopted including electrocautery (heat to destroy cells), cryotherapy (freezing gas to destroy cells), and laser ablation (laser therapy). Since 1990s, however, loop electrosurgical excision procedure (LEEP) has remained the most widely adopted treatment, which is an excisional procedure using a small electrical wire loop to remove abnormal cells from the cervix (30).

CERVICAL CANCER PREVENTION

The recognition of the causal role of high-risk HPV in cervical cancer, as well as development of early detection and treatment methods, have driven shifts in international cancer policy and practice. Cervical cancer morbidity and mortality can be substantially reduced, and theoretically eliminated, through evidence-based primary and secondary prevention methods (31). Primary prevention refers to measures that prevent the onset of illness before it begins; and secondary prevention refers to measures that lead to early diagnosis and prompt treatment of an illness or disease (32).

Primary Prevention: HPV Vaccination

Primary prevention programmes are now available which enable school-aged girls and boys to be vaccinated against HPV. Worldwide, HPV vaccinations have gradually been introduced into health care services and national programmes. The U.S. Food and Drugs Administration approved the first HPV vaccine in 2006 under the trade name ‘Gardasil’, which protects against the four HPV types most commonly responsible for cervical cancer and genital warts (6, 11, 16, 18). Another similar HPV vaccine known as ‘Cervarix’ was approved shortly after this in early 2007, and protects against the two main cervical cancer types (33).
high-risk HPV types (16 and 18). Most recently in 2014, ‘Gardasil 9’ was approved which provides protection against nine HPV types (types 6, 11, 16, 18, 31, 33, 45, 52, and 58). HPV vaccines work optimally if administered prior to HPV exposure and they cannot be used to treat HPV infections (1). Hence, they are routinely recommended for school-aged children before the likely age of sexual activity.

In the UK, state-funded HPV vaccinations were introduced in September 2008 as part of the national immunisation programme for girls aged 12–13. Catch up vaccinations were also offered to girls aged 16-18. Cervarix was the HPV vaccine offered until 2012; followed by Gardasil 4 from September 2012, due its additional protection against genital warts (33). From September 2019, boys aged 12-13 were also offered the HPV vaccine; as well as men who have sex with men up to the age of 45 from April 2018 (34).

Since the introduction of the HPV vaccination in England, infections with high-risk HPV types 16 and 18 in vaccinated cohorts have reduced dramatically. Infection rates have declined by 86% in women aged 16-21 years (35). Similar effects have also been observed in Scotland, where vaccinated cohorts have shown substantial reductions in pre-invasive cervical lesions, and there has also been preliminary evidence of herd protection in unvaccinated women (36).

Secondary Prevention: Cervical Cancer Screening

Conventional cytology (The Pap Smear)

Cervical cancer screening aims to detect precancerous abnormalities in the cervix and, where necessary, remove moderate-high grade abnormal cells (CIN grade 2+) to prevent cancer from developing. Treatment of precancerous cervical abnormalities, detected by cell examination, has been the cornerstone of secondary prevention since the first cervical screening clinic was conceived by Greek physician, Dr Georges Papanicolaou, in 1945 (37). Dr Papanicolaou’s screening method, coined as the ‘Pap smear’, displayed the criteria which was later recommended for use in cancer screening programmes by Cochrane and Holland in 1971 (see Table 1.1) (38). It also met the Wilson and Jungner (1968) criteria advocated by the World Health Organisation for appraising the validity of
a screening programme (39). The Pap smear has been incorporated as part of both opportunistic and organised cervical screening programmes worldwide.

Table 1.1 - Cochrane and Holland (1971) recommended criteria for cancer screening

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Cochrane and Holland (1971) Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplicity</td>
<td>The sample should be easy to take.</td>
</tr>
<tr>
<td>Acceptability</td>
<td>The method of sampling must be acceptable to the population involved.</td>
</tr>
<tr>
<td>Accuracy</td>
<td>The test results must give a true measurement of the disease under investigation.</td>
</tr>
<tr>
<td>Cost</td>
<td>The expense of screening must be considered in relation to benefits of early detection of disease.</td>
</tr>
<tr>
<td>Precision</td>
<td>The tests must give consistent results in repeated trials.</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>The test should be able to detect all individuals with the disease.</td>
</tr>
<tr>
<td>Specificity</td>
<td>The test should not identify positive results in non-diseased individuals.</td>
</tr>
</tbody>
</table>

Adapted from (40).

Trends in Cervical Screening

Over time, methods of cervical screening have evolved and continue to vary across countries. The methods adopted largely depend on a country’s economic status, access to resources and workforce, and health system governance structures. In LMIC, there is usually limited access to efficacious cervical screening methods; therefore, cervical cancer is often identified at advanced symptomatic stages (14). In contrast, incidence and mortality from invasive cervical cancer have decreased substantially in most UMIC and HIC countries. This is largely due to the adoption of widespread cervical screening programmes. High coverage (the percentage of eligible women in a population who are screened) and successful implementation of cervical screening programmes are strongly associated with lower cervical cancer incidence and mortality (41). Some HIC offer cervical screening methods via opportunistic (ad-hoc) screening rather than a national organised programme, which can reduce cancer incidence but is suboptimal (42). See Table 1.2 for an overview of the main cervical cancer screening methods since the 1930s.
Table 1.2 - Overview of the main cervical screening methods adopted since 1930s.

<table>
<thead>
<tr>
<th>Type of screening</th>
<th>Decade introduced</th>
<th>Countries mainly adopting the method in 2010s</th>
<th>Brief description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual inspection</td>
<td>1930s</td>
<td>Low income</td>
<td>Acetic acid (vinegar) or iodine is applied to the cervix, which is then visually inspected. Changes in colour and/or appearance indicate cervical abnormalities or cancer. Often used in low-resource countries because it is inexpensive and provides immediate results. Variable sensitivity and specificity depending on the level of training of the examiner. High likelihood of overtreatment compared to other methods (43).</td>
</tr>
<tr>
<td>Conventional cytology (Pap test)</td>
<td>1940s</td>
<td>Middle and high income</td>
<td>Cervical cell samples are collected and 'smeared' on a microscope slide. They are then sent to a laboratory and evaluated under a microscope for abnormalities. Provides moderate sensitivity and high specificity for detection of high grade lesions; however, absence of quality control for many countries means sensitivity is highly variable (43, 44).</td>
</tr>
<tr>
<td>Liquid-based cytology</td>
<td>2000s</td>
<td>Middle and high income</td>
<td>Cervical cell samples are collected and placed in a vial filled with liquid used to preserve the cells. They are then sent to a laboratory for examination using light microscopy. Produces moderate sensitivity and high specificity for detecting high grade lesions (same as conventional cytology). The main advantage of liquid-based cytology over conventional cytology is that it reduces the number of samples which are deemed inadequate (avoiding repeat testing) (44, 45).</td>
</tr>
<tr>
<td>HPV triage</td>
<td>2000s</td>
<td>High income</td>
<td>HPV triage is the process used to manage women with low grade cervical abnormalities. Cervical cells are first tested using conventional or liquid-based cytology (see descriptions above). Samples showing low grade or borderline changes are reflexively tested for high-risk HPV. Women are sent for further examination (colposcopy) if they test HPV positive. High sensitivity and moderate specificity for detecting high grade lesions (46).</td>
</tr>
<tr>
<td>HPV test of cure</td>
<td>2000s</td>
<td>High income</td>
<td>HPV test is performed on women who have undergone treatment for cervical</td>
</tr>
</tbody>
</table>
abnormalities. Test of cure is used at follow-up to help determine whether treatment has been successful (47).

| **HPV primary testing** | **2010s** | **High income** | HPV is used as the primary (first) test on cervical cell samples. Only HPV positive cell samples are tested using cytology (an additional test on the same cell sample). High sensitivity and high specificity for detecting high-grade lesions. Also more cost-effective than HPV triage. (48-52) See Figure 1.2 for more details. |

**Transition to HPV Testing in Cervical Screening**

Although cytology-based screening has undoubtedly led to major declines in cervical cancer burden in many UMIC and HIC, these trends have largely stabilised or begun to rise in countries adopting longstanding high-quality Pap smear-based programmes (14). Therefore, over the last decade, significant efforts have been directed toward establishing widespread HPV testing in cervical screening (41).

Meta analytic evidence across randomised controlled trials and cross-sectional clinical studies have shown that integration of HPV testing into cervical screening provides higher sensitivity for the detection of high-grade precancerous lesions, compared with cytology-based testing alone (53). Consequently, use of HPV testing in cervical screening is now recommended by a majority of health organisations, including the World Health Organisation, US Preventative Services Taskforce, European Union, and Australian and New Zealand Governments (53-55). Since 2000s, HPV testing has been implemented mostly in HIC and some UMIC, most often as a way of triaging borderline-low grade cytology results and/or as a test of cure following treatment of abnormalities (56). Most recently in 2010s, policymakers have recommended using HPV as the primary (first) test in cervical screening (53-55), a method often referred to as ‘HPV primary screening’ or ‘HPV primary testing’. More details of these screening methods can be found in Table 1.2. By 2015, 84 countries had established national HPV screening programs and 38 had started pilot programs (using HPV triage, HPV test of cure or HPV primary testing). Since then, other countries have continued to adopt HPV-based testing in routine cervical screening (57).
The recent transition to HPV primary screening is following evidence of increased sensitivity for detecting precancerous abnormalities whilst maintaining cost-effectiveness, when compared with other HPV and cytology-based methods. It is considered to be the gold standard screening method in many high-income countries (48-52). In HPV primary screening, cervical cell samples are first tested for HPV. Samples which test HPV-positive are further tested using cytology, sometimes using genotyping to identify the most aggressive high-risk HPV types (16 and 18). Follow-up procedures and screening intervals are determined according to HPV and cytology (and/or genotyping) results combined. Samples testing negative for HPV undergo no further testing and women return to routine recall, which is usually 3-5 years. The extension of screening intervals up to five years or beyond has been supported for women who test HPV negative (51, 57), though this has not been recommended in many countries as yet. Further advancements in optimising HPV primary screening methods are underway, with recent research exploring effective ways of triaging HPV-positive results, such as by using dual-stain cytology testing (staining proteins which are markers of cell-cycle deregulation) or DNA methylation (checking DNA for alterations in gene function indicative of progressed HPV) (58, 59).

The Netherlands and Australia were among the first countries to fully implement HPV primary screening in 2017 (60, 61). Several other HIC are also in the piloting or implementation stages (e.g. Sweden, Italy, Turkey, Norway, New Zealand, Finland, and UK) (56).

**Cervical Cancer Screening in England**

*Establishment of the NHSCSP*

Cervical cancer screening was introduced in England in 1964. Cervical cell samples were usually taken opportunistically and often abnormal test results were not followed up. As screening policies were still in their infancy, there was little organisation or agreement regarding which women to screen or the optimal methods to employ. The lack of classification system for level of abnormal changes paired with relatively harsh treatments led to challenges for over-diagnosis and overtreatment. By the mid 1980’s, a rise in cervical abnormalities led to large sample testing backlogs, exposing its
limitations. Shortly after, concurrent with evolving research evidence, the UK Department of Health announced plans for an organised screening programme using a centralised computer registry to recall women at the population level, grounded in public health governance (62).

In 1988, the National Health Service Cervical Screening Programme (NHSCSP) was established as the primary national body responsible for cervical screening in England. Imperative to the NHSCSP’s success, it agreed a centralised policy for identifying which women to screen and when to treat them. Women aged 20-64 were invited to screening every three years until 2003, after which the screening age was changed to 25-49 every three years and 50-64 every five years, based on updated evidence (which remains today). The NHSCSP led to substantial increases in the numbers of women screened in England and hence reduced cervical cancer incidence, which now remains relatively stable (63). Since the NHSCSP was established, cervical cancer mortality rates have fallen by around 70%. It continues as the national cervical screening authority in England and is estimated to prevent 70% of cervical cancer deaths, which could increase to 83% if full coverage was achieved (64).

**Implementation of HPV Primary Screening**

Today, over 3-million women in England attend cervical screening every year (65) and around 2,600 new cases of cervical cancer are identified, accounting for 2% of all new female cancers (2). From 2011 to 2019, the NHSCSP adopted primary cytology testing with HPV triage (see Table 1.2) where borderline/low grade abnormal cytology samples were reflexively tested for HPV, and women were referred for colposcopy or returned to routine screening depending on their HPV result. However, between 2013 and 2017, the NHSCSP also piloted HPV primary screening in six geographical regions in England: Manchester, London, Norwich, Bristol, Sheffield, and Liverpool (see Table 1.2). Figure 1.2 provides a detailed overview of the NHSCSP HPV primary screening algorithm in England and the protocol used for women who test positive or negative for HPV.

The English HPV primary screening pilot was the largest in Europe and included 578,547 women attending cervical screening through primary care sites between May 2013 and May 2017. It compared 183,970 (32%) women screened with HPV primary testing vs.
394,577 (68%) screened with HPV triage/liquid-based cytology (51). The pilot found that HPV primary screening increased the detection of severe cervical abnormalities (CIN grade 3 or worse) and cervical cancer by approximately 40% and 30%, respectively, when compared with HPV triage/liquid-based cytology. It also found very low incidence of severe (high-grade) cervical abnormalities three years later in HPV-negative women at HPV primary testing, supporting the potential extension of the screening interval beyond three years in England.

Following the successful pilot, the UK Health Minister announced plans for HPV primary screening to be rolled out across England by the end of 2019. The NHSCSP achieved this with full implementation in place by December 2019 (66). HPV primary screening in England is forecast to prevent almost 500 additional cancers per year (48-50, 52, 67). In particular, predictive modelling has estimated that by 2028–32 cervical cancer rates for 25–64 year olds will decline by 19% as a result of HPV primary screening and the HPV vaccine. Emphasising the magnitude of effect with this method, the delay in the introduction of HPV primary screening by even 2-years, from 2017 to 2019, is thought to have resulted in 1,400 extra cervical cancers (which will be diagnosed between 2018 and 2028) (68).

Aside from improving cervical cancer mortality and incidence outcomes, one of the main differences with HPV primary screening is its higher HPV positivity rates. In comparison with cytology-based HPV triage screening in England, an additional 8.9% women were found to test positive for HPV each year (translating to an extra 290,045 annually) (51). Also, the HPV primary screening algorithm generates a new test result where women can test HPV-positive with normal cytology (normal cells; no abnormalities). In fact, the majority of HPV-positive women will receive this result at HPV primary screening; around 277,000 women (8.5%) each year; and this result has not been routinely administered through cervical screening previously. Table 1.3 provides estimated numbers receiving different test results at HPV primary screening vs. primary cytology with HPV triage in England.
Table 1.3 – Estimated numbers receiving test results at cervical screening in England annually, comparing HPV primary screening with primary cytology using HPV triage

<table>
<thead>
<tr>
<th></th>
<th>Annual estimated numbers in England (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary HPV screening using cytology triage</td>
</tr>
<tr>
<td>HPV+, normal cytology</td>
<td>277,009 (8.5%)</td>
</tr>
<tr>
<td>HPV+, abnormal cytology</td>
<td>136,875 (4.2%)</td>
</tr>
<tr>
<td>HPV-, no cytology test</td>
<td>2,841,784 (87.2%)</td>
</tr>
<tr>
<td>Normal cytology, no HPV test</td>
<td>-</td>
</tr>
</tbody>
</table>

Percentages taken from the English HPV primary screening pilot (51), with the estimated numbers calculated by using an annual cervical screening attendance figure of 3,258,927 from 2018-19 (69).
Figure 1.2 – HPV primary screening management algorithm in England, taken from the Public Health England screening blog (70). *HR-HPV = high-risk HPV.
Psychological considerations are central to the successful implementation of HPV primary screening worldwide. Unlike other screening protocols, HPV primary screening methods mean that all women who attend will be routinely told whether they test positive or negative for high-risk HPV. From the patients’ perspective, this means that millions of women will be told they test positive for a potentially cancer-causing STI. As indicated in Table 1.3, 12.7% of women who attend HPV primary screening in England will receive an HPV-positive result (51), translating to around 414,000 each year. The majority of these women will receive the new test result (HPV-positive with normal cytology; 277,000 each year), and would have previously received a normal cytology result under HPV triage.

Psychological Response to Cervical Screening Results

Prior to HPV testing at cervical screening, most of the early psychological research in the 1980-90s focussed on women receiving high-grade abnormal smears, and recruited women via colposcopy clinics. High-grade abnormal smear results were found to be associated with heightened anxiety, distress, and fear about cancer (71-75). Some women reported negative feelings about their body and were concerned about potential infertility (74, 76). Interestingly, even though women had not been tested for HPV, some studies found reports of self-blame and sexual guilt after receiving an abnormal smear, suggesting connotations of sexual stigma (77-79).

Although adverse psychological impacts had been identified in these early studies, it was anticipated that some findings were conflated with procedural distress from examination at colposcopy (80); undergoing colposcopy procedures have been associated high distress (81, 82). Further, given that high-grade abnormal results are associated with a high relative risk of cervical cancer, women’s reactions arguably formed part of a normal and adaptive response to a perceivably imminent health threat. The psychological impact of low-grade abnormal smear results, where cancer risk was much lower, was largely unknown. This was important given low-grade abnormal smears accounted for the majority of abnormal results detected at screening (80).
Subsequent clinical trials in 2000s, therefore, started to embed psychological evaluations which recruited women via routine screening (as opposed to colposcopy clinics), and aimed to assess the impact of low-grade abnormal smears. For example, from 2001 to 2003, over 3,500 women were recruited as part of the UK TOMBOLA study (Trial Of Management of Borderline and Other Low-grade Abnormal smears). Interestingly, TOMBOLA revealed that anxiety levels associated with low-grade abnormal results were similar to those observed in previous studies, where women had received high-grade results. The authors concluded that unnecessary psychological consequences from cervical screening were evident, and interventions should be developed to focus on women's understanding of low-grade abnormal results and the meaning of cervical pre-cancer (80).

**Psychological Response and the Integration of HPV testing**

As HPV-based testing methods were integrated into cervical screening in 2000s, research began to explore potential additional impacts associated with HPV test results. Broadly, across HPV-based screening methods (triage, co-testing, standalone), testing positive for HPV was found to be associated with elevated anxiety, fear, and concern related to the possible development of cervical cancer (83-87). When HPV testing was used to triage women with borderline or mild cervical abnormalities, anxiety and distress were found to be higher in women testing HPV-positive than those testing negative or who had not been tested for HPV (85); though the differences were relatively short-lived (88). Further, similar to some of the early findings on high-grade abnormal smear results, qualitative studies found that HPV carried a negative label due to its sexually transmitted nature, sometimes resulting in reports of shame, stigma, and concerns about relationships (86, 89, 90). In particular, confusion around the source of HPV was reported to trigger anxiety which related to relationship infidelity and the possibility of future transmission (90, 91).
HPV Knowledge and Understanding

**HPV awareness**

Although global awareness of HPV is rising, in part due to the introduction of HPV vaccination, public knowledge of the virus and its links with cervical cancer remain low (92-96). However, relatively few knowledge-based surveys have been conducted in the past five years; therefore, it is possible that knowledge of HPV may have increased in some countries due to rising implementation of vaccination programmes, awareness campaigns, and/or the introduction of HPV primary screening.

Drawing on the available literature, a large international study in 2013 compared HPV awareness in the UK, Australia, and US and found higher awareness in the US compared with the UK and Australia; though gaps in knowledge were identified across all three countries (97). In some instances, little or no knowledge of HPV have extended to women diagnosed with an HPV-related gynaecological cancer (Austrian study in 2014) (98). Similar trends have been observed in younger women offered the HPV vaccine in the UK (in 2013) (99).

In the UK in 2014, a general cancer population survey of approximately 2,000 participants found that only 0.1% could recall HPV when asked to list known cancer risk factors; and 29.4% correctly endorsed HPV when presented as a possible risk factor (100). A smaller internet-based HPV knowledge survey of 246 women aged 25 and over, conducted between 2014 and 2015, found more favourable results; with over two-thirds endorsing that HPV was common; and over 80% endorsing that they were aware of the link between HPV and cervical cancer. However, only 31% knew that an HPV-negative result was associated very low risk of cervical cancer (101). Consistent with this, previous work has shown that high knowledge of HPV does not necessarily equate to personalised meaning or awareness of HPV testing being used in cervical screening (93). Most recently in 2017, Australian women taking part in focus groups reported confusion about what it means to have HPV and expressed questions about how HPV links to cancer (102).

Overall, since the early 2000’s, questions about HPV and cancer risk, transmission, disclosure, risk to partner, and treatment appear to have presented as recurring themes in the literature across countries where HPV-based screening programmes are active (both
in population samples and in women who have participated in screening) (90, 103, 104). Lower levels of educational attainment have been associated with lower awareness of HPV (93, 97); and higher levels of education have been associated with increased knowledge of HPV testing being used in cervical screening (101).

**Importance of Knowledge in the Context of HPV Primary Screening**

Given that the implementation of HPV primary testing in England has led to a significant increase in the numbers of women receiving HPV-positive results, emphasis has been placed on the need for public health efforts to improve HPV-related knowledge (101). In 2018, a qualitative study in England which explored women’s awareness and attitudes towards HPV testing/screening found that women were largely unaware of the upcoming switch to HPV primary testing, and lacked knowledge about the meaning of HPV-positive results (105).

If women receiving HPV-positive results are unable to understand its meaning and/or interpret their own cancer risk, this may increase the likelihood of adverse psychological and behavioural consequences at HPV primary screening (105). Supporting this notion, low knowledge of HPV and poor understanding of results have been found to be predictive of higher anxiety, worry, and concern (85). In contrast, higher knowledge about HPV has been associated with lower anxiety, concern, and perceived risk of developing cervical cancer; as well as increased likelihood of attendance at cervical screening (87, 106, 107). Further, in other cancers it has been suggested that high levels of cancer-related fear or worry may adversely influence receptiveness to information about cancer screening (108, 109). It therefore seems possible that low knowledge of HPV could facilitate adverse psychological impacts associated with an HPV-positive result, which could reduce the likelihood of women processing information on their test result meaning.
**Information Provision at HPV Primary Screening**

In the English NHSCSP, information about cervical screening is communicated to women in the form of a standard ‘helping you decide’ leaflet posted alongside their screening invitation letter (110). Since the implementation of HPV primary screening, an updated leaflet providing an overview of the new screening methods has been included (111). For those NHS sites taking part in the pilot prior to full implementation, an additional information sheet was posted alongside the standard leaflet (see Supplementary File 1.1). The aim of the new leaflet was to provide information on HPV primary screening and the meaning of possible HPV positive and negative results. Figures 1.3 and 1.4 display the cervical screening invitation letter and cover of the accompanying leaflet that women receive. Supplementary File 1.2 provides the HPV primary screening leaflet.

Despite the provision of basic information at the time of invitation, complexities in the relationship between HPV and cancer means that concepts related to cause, transience, and cancer risk are notoriously difficult to communicate to patients. This is especially applicable for patients in low health literacy groups and/or where English is not their first language (107). Based on the previous research for knowledge and understanding, it seems probable that a large number of women may not fully understand their HPV result and/or may misinterpret its meaning at HPV primary screening.

The NHSCSP aims to promote person-centred care and accurately inform patients of their screening result whilst minimising unnecessary psychological harm and unintended behavioural consequences. Implementation of HPV primary screening in England, therefore, presents a challenge for policymakers in terms of how to best communicate test results at population level, where concepts of risk are complex and information needs vary. Result delivery via mailed letter without direct clinical interaction may be particularly problematic. A recent study indicated that women with lower educational attainment had poorer understanding of the NHS cervical screening information leaflet and concluded that the content may be too complex for some recipients (112). This highlights the potential for inequalities to manifest in terms of psychological burden and informed decision making.
Dear <<PATIENT NAME>>

We are writing to invite you for NHS cervical screening (previously called the ‘smear test’). We offer screening to help prevent cervical cancer and to save lives.

Please contact your GP practice to make an appointment. In some areas, local sexual health clinics may also offer screening. The test only takes a few minutes, and you can ask for a female nurse or doctor.

We invite women aged 25 to 64 and registered with a GP. You should consider having cervical screening regardless of your sexual orientation, sexual history or whether you have had the human papillomavirus (HPV) vaccination.

Cervical screening now tests for HPV. HPV can cause changes in the cells of the cervix. If we find HPV in your screening sample, we then check it for abnormal cells. By finding and treating these early, we can prevent most cases of cervical cancer.

Please read the enclosed leaflet about cervical screening even if you have had screening before. The leaflet is to help you decide whether to have the test. More information is available at www.nhs.uk/cervical.

We will send your screening result to you by post. The nurse or doctor who does your screening will tell you when you can expect to get your letter, and they will also get a copy. Please make sure you tell your GP practice about any changes to your address.

Screening cannot prevent every cervical cancer. Cancer can start to develop in between screening tests. If you have any symptoms such as bleeding between periods, after sex or after the menopause, or changes to vaginal discharge, please tell your GP as soon as possible.

If you have any concerns or questions about cervical screening please speak with your GP or practice nurse.

Figure 1.3 - HPV primary screening invitation letter sent to all screening-aged women in England.
HPV Positive with Normal Cytology: The New Result Group

Of particular relevance at HPV primary screening is the new group of women created from the algorithm, who test positive for HPV with normal cytology (normal cervical cells; no abnormalities) (see Figure 1.2). Due to the absence of cytological abnormalities, an HPV-positive with normal cytology result carries a very low absolute risk of cervical cancer. However, given that HPV has been detected, relative risk is higher than average and women are recalled early for repeat screening at 12-months rather than 3 or 5 years (standard recall). Women testing HPV-positive with normal cytology are referred to colposcopy if they receive this result three consecutive times at 12-month intervals.

The complexity of this result, e.g. in terms of cancer risk, along with its mode of delivery via letter, mean that it has strong potential to cause confusion. Figure 1.5 displays the
result letter sent to women testing HPV-positive with normal cytology. Misinterpreting this result may cause unnecessary anxiety if women overestimate their risk of cancer after testing HPV positive or cause false reassurance if they underestimate their risk. It is also possible that in the absence of cytology results women may place more focus on the sexually transmitted nature of HPV, potentially leading to psychosexual burden.

Importantly, the 12-month follow-up interval associated with this result means no routine clinical contact in the interim, which could cause and/or intensify psychological consequences. Reassuringly, a recent study in Norway found little evidence of long-term distress in women testing positive for HPV with normal cytology when cross-sectionally examining them up to 12 months after their result (113). However, this study used a crude four-item measure of distress and combined all distress responses between 4 and 12 months after result. Short-term psychological response to testing positive for HPV with normal cytology at routine HPV primary screening is unknown.
Dear <<PATIENT NAME>>

Thank you for coming for NHS cervical screening.

Your screening sample was tested for the human papillomavirus (HPV), and evidence of the virus was found. This is called an 'HPV positive' result.

Your screening sample was also tested for abnormal cervical cells. This test is called 'cytology'. The results were normal (no abnormal cells were found).

Because HPV was found in your sample, we would like you to come back for screening again sooner than usual. This is so that we can check that the HPV has been cleared by your immune system (like getting rid of a cold).

Your next screening test is due on or around <<PAT_REC_DATE>>. We will send you a reminder letter nearer the time.

Cervical screening, like other medical tests, isn't perfect. If you have any unusual symptoms such as a discharge, or bleeding between periods or after sex, then please speak to a GP. Cervical screening is not a test for symptoms.

If you have any questions about your test result or would like more information about cervical screening or HPV testing, please contact a GP or the person who did your last test.

Figure 1.5 - Result letter sent to women testing HPV-positive with normal cytology in the English HPV primary screening pilot.
Re-Attendance at 12-Month Recall

To maximise the sensitivity gains and mortality-reduction from switching to HPV primary screening, women who test HPV-positive with normal cytology need to re-attend their recall at 12-months. This is especially relevant in the context that, more generally, uptake of cervical screening is the lowest it has been in England since 1997, with a decline of 4.3% from 2011 to 2018 (114). Early findings from the English HPV primary screening pilot indicate that around 15% of women who test HPV-positive with normal cytology do not attend their follow-up screen, translating to over 40,000 each year (51, 115). Non-attendance at cancer screening is usually highly socially graded (116, 117); however, sociodemographic inequalities associated with 12-month early recall have so far been found to be minimal (115). This could indicate that psychological factors may be central in non-re-attendance at 12-months; consistent with this subgroup having already attended screening, therefore eliminating many of the known sociodemographic and practical barriers initially preventing access.

Varying levels of affective response (e.g. anxiety and fear) could play mediating or moderating roles in 12-month cervical screening re-attendance. In other cancer areas, such as breast cancer, meta-analytic evidence has shown that cancer-related worry has a small but positive effect on screening uptake (118). Similarly, generalised fear of cancer has been found to be positively associated with screening uptake (119). Other studies have suggested more nuanced relationships, where moderate levels of fear have increased motivation to attend cancer screening, but low or high levels have reduced the likelihood of attendance (120, 121). From a theoretical formulation perspective, evidence broadly suggests that individual differences in affect-regulation can lead to avoidance vs. approach directed behaviours (122-125). It therefore seems plausible that heightened affect (e.g. cancer fear) following an HPV-positive result may motivate the majority of women who re-attend screening, but could trigger avoidance mechanisms in some. Equally, apathy or indifference following an HPV-positive result could lead to low motivation and inactivity in the form of non-re-attendance.
THEORETICAL APPROACH

Attempts to explain psychological response to HPV have been largely atheoretical to date. One study considered the role of illness representations and emotion in women with abnormal cervical screening results (without explicit HPV diagnosis), and found that emotion was explained by independent effects of a combination of demographic, cognitive, and emotional representations (126). Leventhal’s Common Sense Model (122) and Cognitive Behavioural Theory (127) have also been used by few studies to guide HPV-related interview or survey questions, reportedly proving useful frameworks (104, 128) but they have not provided further critique or testing. Drawing from theories and models of emotional adjustment, it is possible that appraisal and representations related to HPV diagnosis (e.g. sexually transmitted cause, lack of cure, perceived seriousness or control) (122, 129), concerns about cervical screening or treatment (130), cultural/social norms and access to social support (131), and coping or attachment style (132, 133) may be important for understanding psychological response. Further work is needed to determine the most valid and relevant theories in the HPV and cervical screening context.

Although there are several theoretical models and approaches which could be applied to the field of HPV, two theories have been embedded in the overarching methodology of this PhD: 1) Cognitive Behavioural Theory (CBT); and 2) Leventhal’s Common Sense Model of Self-Regulation (CSM). The reasons for choosing these theories partially stemmed from their wide usage and proven validity across various health conditions, and the fact that previous literature had highlighted them as potentially useful in HPV (104, 128). Importantly, they both clearly integrate affect regulation as a core and dynamic construct alongside cognitive and behavioural pathways, which other health psychology models often neglect (e.g. several social cognition theories). Further, it was anticipated that the CBT and CSM would complement each other at different stages of this PhD. The encompassing framework of CBT would allow for preliminary but comprehensive formulations; and the focussed health-specific CSM would help explain processes and identify HPV-specific beliefs.
Cognitive Behavioural Theory

Cognitive Behavioural Theory (CBT), which underpins cognitive behavioural therapy, may act as a promising theoretical framework for provisionally mapping emotional responses and their related constructs. The origins of cognitive behavioural theory stem from the merging of cognitive and behavioural techniques during the 1980s and 1990s, and was largely pioneered by American psychiatrist, Dr Aaron Beck (134). Prior to this, Cognitive Theory and Behavioural Theory each operated as independent and often competing approaches in psychological treatment (135).

In the modern application of CBT in 2010s, the model usually encompasses interacting dynamics between affect, cognitions, behaviours, and physiological sensations; each construct has the potential to (in)directly influence the other three constructs. The CBT model has been applied widely across various mental and physical health domains (136, 137). In the context of anxiety, several meta-analyses have demonstrated moderate-high efficacy and effectiveness for the use of CBT. Globally, it has been recognised as one of the gold-standard models for guiding psychological assessment and formulation (138-141). In particular, research suggests that heightened and/or exaggerated appraisal of a threat is a central element which underpins both normal (adaptive) and pathological anxiety (142, 143). Whilst there are variations in individual experiences and/or triggers of anxiety, research has suggested that different forms of anxiety share core underlying features irrespective of context (144). When CBT-guided interventions are adopted for anxiety, they therefore usually aim to target maladaptive emotions and beliefs related to the true likelihood and costs of anticipated harms by using various cognitive (e.g., cognitive restructuring), affective (e.g. self-awareness tasks), behavioural (e.g. graded exposure), and physiological (e.g. breathing exercises) techniques (145, 146).

See Figure 1.6 for an overview of the Cognitive Behavioural Model.
Given that researchers working on psychological aspects of HPV (e.g. heightened anxiety) are yet to establish a cogent theoretical framework, the CBT model may facilitate the identification of relevant cognitive, affective, behavioural, and physiological responses for women receiving this diagnosis. Based on the previous HPV literature (detailed under the section on psychological considerations at cervical screening), cognitive behavioural theory is particularly relevant given adverse emotional responses to testing positive for HPV are likely linked to several other potentially interacting cognitive (e.g. perceived cancer risk, questions about sexual transmission) and behavioural outcomes (e.g. screening re-attendance, sexual relationships). CBT may, therefore, help establish which factors in the literature are most relevant to HPV and identify those constructs most influential in anxiety.

Overall, in the context of this PhD, the CBT model will be used as an overarching framework to map emotional, cognitive, behavioural, and physiological factors, where relevant. It is hoped that adopting this comprehensive approach will act as a springboard for the development of a cogent theoretical literature and isolate areas for further concentrated theoretical developments.
Another relevant theoretical framework for understanding processes and variations in adaption to health conditions is Leventhal’s Common-Sense Model of Self-regulation (CSM (148, 149)). American psychologist Howard Leventhal describes the CSM as “a dynamic, multi-level process that generates individuals’ representations of threats to health, procedures for management, and a system for creating action-plans and implementing action” (122). The origins of the CSM are not defined and clear cut, but instead built on several studies and theoretical developments from late 1940s, until it was coined as the ‘CSM’ in 1980s (148-150). Since then, the CSM has continued to evolve and incorporate sophisticated nuances as the data and theoretical concepts have advanced (122). A novel aspect of the CSM compared with other health behaviour and health psychology theories is that it integrates multi-level dynamic processes of parallel cognitive and affective pathways (122, 151).

The CSM posits that the self-regulatory process is initiated by perceptions of somatic sensations and deviations from normal function (e.g. experiencing symptoms or injury), as well as by social and/or environmental cues (e.g. medical diagnosis, discussion with others, media). ‘Prototypes’ or ‘schemata’ are then activated, which are cognitive memory structures and normative guidelines about perceptions of one’s self, past experiences, and treatments or lifestyle. These prototypes or schemata then generate mental ‘representations’ about illness threats, treatments, and action plans. Representations refer to “mental models activated at specific instances in time” and present as beliefs and expectations about an illness or somatic symptom (122). Specifically, illness representations are emphasised as cognitions relating to attributes in five key dimensions: (i) identity (label or symptoms related to illness/condition); (ii) timeline (perceived rate of onset, duration, and decline); (iii) consequences (impact and anticipated disruption); (iv) causes (e.g. perceived biological, environmental, or psychosocial causes); and (v) control (perceived personal and treatment control over illness).

In parallel to this cognitive pathway of the CSM, an affective pathway may be activated which is based on how individuals emotionally regulate, cope, and appraise health threats. Adaptive illness outcomes are reliant on a consistent and stable self-regulatory system between illness representations (cognitive pathway), emotional response (affective...
pathway), coping or behavioural self-management, and appraisal (152). Illness perceptions can alter or worsen over the trajectory of a health condition, and can change dependent on acquisition of new information (153). Figure 1.7 depicts an overview of the CSM based on a revised process model from recent meta-analytic evidence (154).

Associations between Leventhal’s illness representations and psychosocial outcomes, including anxiety and distress, have been studied across a variety of long-term conditions such as diabetes (155), kidney disease (156), coronary heart disease (157), and cancer (158). Recent meta-analytic evidence of the CSM found that perceived control was related to a variety of outcomes, including anxiety and psychological distress which were partially mediated by problem-focused coping and cognitive reappraisal (154). Overall, however, systematic review evidence and meta-analyses have produced differential findings in terms of efficacy for the CSM predicting psychological and behavioural outcomes such as adherence and self-management (154, 159-162). For example, Brandes and Mullan (2014) meta-analysed 23 datasets from 30 studies using the CSM to predict adherence in chronic conditions and found very small effect sizes for many of the illness representation dimensions, as well as moderate to high heterogeneity (160). Leventhal et al. (2016) emphasise that complexities inevitably arise when testing multi-level causal models; and highlight the reluctance of researchers to adopt methodologies which move beyond descriptive linear approaches when testing the CSM (122).

In the context of HPV and cytology cancer screening results, the CSM may help to identify important illness representations linked to adverse psychological response; and to understand nuanced interplays between cognitive and emotion pathways.
Figure 1.7 - An overview of the CSM, taken from Hagger et al. (2017) (154).
AIMS OF THE PHD

Aim

The overarching aim of this PhD is to generate evidence to determine psychological response to testing positive for HPV at cervical cancer screening. This will include exploring which psychological factors are most associated with adverse affective response at HPV primary screening. There will also be particular focus on the new result group created from the HPV primary screening algorithm; HPV positive with normal cytology. It is anticipated that women receiving an HPV-positive with normal cytology result may be the most likely to misinterpret their cancer risk, display unnecessary anxiety, and change the way in which they engage with future cancer screening and/or NHS services. To date, there have been no major studies examining the short-term psychological impact of HPV at primary screening, or with the new group of women.

Objectives

The objectives of this PhD are as follows:

1. To synthesise what is currently known about emotional response to testing positive for HPV at cervical cancer screening.
2. To compare anxiety and distress between women receiving different test results at HPV primary cervical screening.
3. To identify illness representation profiles for women who share distinct beliefs about testing positive for HPV with normal cytology; and examine the relationship between illness representation profiles and anxiety.
4. To explore reasons for variations in anxiety in women testing positive for HPV with normal cytology.
Policy Impact

Evidence-based psychological input into cervical screening communications is critical to ensuring that adverse psychological consequences are minimised, and re-attendance is maximised at HPV primary screening. The end goal of this PhD was to provide the NHSCSP with evidence to help inform cervical screening practice and the communication of HPV results (e.g. further development of test result letters, information materials, and staff training). In particular, the findings were aimed to aid the development of the content in a ‘Frequently Asked Questions’ letter to accompany HPV positive with normal cytology results. It is hoped that clear evidence-based communication will help to ensure that women understand their result and its implications for cancer risk.

Policymakers at Public Health England and the NHSCSP Manager who provided funding for one of the studies in this PhD were collaborators on most projects, and had welcomed input into the patient-centred aspects of the cervical screening programme. Therefore, alongside these research studies, I participated in policy and implementation meetings as part of the national HPV primary screening pilot committee and a working group on patient communications.
SUMMARY OF METHODOLOGY

Overarching Design

A mixed methods design was adopted to investigate psychological response to testing positive for HPV at primary screening, with particular focus on the new result group testing HPV-positive with normal cytology. Mixed methods research requires collecting quantitative and qualitative data, integrating data sets, and juxtaposing findings (163). This methodology is used to generate a deep understanding of a research problem by combining statistical findings (quantitative data) with personal accounts and experiences (qualitative data) (163, 164). In my PhD, this approach was used in the development and corroboration stages, as well as for complementarity purposes (i.e. enhancement and clarification) (165).

Data Source and Population

Data was used from three main sources: (i) secondary data from the existing literature as part of a systematic review and meta-analysis; (ii) data which I collected as part of the NHSCSP psychological evaluation of HPV primary screening; and (iii) data which I collected as part of my NIHR doctoral research fellowship. All primary data was collected from women aged 24-66 who had received cervical screening test results as part of the NHSCSP.

Psychological Impact of HPV Primary Screening (PIPS)

The psychological impact of HPV primary screening (PIPS) study refers to a psychological evaluation of HPV primary screening in England which was commissioned by Public Health England (PHE) in 2015. It was awarded to Dr Jo Waller and Dr Laura Marlow at the Department of Behavioural Science and Health at UCL. I was initially employed to lead on the management and data collection for this project in January 2016, before commencing my PhD in September 2017. Data from this psychological evaluation are used in Chapter 3 (Study 2).
Using Behavioural Science to Understand Anxiety at Cervical Cancer Screening

The ‘Using Behavioural Science to Understand Anxiety at Cervical Cancer Screening’ study refers to projects funded as part of my National Institute for Health Research (NIHR) doctoral research fellowship. I was awarded this fellowship in October 2017 (DRF-2017-10-105). Although this PhD is funded by the NIHR, the views expressed in this thesis are not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care. Data collected as part of my NIHR projects are used in Chapters 4 and 5 (Study 3 and 4).

Overview of Studies

Four original projects are presented. Chapter 2 presents Study 1 (addressing objective 1), which is a mixed method systematic review describing emotional response to testing positive for HPV at cervical cancer screening. Chapter 3 describes Study 2 (objective 2), which is a cross-sectional survey (n=1127) comparing anxiety and distress between women receiving different test results at HPV primary screening. Chapter 4 details Study 3 (objective 3), which is a cross-sectional survey (n=646) exploring illness representation profiles and their relationship with anxiety in women testing positive for HPV with normal cytology. Chapter 5 presents Study 4 (objective 4), which is a comparative qualitative interview study (n=30) exploring reasons for variations in anxiety in women testing positive for HPV with normal cytology.

**Study 1:** Emotional Response to Testing Positive for Human Papillomavirus at Cervical Cancer Screening: A Mixed Method Systematic Review with Meta-Analysis.

**Study 2:** Anxiety and Distress following Receipt of Results from Routine HPV Primary Testing in Cervical Screening: The Psychological Impact of Primary Screening (PIPS) Study.

**Study 3:** Illness Representation Profiles and their Associations with Anxiety in Women Testing Positive for Human Papillomavirus with Normal Cytology

**Study 4:** Exploring Reasons for Variations in Anxiety after Testing Positive for Human Papillomavirus with Normal Cytology: A Comparative Qualitative Study.
The content, structure, and design of Studies 3 and 4 were co-developed and shaped by input from a multi-disciplinary stakeholder team consisting of policymakers, behavioural scientists, third sector representatives, cervical screening nurses, health psychologists, and two patient and public representatives.

Further details on methodology, acknowledgements, roles, and context are described within each Chapter of this thesis.

**Definitions**

Key definitions which are useful for interpreting Studies 1-4 are outlined in Table 1.4. Please note that these definitions are intended to reflect their meaning as used within this thesis; they may not necessarily hold the same meaning in other contexts.

<table>
<thead>
<tr>
<th>Word or phrase</th>
<th>Definition for the purposes of this thesis and alternative terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological Response</td>
<td>Psychological response is used as an umbrella term to refer to emotional, cognitive, and/or behavioural outcomes. It is also sometimes referred to as psychological impact or sequelae.</td>
</tr>
<tr>
<td>Emotional Response</td>
<td>Emotional response is used as an overarching term to describe a range of emotions or psychological experiences with a dominant emotional component. It is also sometimes referred to as affect or affective response.</td>
</tr>
<tr>
<td>Emotion Regulation</td>
<td>Emotion regulation or affect regulation refers to a range of processes that influence the frequency, intensity, and duration of emotional response (166). In the context of anxiety, it is used to depict difficulties which occur in the use of specific emotion regulation strategies to reduce the effect of negative emotional response (167).</td>
</tr>
</tbody>
</table>
Cognitive

Cognitive Behavioural Theory is referred to as CBT (as opposed

Behavioural

to the wider common usage of this acronym to denote cognitive

Theory

behavioural therapy). Depending on the context and application,
it is also sometimes referred to as the cognitive behavioural
model or framework.

Anxiety

Anxiety, as used in this thesis, usually refers to state anxiety
unless otherwise stated. State anxiety describes an emotional
state which is usually short-term and characterised by
apprehension, nervousness, and/or uncertainty related to specific
or future event(s) (168).

Clinically

Clinically significant anxiety is used to refer to a state anxiety

Significant Anxiety score >49 as measured on the state subscale of the State Trait
Anxiety Inventory (168, 169). Depending on the context in
which it was used within a particular study, it is also sometimes
referred to as ‘clinically important anxiety’ or ‘very high
anxiety’. Details are described within the methods of each
Chapter.

54


Emotional response to testing positive for HPV at cervical cancer screening: a mixed method systematic review with meta-analysis

Context and Role:

Study 1 presents a mixed-method systematic review which I produced in collaboration with researchers in the Departments of Medicine and Psychology at McGill University (Montréal, Canada). We formed this collaboration because the research team at McGill were planning to conduct a similar systematic review to me (as per Objective 1 of my PhD) on patient aspects of HPV-positive results at cervical screening, which they had registered on PROSPERO. The McGill research team primarily consisted of Zeev Rosberger (Associate Professor), Ovi Tatar (Research Associate), and Kristina Wade (Research Assistant). My primary supervisor (Jo Waller) introduced me to Zeev Rosberger and, after discussions, we agreed that a collaborative review would strengthen our methods. I would lead the psychological review (in line with my NIHR fellowship aims) and McGill would lead a review on healthcare professionals’ acceptability of HPV primary screening. McGill had already performed an initial database search until October 2017.

I also sourced funding from the Scottish International Education Trust which enabled me to visit McGill University for 5-weeks in Jul-Aug 2018. I used this time to work with the team, update the database searches, and assess their existing articles for eligibility.

I developed the research question, updated the searches, set the eligibility criteria, screened all papers for eligibility, managed the project, led all aspects of the review
including meta-analyses, and drafted the written work. Researchers at McGill set the search strategy, performed the main database search, co-identified papers, and helped analyse data, acting as independent reviewers and coders throughout. More details on roles are described in the methodology section.

The findings from Study 1 were published in Health Psychology Review in May 2020 (see Appendix 2.1 for the full paper):

INTRODUCTION

As described in Chapter 1, over 570,000 new cases of cervical cancer are diagnosed every year worldwide, virtually all caused by persistent infection with high-risk HPV. Globally tens-of-millions of women find out they are HPV-positive at cervical cancer screening, and these numbers are set to dramatically increase with the introduction of HPV primary testing in major cervical screening programmes.

Over the last few decades, the psychological impact of testing positive for HPV has attracted substantial research focus with many studies assessing emotional response, e.g. anxiety, concern about result, or worry about cancer. The rationale for research in this domain has usually been orientated towards attempts to mitigate unnecessary adverse psychological consequences (i.e. improve mental health outcomes) and to maximise screening re-attendance or help-seeking (i.e. improve behavioural outcomes). Given that cervical screening is often a population-level intervention, assuming that HPV-diagnosis leads to even small percentages of women experiencing adverse effects, this translates to very large numbers experiencing psychological and/or behavioural sequelae. Hence, efforts to monitor emotional response have been prioritised and commissioned through some national health bodies, including the NHSCSP in England (85, 170, 171).

Despite psychological research in HPV, heterogeneity in local cervical screening protocols (e.g. screening tests used, order of tests) and study designs have meant that some major studies have produced mixed findings. For example, a large cross-sectional study found short-term anxiety and distress in women testing positive for HPV with abnormal cytology (85, 88). Qualitative research has also suggested anxiety, stigma, stress, and concern about sexual relationships following positive HPV results (87, 89). However, a large randomised controlled trial which considered differences in anxiety and distress between women who were told their HPV-positive result vs. not told their result as part of routine screening practice found no overall differences (84). A qualitative study also found that women reported ‘indifference’ as a main theme following HPV-positive results (172).
In addition to some mixed findings, several psychological studies have adopted methodological designs using hypothetical scenarios (173-177). Since these studies ask participants to imagine their emotional response to testing positive for HPV, they lack ecological validity. Other studies have combined women with carcinogenic and non-carcinogenic HPV types, e.g. including women with genital warts (178), or including women receiving treatment for precancerous cervical changes (179, 180). Again, this has meant that emotional response specific to testing positive for HPV at routine cervical screening has been difficult to isolate.

Further, as detailed in Chapter 1, attempts to explain emotional response to HPV have been largely atheoretical to date. As researchers working on psychological aspects of HPV are yet to establish a cogent theoretical framework, Cognitive Behavioural Theory may act as a promising theoretical framework for provisionally mapping emotional responses and their related constructs (127, 134). The CBT model may help organise relevant psychological responses and isolate areas for further concentrated theoretical developments. Research is needed to establish which theoretical constructs are most relevant in HPV.

As it stands, there is a body of research on emotional response to HPV, but a lack of conclusive evidence which is useful for cervical screening programmes or informing theoretical advancement. Despite recent and imminent roll-out of HPV primary screening in several countries and significant international interest, there has been no review or synthesis of the literature on emotional response. Study 1 of this PhD was a mixed methods systematic review to provide a comprehensive overview of the quantitative and qualitative literature, guided by the research questions: how do women emotionally respond to testing positive for HPV at cervical screening; and what influences emotional response to testing positive for HPV at cervical screening? Since emotions interact with, and are dependent upon, other biopsychosocial systems, cognitive behavioural theory was also adopted to provide an overarching theoretical framework, which mapped the systematic review findings for emotional response into related themes of cognitions and behaviours. This helped formulate a preliminary working model of emotional response to HPV, in an otherwise predominantly atheoretical domain.
METHODS

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (181). The protocol was registered on PROSPERO on 15.08.2018 (reg: CRD42018105134).

Search Strategy

Medline, Embase, PsycINFO, CINAHL, Global Health and Web of Science were searched to retrieve articles between 01.01.1980 and 09.11.2019. The year coverage is representative of the earliest available database record until the date the last search was performed. The search concepts (HPV, cervical cancer, screening, psychological) were agreed a priori and informed by breaking down the research questions (research questions are listed at the end of the introduction). The search strategy was developed for Medline, then validated and adapted for the other databases by an experienced librarian. Additional papers were identified by screening reference lists of included papers and searching OpenGrey (www.opengrey.eu). See Appendix 2.2 for the full list of search terms.

Design

We used a results-based convergent synthesis design, where the qualitative and quantitative evidence was analysed and presented separately, then integrated by juxtaposing the findings in a matrix table (182, 183). For the purposes of this review, the integration synthesis was defined as refining, comparing, and contrasting emotion-focused themes across all studies. Analysis of quantitative data estimated the relevance and representativeness of emotional responses, by providing estimates of effect sizes and associations between testing HPV-positive and emotional outcomes; and analysis of qualitative data provided in-depth explanations for emotional response. See Figure 2.1 for an overview of this design.
Figure 2.1 - Overview of the results-based convergent synthesis design.
Eligibility

The titles, abstracts, and full-text papers generated from the searches met the following inclusion criteria:

1. Adult population (18+) diagnosed with HPV in the context of cervical cancer screening.
2. At least one emotional outcome explicitly measured, explored, or emerged.
3. Quantitative, qualitative, or mixed-methods design.
4. Article written in English, French, or German.

Studies were excluded if they:

1. Employed a hypothetical scenario design.
2. Included participants who had cervical cancer or were receiving treatment for cervical lesions.
3. Primarily focused on HPV knowledge without linking to an emotional outcome.
4. Where data on HPV-positive results could not be extracted (e.g. grouped analysis combining test result groups).

Definition of Emotion

Currently, there is no scientific consensus on an agreed definition of emotion. Popular theories, for example Plutchik’s psycho-evolutionary theory of emotion (184), tend to be relatively consistent in how they describe primary emotions such as sadness, fear, happiness, disgust, surprise, anticipation, trust, and anger. However, complex secondary and tertiary emotions, and their fusion with cognitions and physiological or behavioural cues, remain strongly debated across and within disciplines. Therefore, for the purposes of this review, we defined categories of emotion, and related cognitions and behaviours, based on a combination of the American Psychological Association (APA) published definitions (www.dictionary.apa.org/emotion), validated outcomes reported in papers, and the review team’s interpretation in the coding and analysis stages. Table 2.4 outlines the definitions of emotions used which will be reported within the results.
Selection Process

Extracted studies were included/excluded as part of a two-step screening process based on title/abstract and full text. All titles and abstracts were screened by two reviewers (EM, OT or KW). Abstracts that passed the initial screen progressed to full-text review. Each full-text paper was independently assessed by two reviewers (EM, LR, OT) and discrepancies were resolved through independent full-text assessment from a third reviewer (JW), followed by discussion until consensus was reached. Agreement between reviewers prior to consensus was good (Kappa = 0.701). In some cases, authors of identified papers were contacted to request additional information where eligibility was not clear.

Data Extraction

Data extraction was performed independently by two reviewers using customised Excel templates (EM, OT). Each reviewer’s data extractions were compared and integrated to achieve the most comprehensive version. The information extracted across papers included: title, year published, study aims, sample size (total and by results group), population, study setting, participants (age, ethnicity, marital status, and education), design, HPV and cytology results, outcome measures, analysis, and main findings.

Data Synthesis and Meta-Analysis

The data synthesis was conducted in three stages by two reviewers independently (EM, OT) with disagreements resolved through discussion or inclusion of a third reviewer until consensus was achieved (JW or ZR) (185).

Firstly, for quantitative studies, we assessed study designs, outcome measures, and available data for inclusion in meta-analyses. We aimed to compare emotional responses in HPV positive groups with a control group (e.g. HPV negative and/or normal cytology). Out of seventeen quantitative studies identified, six studies did not qualify for meta-analysis because their observational design did not include a comparison (control) group. A further three studies did not report data in a format suitable for inclusion in meta-analysis and corresponding authors were contacted in attempt to retrieve data; one author

Note: initials refer to the authors of the published paper as listed on the cover page of Chapter 2.
no longer had access to the data and two authors did not respond. Non-validated measures (e.g. single-item questions) were also excluded from meta-analyses. From the available data, we were able to perform three meta-analyses for the outcome ‘state-anxiety’, and two meta-analyses representing psychological distress (by analysing outcome measures of general distress, sexual distress and test-specific distress together). We split the meta-analyses by time point (result notification ≤2 months [short-term] vs. >2 months [long-term]) and result group (HPV positive with abnormal or normal cytology, vs. control). Statistical analyses were performed using Review Manager, version 5.2 (186). Random effects models were chosen to account for heterogeneity in populations and design. Unstandardised mean differences with 95% confidence intervals were reported for state anxiety as the included studies used the same outcome measure (State-Trait Anxiety Inventory (168, 169)). Standardised mean differences with 95% confidence intervals were reported for psychological distress as outcome measures differed between studies. Tests of homogeneity were conducted using the $I^2$ statistic (187). Low heterogeneity was depicted by $I^2$ values of <25%, moderate heterogeneity as 50%, and high heterogeneity as >75% (188). Tau-squared ($\tau^2$) was reported to indicate estimates of between-study variance. We were unable to conduct meta-analyses for other emotional outcomes due to lack of data. See Appendix.2.3 for the raw data extracted for inclusion in meta-analyses.

Secondly, we synthesised all quantitative findings (including measures which could not be meta-analysed) by coding each measured outcome into themes of emotion, with related cognitive and behavioural themes also coded where relevant. Similarly for qualitative studies, the data (quotes and author interpretations) were copied verbatim into excel sheets and thematic analysis was performed using descriptive and analytical coding to identify emotion themes, again with related cognitive and behavioural themes also coded where relevant (189).

Thirdly, to integrate the findings of the two syntheses (integrated synthesis stage), we refined the themes of emotion across the quantitative and qualitative studies. A conceptual matrix was then constructed by mapping the emotion themes by study, to allow for comparisons and contrasts. Narrative overviews of the quantitative and qualitative findings for each emotion-focussed theme are presented, with meta-analysis findings integrated.

---

Note: initials refer to the authors of the published paper as listed on the cover page of Chapter 2.
Cognitive Behavioural Framework – Mapping Interacting Constructs

Following the data synthesis stage, the cognitive behavioural model was adopted to provide an overarching and preliminary theoretical framework to map the findings into constructs of emotions, with related cognitions and behaviours (127, 134). This helped address our second aim related to understanding what influences emotional response to HPV. The cognitive behavioural model, which underpins cognitive behavioural therapy, was chosen because it has a strong evidence-base for explaining emotional response across psychology and health domains (190, 191). We used the model in its simplest form as a triad, to illustrate how emotions (feelings), cognitions (thoughts, beliefs, attitudes) and behaviours (actions) may interact to influence one another. In practice, this meant that alongside the primary thematic analysis phase, the qualitative verbatim data and quantitative outcome measures were also coded to represent constructs of cognitions and/or behaviours. These thematic constructs where then illustratively mapped onto the triad model of the cognitive behavioural framework. Two reviewers independently coded and analysed all data (EM, OT), with disagreements resolved through discussion or inclusion of a third reviewer until consensus was achieved (JW or ZR).

Quality Assessment (Risk of Bias)

The Mixed Methods Appraisal Tool v2018 (MMAT) is a critical appraisal tool that has been specially developed for performing quality assessments in mixed method systematic reviews, and was used to assess the methodological quality of the included studies and potential for bias (192). The MMAT has independent sets of quality criteria to guide judgements for qualitative studies, randomised controlled studies, non-randomised studies, observational descriptive studies, and mixed-methods studies. The quality score for each reviewed study was based on criteria specific to the study design, which included five methodological domains and was calculated as an overall percentage. Mixed-methods studies were assessed using the mixed-methods criteria as well as the separate quantitative and qualitative criteria; their quality score could not exceed the weakest component. We intended for the MMAT to be used for illustrative and descriptive purposes and did not weight findings based on quality score alone. Rather, each study was assessed independently on its merits, limitations, and overall design in the cervical

Note: initials refer to the authors of the published paper as listed on the cover page of Chapter 2.
screening context by two reviewers (EM, LR, OT), with discrepancies discussed and resolved with a third reviewer (JW).

Rigour

Rigour was maintained by using a comprehensive search strategy along with documentation of eligibility decisions, which ensured descriptive validity (accuracy of data) (193). Interpretive validity was achieved through use of at least two independent reviewers (EM, OT, LR) in the data extraction phase to create a comprehensive database and perform of quality assessments (189). Following each stage of the data synthesis, two reviewers (EM, OT) plus a third reviewer (JW, ZR) discussed the thematic findings and resolved disagreements to help maintain theoretical validity (reliability of data interpretation) (193). Pragmatic validity (efficacy and transferability of findings) was improved by inclusion of study characteristic tables providing the context around the studies, allowing readers to judge the usefulness of findings (189).
RESULTS

Search Results

The database searches yielded 15,792 papers, with 9,343 titles and abstracts screened after removal of duplicates. Ninety-three papers were fully screened and 33 papers, representing 32 studies, met the selection criteria. See Figure 2.2 for a Prisma Diagram providing an overview of the searches and selection process.

Figure 2.2 - Prisma Flowchart: overview of searches and selection process. Taken from my published paper (194).

1Phase 1 exclusion reasons for titles and abstracts: 1) not population of interest; 2) not outcomes of interest (e.g. HPV attitudes or knowledge without emotional outcome); 3) not empirical study; 4) no abstract; 5) HPV not in the context of cancer screening; 6) no clinical diagnosis of HPV (e.g. hypothetical scenario design); 7) only HPV vaccine related.

2Phase 2 exclusion criteria described in the eligibility section used for full text articles.
Study Characteristics

Seventeen papers reported quantitative studies (84-86, 88, 113, 128, 195-199), fifteen reported qualitative (87, 89, 172, 200-209) and one was mixed-methods (210). A total of 12,789 women aged between 18 and 65 participated in twenty studies (n=12,244 quantitative; n=545 qualitative), of whom 4,305 were reported as having tested positive for HPV (n=3,874 quantitative; n=431 qualitative). Seven studies were conducted in the UK, seven in the USA, six in China, two in Colombia and the remaining eleven in Australia, Austria, Brazil, Canada, Greece, Italy, Ireland, Mexico, Norway, Tanzania, and Turkey. Twenty-one studies reported level of participant education: six used samples predominately educated to tertiary-level or above, and four primary-level or below. Fourteen studies reported a predominantly white ethnicity sample, and others predominantly African and Asian.

Nearly all studies recruited women through clinical settings (e.g. hospitals, primary care), except two which used public advertisements and social media. Most studies ascertained diagnosis of HPV using clinical records; however, some relied on participant self-report. Time between participants receiving their HPV result and recruitment was not reported in the majority of studies (especially qualitative); but in those which did, the time from diagnosis ranged from shortly after receiving result (notification-2 months) to 2 years after result, with two outliers reporting 4.8 and 5 years. There were also variations in the combinations of HPV-positive and cytology result groups between studies: most used HPV-positive with abnormal cytology (any grade or mixed) and some used HPV with normal cytology, HPV with atypical squamous cells of undetermined significance, or HPV alone (no cytology test).

Observational (cross-sectional, prospective longitudinal, or cohort) designs were used in most quantitative studies (13 out of 17). Four quantitative studies used a randomised controlled design (84, 128, 195, 211), but only one directly tested and reported differences between result groups (84). The same RCT study also included additional analyses on the observational findings from women in the study arm where participants were informed about their HPV results. All quantitative studies included at least one outcome with a core emotional component and most used widely-tested, validated scales; although some used single-item or non-validated scales and the mixed-methods study measured emotion.
The most common outcomes measured were state-anxiety, sexual distress, test-specific distress, general distress, depression, fear, and shame/disgust. Fourteen of the qualitative studies conducted interviews and one conducted focus groups (200). All qualitative studies described at least one emotional theme, mainly related to anxiety, test-specific distress, sexual distress, surprise and confusion, fear, shame and disgust, sadness, relief, and indifference.

Summaries presenting descriptive overviews of the studies and summary quality appraisal scores are presented in Tables 2.1 and 2.2.
### Table 2.1 - Descriptive characteristics of quantitative studies (and mixed-methods quantitative component).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Total n</th>
<th>HPV+ n</th>
<th>Cytology</th>
<th>Population and Setting</th>
<th>Study Design</th>
<th>Time point</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alay et al. (2020)</td>
<td>Turkey</td>
<td>80</td>
<td>19 (hrHPV)</td>
<td>Normal</td>
<td>≥30 years old, referred to a gynaecology outpatient clinic upon being diagnosed with an HPV infection by the community-based cervical cancer screening program.</td>
<td>Prospective longitudinal</td>
<td>Baseline (before result) and 2-months later.</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23 (hrHPV)</td>
<td>Abnormal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andreasson et al. (2019)</td>
<td>Norway</td>
<td>487</td>
<td>175</td>
<td>Normal</td>
<td>Women aged 34–69 years living in one of the four implementation counties taking part the NCCSP project which trialled two methods of HPV-based screening (primary HPV vs. primary cytology testing).</td>
<td>Cross-sectional (embedded within a trial)</td>
<td>Ranging between 4-24 months after result.</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>84</td>
<td>Abnormal (any grade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>175</td>
<td>Abnormal (ASCUS and low grade)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daley et al. (2010)</td>
<td>USA</td>
<td>154</td>
<td>154</td>
<td>Abnormal (any grade)</td>
<td>18-45 years, recruited through a student health service and five parenthood planning clinics.</td>
<td>Mixed-methods: cross-sectional</td>
<td>Not reported.</td>
<td>40%</td>
</tr>
<tr>
<td>Ferenidou et al. (2012)</td>
<td>Greece</td>
<td>51</td>
<td>51</td>
<td>Not reported</td>
<td>21-68 years, recruited through a gynaecological outpatient clinic</td>
<td>Cross-sectional</td>
<td>Not reported</td>
<td>60%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------</td>
<td>---------</td>
<td>--------</td>
<td>----------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>---------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Garcés-Palacio et al.</td>
<td>Colombia</td>
<td>675</td>
<td>50</td>
<td>ASCUS</td>
<td>Women aged 20-69 years old, with a first time Atypical Squamous Cells of Undetermined Significance (ASCUS) cytology result. This study was nested within the larger trial ‘Evaluation of Strategies for Optimal Clinical Management of Women with Atypical Squamous Cells of Undetermined Significance’, conducted between 2011 and 2016 in the city of Medellín.</td>
<td>Nested within observational arm of a larger RCT.</td>
<td>Baseline (before result), shortly after result, and 12-months later.</td>
<td>40%</td>
</tr>
<tr>
<td>Guerra Rodriguez et al.</td>
<td>Mexico</td>
<td>201</td>
<td>201</td>
<td>Not reported.</td>
<td>Mexican women aged 18 years and older with an HPV diagnosis for at least 12 months, recruited via mass media (radio, television, and social networks).</td>
<td>Cross-sectional</td>
<td>At least 1-year after result (Mean= 1.85 years)</td>
<td>60%</td>
</tr>
<tr>
<td>Hsu et al. (2018)</td>
<td>Taiwan, China</td>
<td>70</td>
<td>21</td>
<td>Normal</td>
<td>Women 20–65 years old attending a gynaecological clinics.</td>
<td>Prospective longitudinal</td>
<td>One month, 6-months,</td>
<td>80%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>---------</td>
<td>--------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>-----------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Kitchener et al. (2008)</td>
<td>UK (concealed arm)</td>
<td>604</td>
<td>105</td>
<td>Normal</td>
<td>clinic in southern Taiwan for their first follow-up visit after diagnosis.</td>
<td>RCT</td>
<td>20-64 months after result.</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>UK (revealed arm)</td>
<td></td>
<td>417</td>
<td>Normal</td>
<td>Normal (mild/borderline)</td>
<td>Cross-sectional</td>
<td>Approx. 2 weeks after result.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abnormal (mild/borderline)</td>
<td>Abnormal (mild/borderline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwan et al. (2012)</td>
<td>Hong Kong, China</td>
<td>299</td>
<td>157</td>
<td>ASCUS</td>
<td>Mean age across groups of 36.8, recruited via routine cervical screening at one of five community health clinics of the Family Planning Association of Hong Kong.</td>
<td>Prospective cross-sectional</td>
<td>Baseline (result notification) and 6 months after result.</td>
<td>100%</td>
</tr>
<tr>
<td>Maggino et al. (2007)</td>
<td>Italy</td>
<td>72</td>
<td>36</td>
<td>Not reported</td>
<td>20-45 years, during periodical check-up at obstetrics and gynaecology clinic.</td>
<td>RCT</td>
<td>Not reported.</td>
<td>40%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>-----------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-----------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Maissi et al. (2004)</td>
<td>UK</td>
<td>1376</td>
<td>536</td>
<td>Abnormal (mild/borderline)</td>
<td>Mean age across groups of 37.6, recruited through the English pilot study of liquid-based cytology and HPV testing (clinics).</td>
<td>Cross-sectional</td>
<td>Within 4 weeks of result.</td>
<td>100%</td>
</tr>
<tr>
<td>Maissi et al. (2005)</td>
<td>UK</td>
<td>1011</td>
<td>369</td>
<td>Abnormal (mild/borderline)</td>
<td>Mean age across groups of 37.9, initially recruited through the English pilot study of liquid-based cytology and HPV testing (clinics).</td>
<td>Cross-sectional</td>
<td>6-months after result.</td>
<td>80%</td>
</tr>
<tr>
<td>McBride et al. (2020)</td>
<td>UK</td>
<td>1127</td>
<td>258</td>
<td>Normal</td>
<td>Women aged 24–65 who had attended screening at one of five sites piloting HPV primary screening in England, including a control group with normal cytology who were not tested for HPV.</td>
<td>Cross-sectional</td>
<td>Mailed within 1 month after result.</td>
<td>100%</td>
</tr>
<tr>
<td>McCaffery et al. (2004)</td>
<td>UK</td>
<td>428</td>
<td>46</td>
<td>Normal</td>
<td>20-61 years, attending a National Health Service well-woman clinic in central London</td>
<td>Cross-sectional</td>
<td>Within one week of results.</td>
<td>60%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>---------</td>
<td>--------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>-----------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Nagele et al. (2019)</td>
<td>Austria</td>
<td>209</td>
<td>82 from conservative management</td>
<td>Abnormal</td>
<td>Mean age of 37, recruited from a university-based colposcopy clinic after referral for evaluation for suspect precancerous genital lesions.</td>
<td>Prospective cohort</td>
<td>Baseline (not defined), 6- months, and 12-months.</td>
<td>60%</td>
</tr>
<tr>
<td>Ngu et al. (2018)</td>
<td>Hong Kong, China</td>
<td>121</td>
<td>121</td>
<td>Normal</td>
<td>Mean age of 47.5, recruited through clinics in another RCT on primary screening in Hong Kong.</td>
<td>RCT</td>
<td>Not reported.</td>
<td>60%</td>
</tr>
<tr>
<td>Wang, Jeng et al. (2010)</td>
<td>Taiwan, China</td>
<td>249</td>
<td>44</td>
<td>Abnormal (any grade)</td>
<td>18-35 years, recruited through three hospitals in Taiwan.</td>
<td>Cross-sectional</td>
<td>Within 3-months of result.</td>
<td>60%</td>
</tr>
<tr>
<td>Wang, Shi et al. (2011)</td>
<td>China</td>
<td>2605</td>
<td>179</td>
<td>Abnormal (any grade)</td>
<td>18-65 years, recruited through multicentre hospitals.</td>
<td>Cross-sectional</td>
<td>Within 3-months of result.</td>
<td>80%</td>
</tr>
</tbody>
</table>

* hrHPV = high risk HPV (type 16/18) extracted from available data. ASCUS = atypical squamous cells of undetermined significance. RCT = randomised controlled trial.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Total n</th>
<th>HPV+ n</th>
<th>Cytology</th>
<th>Population and Setting</th>
<th>Study Design</th>
<th>Time point</th>
<th>Quality Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrera-Clavijo et al. (2015)</td>
<td>Colombia</td>
<td>93</td>
<td>55</td>
<td>Not reported</td>
<td>30-65 years, participating in the Columbian HPV testing screening pilot.</td>
<td>Focus groups</td>
<td>Not reported</td>
<td>80%</td>
</tr>
<tr>
<td>Barreto et al. (2016)</td>
<td>Brazil</td>
<td>14</td>
<td>14</td>
<td>No cytology test</td>
<td>20-42 years, attending a Specialised Medical Care Service.</td>
<td>Semi-structured Interviews</td>
<td>Not reported</td>
<td>60%</td>
</tr>
<tr>
<td>Bertram et al (2007)</td>
<td>USA</td>
<td>10</td>
<td></td>
<td>Abnormal (mixed)</td>
<td>18-35 years, purposive sample of demographically diverse women who attended one Women’s Health outpatient clinic that typically serves a multiethnic, low-income population.</td>
<td>Semi-structured Interviews</td>
<td>Within 5 years from test result</td>
<td>100%</td>
</tr>
<tr>
<td>Daley et al. (2010)</td>
<td>USA</td>
<td>52</td>
<td>52</td>
<td>Abnormal (any grade)</td>
<td>18-45 years, recruited through a student health mixed-methods: semi-</td>
<td>Not reported</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------</td>
<td>---------</td>
<td>--------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>---------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Head et al. (2017)</td>
<td>USA</td>
<td>30</td>
<td>17</td>
<td>Normal cytology</td>
<td>Mean age of 27.8 years, attending for two clinical visits approximately 6 weeks apart.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abnormal cytology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kosenko et al. (2012)</td>
<td>USA</td>
<td>25</td>
<td>25</td>
<td>Not reported</td>
<td>19-56 years, recruited through advertisements posted across cities in southeastern USA and on social media.</td>
<td>Semi-structured interviews</td>
<td>Average of 4.8 years after HPV diagnosis</td>
<td>100%</td>
</tr>
<tr>
<td>Lin et al. (2017)</td>
<td>Taiwan, China</td>
<td>20</td>
<td>20</td>
<td>Not reported</td>
<td>20-60 years, recruited using purposeful sampling through a gynaecology outpatient clinic in a university-based hospital.</td>
<td>Semi-structured interview</td>
<td>Not reported</td>
<td>40%</td>
</tr>
<tr>
<td>Linde et al. (2019)</td>
<td>Tanzania</td>
<td>15</td>
<td>15</td>
<td>Not reported</td>
<td>Women aged 27-55 who had tested HPV-positive during a patient-initiated screening</td>
<td>Semi-structured interviews</td>
<td>At least 14 months after result.</td>
<td>100%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>--------------</td>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td>McCaffery and Irwig (2005)</td>
<td>Australia</td>
<td>19</td>
<td>19</td>
<td>Abnormal (mixed)</td>
<td>and been appointed for a follow-up screening 14 months later.</td>
<td>Unstructured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>McCaffery et al. (2006)</td>
<td>UK</td>
<td>74</td>
<td>57</td>
<td>Abnormal and normal cytology</td>
<td>53% &lt;35 years and 47% &gt;35 years, recruited through general practice, family planning clinics, and specialist gynaecologists.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>McCurdy et al. (2011)</td>
<td>USA</td>
<td>18</td>
<td>18</td>
<td>Abnormal (mixed)</td>
<td>21-45 years, who attended one of three clinics open to the general public in a medically underserved area in Cameron County, Texas.</td>
<td>Structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>----------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>O’Connor et al. (2014)</td>
<td>Ireland</td>
<td>27</td>
<td>6</td>
<td>Abnormal (mixed)</td>
<td>26-61 years, recruited via colposcopy clinics in Ireland.</td>
<td>Semi-structured interviews</td>
<td>Within 6-months from HPV test</td>
<td>100%</td>
</tr>
<tr>
<td>Perrin et al. (2008)</td>
<td>USA</td>
<td>52</td>
<td>52</td>
<td>Abnormal (mixed)</td>
<td>18-44 years, recruited via three clinical sites in west central Florida – two Planned Parenthood clinics and the Student Health Service clinic at the University of South Florida (Tampa campus).</td>
<td>Semi-structured interviews</td>
<td>Within 1 week of HPV result</td>
<td>100%</td>
</tr>
<tr>
<td>Tiro et al. (2019)</td>
<td>USA</td>
<td>46</td>
<td>15 (hrHPV) 31 (other HPV type)</td>
<td>Mixed</td>
<td>Mean age 55.5 years, recruited a subset of women who were randomized as part of a pragmatic trial to receive an unsolicited mailed high risk HPV self-sampling kit, returned the kit, and tested positive.</td>
<td>Semi-structured interviews</td>
<td>Not reported.</td>
<td>100%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and Setting</td>
<td>Study Design</td>
<td>Time point</td>
<td>Quality Score</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
<td>---------</td>
<td>-----------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-----------------------</td>
<td>-----------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Waller et al. (2007)</td>
<td>UK</td>
<td>30</td>
<td>30 (at baseline)</td>
<td>Normal cytology</td>
<td>Above 20 years, recruited through the ARTISTIC trial (UK clinical screening trial)</td>
<td>Semi-structured interviews</td>
<td>Not reported after second HPV test.</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 (at 12-months)</td>
<td>No cytology test</td>
<td>12-months after testing HPV-positive with normal cytology.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wyndham-West et al.</td>
<td>Canada</td>
<td>20</td>
<td>Not reported</td>
<td>Not reported</td>
<td>20s-40 years, recruited through an HPV vaccination clinic in Toronto, Ontario.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
</tbody>
</table>

* hrHPV = high risk HPV (type 16/18).
Quality Assessment

Overall, MMAT quality scores ranged from 40% to 100%. Qualitative studies scored highest for quality (median=100%, range 40 to 100%), followed by quantitative studies (median=60%, range 40 to 100%), and the mixed methods study (40%). The main reasons for quality deductions in the quantitative studies were non-complete reporting of data and not using appropriate measures; and in qualitative studies, not sufficiently substantiating result interpretation with data. See Table 2.3 for a breakdown of the quality scores by study and design.

Emotional Response

We identified eight main themes of emotion which were measured or had emerged in women testing positive for HPV: anxiety; psychological distress (three types: sexual, test-specific, and general); fear; surprise; shame and disgust; sadness; positive affect; and apathy. Each of these emotions are discussed separately with an overview of the synthesised evidence. See Table 2.4 for a brief definition these emotions. The main findings from the primary mixed methods study (210) were integrated with the relevant quantitative and qualitative components throughout.

Tables 2.5 and 2.6 provide an overview of the main results for the quantitative and qualitative studies respectively. Table 2.7 provides the integration matrix of the themes measured or emerged across all studies.
<table>
<thead>
<tr>
<th>Article</th>
<th>Study Design</th>
<th>Criterion 1</th>
<th>Criterion 2</th>
<th>Criterion 3</th>
<th>Criterion 4</th>
<th>Criterion 5</th>
<th>Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alay et al.</td>
<td>Quantitative non-randomised</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td>Andreassen et al.</td>
<td>Quantitative non-randomised</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Barrera-Clavijo et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>80</td>
</tr>
<tr>
<td>Barreto et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>N</td>
<td>60</td>
</tr>
<tr>
<td>Bertram et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Daley et al.</td>
<td>Mixed methods</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Quantitative descriptive</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>-</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td>Ferenidou et al.</td>
<td>Quantitative descriptive</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td>Garces-Palacio et al.</td>
<td>Quantitative RCT</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>40</td>
</tr>
<tr>
<td>Guerra Rodriguez et al.</td>
<td>Quantitative descriptive</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>-</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td>Head et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Hsu et al.</td>
<td>Quantitative non-randomised</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>80</td>
</tr>
<tr>
<td>Kitchener et al.</td>
<td>Quantitative RCT</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Kosenko et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>40</td>
</tr>
<tr>
<td>Linde et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Maggino et al. (04)</td>
<td>Quantitative non-randomised</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>40</td>
</tr>
<tr>
<td>Maissi et al. (05)</td>
<td>Quantitative non-randomised</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Maissi et al. (05)</td>
<td>Quantitative non-randomised</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>80</td>
</tr>
<tr>
<td>Article</td>
<td>Study Design</td>
<td>Criterion 1</td>
<td>Criterion 2</td>
<td>Criterion 3</td>
<td>Criterion 4</td>
<td>Criterion 5</td>
<td>Score (%)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>McBride et al.</td>
<td>Quantitative non-</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery et al. (04)</td>
<td>Quantitative non-</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery et al. (05)</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>McCaffery et al. (06)</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>McCurdy et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>O'Connor et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Nagele et al.</td>
<td>Quantitative non-</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ngu et al.</td>
<td>Quantitative RCT</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>-</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td>Perrin et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Tiro et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Waller et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
<tr>
<td>Wang, Jeng, et al.</td>
<td>Quantitative non-</td>
<td>Y</td>
<td>Y</td>
<td>-</td>
<td>N</td>
<td>Y</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>randomised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wyndham-West et al.</td>
<td>Qualitative</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>100</td>
</tr>
</tbody>
</table>

Footnote: Each criterion was assessed using questions specific to the study design, outlined in the MMAT (2018).
Y = Criterion fulfilled; N = Criterion not fulfilled; - = Unable to determine if criterion was fulfilled.
<table>
<thead>
<tr>
<th>Definitions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td>Anxiety describes an emotional state often characterised by apprehension, nervousness, and/or uncertainty related to specific or future event(s) (168).</td>
</tr>
<tr>
<td><strong>Distress</strong></td>
<td>Psychological distress is a term to describe a collection of negative emotions or type of stress that results from being overwhelmed by demands or perceived threats. Distress can impact on everyday functioning related to general or specific events (212).</td>
</tr>
<tr>
<td><strong>Fear</strong></td>
<td>Fear is an intense basic emotion induced by perceived danger or threat(s) (213).</td>
</tr>
<tr>
<td><strong>Disgust and Shame</strong></td>
<td>Disgust is characterised by strong aversion to something deemed unpleasant. Shame can stem from disgust and is characterised by a highly unpleasant feeling of humiliation or distress caused by the belief (or perception that others believe) that one has been dishonourable, immodest, or indecorous (214).</td>
</tr>
<tr>
<td><strong>Surprise</strong></td>
<td>Surprise is described as feelings of sudden unexpectedness. It results from violations of an expectation or detection of novelty in the environment (215), often followed by confusion.</td>
</tr>
<tr>
<td><strong>Sadness</strong></td>
<td>Sadness and depressive mood are usually temporary emotional states usually aroused by the loss of something that is highly valued (216). Clinical depression shares core characteristics with sadness but differs in that it is a serious longer-term mental illness which significantly impairs everyday functioning.</td>
</tr>
<tr>
<td><strong>Positive Affect</strong></td>
<td>Positive affect is a broad and generic term for the internal feeling that occurs when a goal has been achieved, a source of a threat has been avoided, or one is satisfied with their current situation (217).</td>
</tr>
<tr>
<td><strong>Apathy</strong></td>
<td>Apathy is a lack of motivation or the absence or suppression of emotion, interest, or concern, and presents as a state of indifference (218).</td>
</tr>
</tbody>
</table>
Table 2.5 - Results of quantitative studies (or mixed-methods quantitative components) included in the review.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Psychological Aim</th>
<th>Outcomes</th>
<th>Measure(s)</th>
<th>Main relevant findings</th>
<th>Direction of effect for emotion in HPV+</th>
<th>Predictors of adverse emotion in HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alay et al.</td>
<td>To assess HPV-infected women’s sexual functions and anxiety levels before and after being informed about their HPV genotype (high-risk vs. low-risk) and cytology results.</td>
<td>Anxiety; Sexual function.</td>
<td>BAI (219); FSFI (220)</td>
<td>Women who had high-risk HPV genotypes 16/18 with normal or abnormal cytology had significantly higher anxiety levels after being informed of their result, compared to low-risk HPV genotypes with normal cytology. Women who tested positive for high-risk HPV 16/18 had significantly less sexual desire (one domain of the FSFI) after being informed about their test result; though there were no differences in total sexual function score.</td>
<td>Higher anxiety after being informed of high-risk HPV result; Less sexual desire after being informed of high-risk HPV result; however, no differences in overall sexual function.</td>
<td>N/A</td>
</tr>
<tr>
<td>Andreasson et al. (2019)</td>
<td><strong>Note: data from the watchful waiting arm</strong> To compare long-term anxiety and depression scores between women allocated to primary HPV screening vs.</td>
<td>Anxiety and Depression (Combined)</td>
<td>PHQ-4 (221)</td>
<td>Women with HPV-positive results and normal or abnormal cytology were no more likely to have mild vs. normal vs. moderate/severe anxiety and depression scores, compared with normal cytology at 4-24 months post-result.</td>
<td>No effect for combined anxiety and depression at 4-24 months.</td>
<td>N/A</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>-----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Daley et al. (2010)</td>
<td>To assess the emotional impact and behavioural consequences following HPV diagnosis among women who had received abnormal Pap test results.</td>
<td>Stigma; Fear; Self-blame; Powerlessness; Anger; Additional emotion items; Additional attitudinal items.</td>
<td>Non-validated single item questions in each of the categories.</td>
<td>Majority (%) endorsed ‘agree’ or ‘strongly agree’ for domains that the authors categorised as: stigma; fear; self-blame; anger; several additional emotion and attitudinal items.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Ferenidou et al. (2012)</td>
<td>To demonstrate the impact of HPV diagnosis on sexual function and mental health of Greek women.</td>
<td>Anxiety, physical distress, guilt, anger, shame, self-confidence, stigma, fear, sexual impact</td>
<td>Non-validated single item questions, except for sexual function which used a sexual</td>
<td>Majority (%) endorsed that they experienced anxiety (76.5%) after HPV diagnosis as well as fear regarding health in the future (82.4%). Nearly half of the women endorsed guilt (41.1%) and anger (43.1%). A minority endorsed distress, shame, reduction in self-esteem and stigmatization (all &lt; 22%). Reduced</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Garcés-Palacio et al.</td>
<td>To assess the psychosocial impact of HPV testing, colposcopy, and Pap-smear, as</td>
<td>Sexual interest; Anxiety;</td>
<td>Rosenberg Scale (222); STAI (168);</td>
<td>Women testing positive for HPV with ASCUS had higher anxiety and psychosocial burden</td>
<td>Higher anxiety and psychosocial burden</td>
<td>N/A</td>
</tr>
<tr>
<td>(2019)</td>
<td>triage strategies after a Pap-smear with atypical squamous cells of undetermined</td>
<td>Psychosocial burden of HPV.</td>
<td>HPV-Impact Profile (HIP) (223).</td>
<td>scores shortly after their result, compared with HPV-negative women with ASCUS; however,</td>
<td>shortly after result but not 12-months later.</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>significance (ASCUS), and evaluate the psychosocial impact based on the results</td>
<td></td>
<td></td>
<td>there were no differences at 12-months.</td>
<td>No effect for self-esteem.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of the strategies.</td>
<td></td>
<td></td>
<td>Self-esteem scores did not differ shortly after result or at 12-months.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guerra Rodriguez et</td>
<td>To assess correlative factors that facilitate and inhibit transition</td>
<td>HIV Stigma Scale adapted 224;</td>
<td></td>
<td>Higher levels of stigma were significantly correlated with utilising fewer coping</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>al. (2019)</td>
<td>Stigma related to coping with HPV</td>
<td></td>
<td></td>
<td>strategies (r = -0.278,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>----------</td>
<td>------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Hsu et al. (2018)</td>
<td>To examine the psychosocial adjustment trajectory, focusing on sexual distress; Psychosocial adjustment to PEAPS-Q (226); PAIS-SR psychological</td>
<td>Sexual distress; Psychosocial adjustment to PEAPS-Q (226); PAIS-SR psychological</td>
<td>Brief COPE adapted – Spanish version (225); Non-validated measure measuring stable sexual partner defined by condom use, cervical cytology control, and protective communication in sexual health.</td>
<td>p&lt;.01) and less protective behaviour (r = -0.163, p&lt;.05).</td>
<td>N/A</td>
<td>Current sexual activity; Presence of genital warts;</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Kitchener et al. (2008)</td>
<td>To assess the psychosocial impact of HPV testing as an adjunct to cytology in routine primary cervical screening.</td>
<td>Anxiety (state and trait); General psychological distress; Sexual satisfaction.</td>
<td>STAI-40 (168) GHQ-28 (228) Sexual Rating Scale (229)</td>
<td>Women who knew they were HPV+ with mildly abnormal or normal cytology displayed no differences in anxiety or distress, when compared with those who did not know they were HPV+. Sexual satisfaction was lower in those who knew they were HPV+ with normal cytology, compared to those who did not know; but there were no differences for HPV+ with abnormal cytology who knew vs. did not know.</td>
<td>1. RCT: no effect for anxiety or general distress; higher sexual distress for those with normal cytology only.</td>
<td>N/A</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td>-----------------------------------------</td>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Kwan et al.</td>
<td>To assess the psychological burden of testing positive for high-risk human papillomavirus (HPV) on Chinese women with atypical squamous cells of undetermined significance (ASCUS).</td>
<td>Anxiety (state); Cervical cancer worry; Psychosocial burden of HPV (test-specific distress).</td>
<td>S-STA1-6 (169); Adapted Breast Cancer Worry Scale (119); HPV-Impact Profile (HIP) (223)</td>
<td>At result notification (baseline), regardless of whether women reported knowing their HPV result, the HPV+ group with abnormal cells had significantly higher state anxiety, cervical cancer worry, and HPV-impact score, compared to the HPV- with abnormal cells group.</td>
<td>1. Regardless of whether women knew their HPV result, higher anxiety, fear about cervical cancer, and test-specific distress at result notification (baseline).</td>
<td>N/A</td>
</tr>
</tbody>
</table>

S - STAI - 6 (169); Adapted Breast Cancer Worry Scale (119); HPV-Impact Profile (HIP) (223)

Sub-analyses on women who reported knowing vs. not knowing their HPV result at notification (baseline), revealed no differences in anxiety, cancer worry, relationship, and sexual satisfaction between HPV+ and HPV-; however, those who knew their HPV+ result had higher HIP-impact scores (psychosocial burden/sexual distress).

2. When women knew their HPV result, higher test-specific distress. No effect on anxiety, cancer worry, relationship and sexual satisfaction.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Psychological Aim</th>
<th>Outcomes</th>
<th>Measure(s)</th>
<th>Main relevant findings</th>
<th>Direction of effect for emotion in HPV+</th>
<th>Predictors of adverse emotion in HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maggino et al. (2007)</td>
<td>To evaluate the impact of the communication of an HPV diagnosis on the cognitive-behavioural aspect, emotional experiences, psychic-physical well-being, and psychosexual sphere.</td>
<td>Anxiety (state and trait); Psycho-physiological reactions; Fears; Depressive thoughts; Intrusive thoughts and compulsive behaviours; Cognitive Behavioural Assessment (CBA 2.0) (230) SAT-P (231) BISF-W (232)</td>
<td>Most frequent emotional reactions to HPV were fear (25%), anxiety (17%). 38% endorsed no emotional reaction. Higher state anxiety and intrusive thoughts and compulsive behaviours in HPV+ group compared to no HPV. No differences in quality of life or sexual functioning.</td>
<td>Irrespective of HPV result, all outcome scores decreased over time. At 6-months post-result, there were no significant differences between groups for anxiety and cervical cancer worry. However, HPV-impact score (psychosocial burden/sexual distress) remained higher for the HPV+ group.</td>
<td>No effect for anxiety and fear about cancer at 6-months. Higher sexual distress at 6-months.</td>
<td>N/A</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Maissi et al. (2004)</td>
<td>To describe the psychological impact on women of being tested for HPV when smear test results are borderline or mildly dyskaryotic.</td>
<td>Anxiety (state); General psychological distress; Concern about result.</td>
<td>S-STA1-6 (169) GHQ-12 (228) Non-validated 2-item questionnaire (concern)</td>
<td>Higher state anxiety, distress, and concern in HPV+ group compared to other test result groups.</td>
<td>Higher anxiety, general distress, and test-specific distress.</td>
<td>Younger age ($\beta=-0.11$), higher perceived risk of cancer ($\beta=0.17$) and reporting not understanding results ($\beta=0.17$) predicted higher anxiety. No effect found for other demographic factors, awareness/ importance of HPV, and perceived severity of cancer. N/A</td>
</tr>
<tr>
<td>Maissi et al. (2005)</td>
<td>To describe the psychological impact on women of being tested for HPV when smear test results are</td>
<td>Anxiety (state); General psychological distress;</td>
<td>S-STA1-6 (169) GHQ-12 (228) Non-validated 2-item</td>
<td>No differences in state anxiety and general distress at 6 months.</td>
<td>No differences for anxiety and distress.</td>
<td>Higher concern about result and sexual distress.</td>
</tr>
</tbody>
</table>

Quality of life; Sexual Functioning.
<p>| Authors          | Psychological Aim                                                                 | Outcomes                                      | Measure(s)                              | Main relevant findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Direction of effect for emotion in HPV+                  | Predictors of adverse emotion in HPV+ |
|------------------|----------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                           |                                      |
| McBride et al    | To examine short-term anxiety and distress in women receiving different results following routine HPV primary testing at cervical screening. | Anxiety (state); General Psychological distress; Concern about result; Reassurance by result; Worry about cancer. | S-STAI-6 (169); GHQ-12 (228); Non-validated questions assessing concern, reassurance, and worry. | Anxiety was significantly higher in women testing HPV-positive with either normal cytology or abnormal cytology, compared with the control group (normal cytology). Distress was slightly higher in women who tested HPV-positive with abnormal cytology, compared with the control group. There were also increased odds of very high anxiety (STAI score &gt;49) in women who tested HPV-positive with normal or abnormal cytology compared to the control group. This pattern of results was only observed among women receiving their first HPV-positive result, not among women found to have persistent HPV at 12-month follow-up. Odds of concern and worry were higher, and reassurance lower, in women testing HPV-positive with either normal cytology or abnormal cytology, compared with the control group (normal cytology). | Higher anxiety shortly after HPV-positive with normal cytology (for first time) or abnormal cytology. General distress higher only for HPV-positive and abnormal cytology. Higher concern and worry, and lower reassurance. | N/A                                      |
|                 |                                                                                   | Concern about result; Sexual health worries. | questionnaire (concern) PEAPS-Q (226)   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                           |                                      |</p>
<table>
<thead>
<tr>
<th>Authors</th>
<th>Psychological Aim</th>
<th>Outcomes</th>
<th>Measure(s)</th>
<th>Main relevant findings</th>
<th>Direction of effect for emotion in HPV+</th>
<th>Predictors of adverse emotion in HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCaffery et al. (2004)</td>
<td>To examine the psychosocial impact of testing positive for high risk HPV among women attending primary cervical screening.</td>
<td>Anxiety (state); Screening/test-specific distress; Feelings towards sexual partner.</td>
<td>S-STAI-6 (169) CSQ (233) Non-validated 3-item questionnaire (feelings towards sexual partner).</td>
<td>Higher anxiety and test-specific distress in HPV+ with normal cytology, compared with HPV- with normal cytology. No differences in anxiety and test-specific distress for HPV+ with abnormal or unsatisfactory cytology, compared to HPV- with same cytology result. HPV+ had worse feelings towards sexual partner, regardless of cytology result.</td>
<td>Higher anxiety, test-specific distress, and sexual distress.</td>
<td>N/A</td>
</tr>
<tr>
<td>Nagele et al. (2019)</td>
<td>To examine the impact of different treatment strategies - surgical treatment or watchful waiting - on sexual activity, psychosocial distress, and fear of progression</td>
<td>Fear of Progression; Sexual distress.</td>
<td>FoP-Q (234); CDDQ sexual &amp; reproductive consequences subscale (235).</td>
<td>During an observational period of 12 months (baseline, 6 months, 12 months) there were no significant differences in fear of progression or sexual distress.</td>
<td>No effect over 12-months.</td>
<td>N/A</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Ngu et al. (2018)</td>
<td>To compare the effect of two educational interventions on the psychosocial wellbeing.</td>
<td>Anxiety and Depression; Cervical cancer worry; Screening-related anxiety; HPV-related shame.</td>
<td>HADS (236) CSQ (233) Adapted Breast Cancer Worry Scale (237) Adapted STD-related shame questionnaire (238)</td>
<td>Before randomisation to leaflet vs. counselling, 38.0% and 14.9% of women had clinical relevant anxiety and depression scores respectively. Anxiety and cervical cancer worry were slightly lowered after receiving information in the form of a leaflet, but there were no differences in depression scores. Anxiety and cervical cancer worry decreased over time. There were no differences in HPV-related shame over time.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang, Jeng et al. (2010)</td>
<td>To describe the psychological impact of HPV.</td>
<td>Psychosocial burden of HPV (test-HPV-Impact Profile (HIP) (223))</td>
<td>Higher HPV-impact score in HPV+ with abnormal cytology compared to normal cytology.</td>
<td>Higher test-specific and sexual distress</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Authors</td>
<td>Psychological Aim</td>
<td>Outcomes</td>
<td>Measure(s)</td>
<td>Main relevant findings</td>
<td>Direction of effect for emotion in HPV+</td>
<td>Predictors of adverse emotion in HPV+</td>
</tr>
<tr>
<td>---------</td>
<td>-------------------</td>
<td>----------</td>
<td>------------</td>
<td>------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Wang, Shi et al. (2011)</td>
<td>To assess the psychological burden of Chinese women with different HPV-related diseases.</td>
<td>Psychosocial burden of HPV (test-specific distress).</td>
<td>HPV-Impact Profile (HIP) (223)</td>
<td>Higher HPV-impact score in HPV+ with abnormal cytology compared to normal cytology. HIP domains “sexual impact”, “self-image”, and “control/life impact” had the highest scores. HPV+ with abnormal cytology showed sustained burden at 30 days, compared to HPV- with abnormal cytology which decreased.</td>
<td>Higher test-specific and sexual distress.</td>
<td>Psychosocial burden higher for women living in urban areas compared to rural.</td>
</tr>
</tbody>
</table>
Table 2.6 - Results of qualitative studies (or mixed-methods qualitative components) included in the review.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim</th>
<th>Main themes relating to emotional outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrera-Clavijo et al.</td>
<td>To evaluate the effect of communication and education strategies designed for women aged 30–65 years who participated in the comparative HPV testing and cervical cancer screening study as an alternative technique to cervical cytology.</td>
<td>Anxiety, fear of cancer, and fatalism in HPV-positive women. Also, blame towards partner. Face-to-face discussion with a health care professional reduced anxiety for many women.</td>
</tr>
<tr>
<td>Barreto et al. (2016)</td>
<td>To understand the feelings of women infected with HPV.</td>
<td>Fear, sadness, and shame in HPV+ women.</td>
</tr>
<tr>
<td>Bertram et al (2007)</td>
<td>To describe the experience of women with abnormal Papanicolaou (Pap) smears with a particular focus on their informational needs.</td>
<td>Initial anxiety at disclosure. Stigma associated with a sexually transmitted disease (STD) and a dearth of information available for male partners were problematic and influenced decisions about disclosure of human papillomavirus (HPV) infection to current or future partners.</td>
</tr>
<tr>
<td>Daley et al. (2010)</td>
<td>To assess the emotional impact and behavioural consequences following HPV diagnosis among women who had received abnormal Pap test results.</td>
<td>Fear, self-blame, stigma, powerlessness, anger.</td>
</tr>
<tr>
<td>Authors</td>
<td>Aim</td>
<td>Main themes relating to emotional outcomes</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Head et al. (2017)</td>
<td>Evaluate understanding of test results (Pap and HPV)</td>
<td>Confusion and anxiety in HPV+ women.</td>
</tr>
<tr>
<td>Kosenko et al. (2012)</td>
<td>To determine the sources of uncertainty experienced by women living with HPV</td>
<td>Seven sources of uncertainty: meaning of diagnosis; potential for disease progression; source of the infection; disclosure; sex and reproduction; and the HPV vaccine.</td>
</tr>
<tr>
<td>Lin et al. (2017)</td>
<td>To determine the psychological response of HPV infected women and their responses in terms of cognition, emotions, and behaviour.</td>
<td>Primarily fear, worry and suspicion. Also, disgust, shock, denial, disgust, guilt, and self-blame.</td>
</tr>
<tr>
<td>Linde et al. (2019)</td>
<td>To understand causes of attendance and non-attendance to a follow-up cervical cancer screening among HPV-positive women.</td>
<td>Fear of cancer, confusion, and relief that HPV was not cancer.</td>
</tr>
<tr>
<td>McCaffery and Irwig (2005)</td>
<td>To explore women's understanding of HPV, their information needs and experience of HPV infection using a method grounded in women's experience.</td>
<td>Anxiety and negative psychological response moderated by uncertainty about HPV, clinical communication, and mode of delivery of result. Anxiety most associated with receiving the test result by letter and searching the internet for further information.</td>
</tr>
<tr>
<td>McCaffery, Waller et al. (2006)</td>
<td>To examine the social and psychological impact of HPV testing in the context of cervical cancer screening.</td>
<td>Stigma, anxiety, stress, concern about sexual relationships, and worry about disclosure. Psychological burden related to relationship status and history, social and cultural norms, and understanding of key features of HPV.</td>
</tr>
<tr>
<td>Authors</td>
<td>Aim</td>
<td>Main themes relating to emotional outcomes</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>McCurdy et al. (2011)</td>
<td>To examine Hispanic women’s responses to learning they were HPV+, their decisions to disclose their HPV+ status, and their own and others’ reactions to their disclosure.</td>
<td>All expressed surprise and fear; some expressed issues with disclosure. Higher concern expressed in single, unattached women under 28 years.</td>
</tr>
<tr>
<td>O’Connor et al. (2014)</td>
<td>To explore emotional responses and predictors of negative reactions among women undergoing HPV tests in routine clinical practice.</td>
<td>Adverse emotional response (shame, embarrassment, stigma, regret, self-blame, anxiety, worry) linked to HPV infection rather than testing. Negative emotional response primarily influenced by concerns about abnormal cytology or diagnosis of CIN. Also, to a lesser extent, by HPV knowledge, awareness of HPV being sexually transmitted, awareness of HPV prevalence, and HPV information needs.</td>
</tr>
<tr>
<td>Perrin et al. (2008)</td>
<td>To explore women’s reactions to HPV diagnosis.</td>
<td>Emotions related primarily to stigma, fear, self-blame, powerlessness, and anger.</td>
</tr>
<tr>
<td>Tiro et al. (2019)</td>
<td>To explore patient perspectives after a positive HPV self-sampling result.</td>
<td>Two main relevant emotional themes: intense affect after receiving positive results (e.g. fear of cancer and shock); and confusion about purpose and meaning of HPV testing. Also, relief after speaking to a healthcare professional and apathy (indifference).</td>
</tr>
<tr>
<td>Waller et al. (2007)</td>
<td>To examine the way in which anxiety and concern transitioned over the course of the 12 months between two HPV tests; to explore the impact of a second HPV result on disclosure behaviour; and to explore women’s choice of management of persistent HPV infection.</td>
<td>Adverse emotional impact (anxiety, shock, confusion, distress) reported initially for first test result. However, this did not generally last in the year between the two test results. The emotional impact of a second positive HPV result 12-months later was greater for many women, sometimes causing them to disclose their result and seek support.</td>
</tr>
<tr>
<td>Authors</td>
<td>Aim</td>
<td>Main themes relating to emotional outcomes</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Wyndham-West et al.</td>
<td>To determine experiences surrounding HPV infections and</td>
<td>Anxiety, shame, stigma, ‘containment’ of the infection (prevention), disclosure</td>
</tr>
</tbody>
</table>
## Table 2.7 – Integration matrix of themes of emotion generated from the quantitative and qualitative syntheses.

<table>
<thead>
<tr>
<th></th>
<th>Anxiety</th>
<th>Test-specific Distress</th>
<th>Sexual Distress</th>
<th>General Distress</th>
<th>Fear</th>
<th>Disgust and Shame</th>
<th>Surprise</th>
<th>Sadness</th>
<th>Positive Affect</th>
<th>Apathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alay et al. (2020)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Andreassen et al. (2019)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrera-Clavijo et al (2016)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barreto et al (2016)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garces-Palacio et al. (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guerra Rodriguez et al. (2019)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head et al (2017)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsu et al. (2018)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Anxiety</td>
<td>Test-specific Distress</td>
<td>Sexual Distress</td>
<td>General Distress</td>
<td>Fear</td>
<td>Disgust and Shame</td>
<td>Surprise</td>
<td>Sadness</td>
<td>Positive Affect</td>
<td>Apathy</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>------</td>
<td>------------------</td>
<td>----------</td>
<td>---------</td>
<td>----------------</td>
<td>--------</td>
</tr>
<tr>
<td>Kosenko et al. (2012)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kwan et al. (2011)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lin et al. (2011)</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linde et al. (2009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maggino et al. (2007)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maissi et al. (2004)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maissi et al. (2005)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McBride et al. (2020)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery et al. (2004)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery et al. (2005)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery et al. (2006)</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCurdy et al. (2011)</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nagele et al. (2019)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>Test-specific Distress</td>
<td>Sexual Distress</td>
<td>General Distress</td>
<td>Fear</td>
<td>Disgust and Shame</td>
<td>Surprise</td>
<td>Sadness</td>
<td>Positive Affect</td>
<td>Apathy</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>------------------</td>
<td>------</td>
<td>-------------------</td>
<td>----------</td>
<td>---------</td>
<td>-----------------</td>
<td>--------</td>
</tr>
<tr>
<td><em>Ngu et al (2018)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>O’Connor et al (2014)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Perrin et al (2008)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Tiro et al. (2019)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Waller et al (2006)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Wang et al (2006)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Wang et al (2011)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Wyndham-West (2018)</em></td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Overlap between the main themes of emotion measured or emerged by eligible article (quantitative, qualitative, and mixed methods).
Anxiety

Quantitative (anxiety)

Ten quantitative studies measured anxiety at different time points (84-86, 88, 128, 195, 198, 211, 239, 240) mostly using the state subscale from the state-trait anxiety inventory (STAI) (168, 169).

We were able to perform meta-analyses including seven out of eleven studies, comparing HPV-positive with abnormal cytology groups vs. control groups (normal or negative results) for both short-term anxiety (result notification ≤2 months) and long-term anxiety (>2 months). Results revealed higher short-term anxiety for women who were HPV-positive with abnormal cytology compared to the control groups across six studies (mean difference [MD] in STAI of 7.6, 95% CI: 4.59 - 10.60, p<.001, τ²=11.11, I²=85%); however no differences were observed for long-term anxiety across four studies (MD = 0.03 95% CI: -1.45 – 1.51, p=0.96, τ²=0, I²=0%). A small meta-analysis of three studies also compared HPV-positive with normal cytology groups vs. controls, which revealed higher short-term anxiety for HPV-positive with normal cytology (MD = 6.33, 95% CI: 1.31 – 11.35, p=.01, τ²=17.55, I²=91%). It is worth noting that although the direction of effects were consistent across studies, high levels of statistical heterogeneity were identified in significant meta-analyses (I²>75%), therefore caution is warranted in the interpretation. See Figures 2.3 - 2.5 for the meta-analysis findings and papers included.

Four studies which measured anxiety could not be meta-analysed due to study design (e.g. no suitable control group (195); or lack of published data in the necessary format for extraction (128, 171, 239)). Consistent with the meta-analysis findings, two of these studies, where data could not be extracted, reported higher short-term anxiety in HPV-positive groups compared to controls (128, 239) but not long-term anxiety (171); and one study without a suitable control group found that anxiety decreased over time (195).

Interestingly, an RCT which considered differences in anxiety between HPV-positive women who were told (revealed) vs. not told (concealed) their HPV status as part of an embedded trial in routine practice, found no differences between the groups (84). Predictors of anxiety in HPV-positive women were also explored in one study (85): younger age, higher perceived risk of cervical cancer, and not understanding the meaning
of test results predicted higher anxiety within 4-weeks of results; but no predictive relationships were found for perceived importance of HPV and perceived severity of cervical cancer.
Figure 2.3 - Forest plot comparing short-term anxiety (result notification ≤ 2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups). Taken from my published paper (194).

Figure 2.4 - Forest plot comparing short-term anxiety (result notification ≤ 2 months) between those testing positive for HPV with normal cytology and control groups (HPV-negative and/or normal cytology groups). Taken from my published paper (194).
Figure 2.5 - Forest plot comparing long-term anxiety (>2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups). Taken from my published paper (194).
**Qualitative (anxiety)**

Ten qualitative studies reported anxiety as a theme following HPV-positive results (87, 89, 172, 200, 202, 203, 205, 207, 208, 210). Women who were anxious often had poor understanding of their results and/or HPV, expressed uncertainty about HPV, had often received their results by letter, and reported searching for further information on the internet (87, 89, 202, 203, 205). Two studies found that women who had discussed their results face-to-face with a healthcare professional were less anxious (200, 205). One study (87) interviewed women after two HPV test results (12-months apart) and found that anxiety was a dominant theme shortly after a first or second HPV-positive result, but that it did not generally persist in the time between the two tests. A second HPV-positive test compared to a first one, however, was described as being more anxiety-inducing for some women.

**Distress**

Three forms of psychological distress were identified across studies: test-specific distress, sexual distress, and general distress. Test-specific distress related to the psychological burden of HPV and screening test results. Sexual distress related mostly to impacts on sexual relationships, a partner, or concerns about transmission of HPV. General distress related to adverse impacts on broad everyday functioning (e.g. lack of sleep and concentration).

**Quantitative (distress)**

Sixteen quantitative studies included a measure of psychological distress: ten included test-specific distress (85, 86, 88, 195-199, 211, 240), eleven sexual distress (84, 86, 88, 128, 196-199, 239, 241, 242), and six general distress (84, 85, 88, 171, 240, 241). Test-specific distress was consistently higher (worse) for women testing HPV-positive with any cytology result compared to normal results up to 6-months post-result (88), but not at 12-months post-result (211). There were mixed quantitative findings for sexual distress and general distress. Sexual distress was found to be higher (worse) for women testing HPV-positive in five studies; however one low quality study showed no effect (128), and another high quality found mixed findings depending on how they analysed their data (84). Another small study found lower sexual desire but no differences in overall sexual
function between HPV-positive groups and the control (239); and a descriptive study reported that 33.3% and 43.1% of women endorsed reduced sexual interest and reduced frequency of sexual intercourse, respectively (199). In terms of longer-term impact, sexual distress was found to persist at 6-months in two studies (88, 198); one study examined the trajectory of adjustment to sexual distress over a 12-month period and found that adjustment occurred from one-to-6-months after HPV diagnosis (241). Consistently, another study found no differences over a 12-month period (242). General psychological distress (228) was found to be slightly higher (worse) in women testing HPV-positive with abnormal cytology 4-weeks after their result in two studies (85, 240). However, no differences were found 6-months later in a follow-up study (88) or up to 12 or 24 months later in two other studies (171, 242). The Kitchener et al (2008) trial again had mixed findings for general distress. Among women who were told their HPV result, being HPV-positive (vs. HPV negative) was associated with slightly higher general distress 2-weeks after the result. However, when women who had been told they were HPV-positive were compared with HPV-positive women who had not been told their HPV test result, no differences were found. Hsu et al (2018) found that adjustment to general distress occurred between 1-and-6-months after HPV diagnosis.

We performed meta-analyses to combine the available data for test-specific distress, sexual distress, and general distress, to represent an overall measure of psychological distress in both the short-term (result notification ≤2 months) and long-term (>2 months). One study (88) measured two forms of long-term distress (general and sexual); therefore, two meta-analyses were performed including each of these variables independently, to avoid bias through double-counting in the total sample.

Results revealed higher short-term distress for HPV-positive with abnormal cytology compared to the control across six studies (Standardised Mean Difference [SMD] = 0.68, 95% CI: 0.32 – 1.03, p<.001, \( \tau^2=0.18, I^2=94\% \)). Similarly, higher long-term distress was also observed for HPV-positive with abnormal cytology compared to the control across six studies, irrespective of whether we included the general or sexual distress outcome in the Maissi et al (2005) study (SMD = 0.42, 95% CI: 0.05 - 0.80, p=.03, \( \tau^2=0.19, I^2=92\% \) and SMD = 0.49, 95% CI: 0.19 - 0.80, p=.001, \( \tau^2=0.12, I^2=88\% \), respectively). Long-term effects appeared to be limited to test-specific and sexual distress outcomes, given that the two studies which measured general distress showed no differences (88, 240). Overall,
although direction of effects were relatively consistent across studies, high levels of statistical heterogeneity were identified in all the meta-analyses ($I^2>75\%$), therefore caution is advised in the interpretations. See Figures 2.6 - 2.8 for the meta-analysis findings for psychological distress.
Figure 2.6 – Forest plot comparing short-term distress (result notification ≤ 2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups). Taken from my published paper (194).

Figure 2.7 - Forest plot comparing long-term distress (>2 months) between those testing positive for HPV with normal cytology and control groups (HPV-negative and/or normal cytology groups), using the Maissi et al. (2005) general distress measure. Taken from my published paper (194).
Figure 2.8 - Forest plot comparing long-term distress (>2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups), using the Maissi et al. (2005) sexual distress measure. Taken from my published paper (194).
Qualitative (distress)
Themes indicative of test-specific distress emerged in thirteen qualitative studies (87, 89, 172, 200-209). Clear adverse impacts were reported, with many women describing concerns about HPV infection and/or the meaning of their test results. A small number of women reported that test-specific distress influenced their behaviours through triggering what they believed to be preventive action (often idiosyncratic, e.g. avoiding sharing soap/towels, exercising, or eating fruit (201, 207)). One study reported that test-specific distress primarily arose from concerns about abnormal cytology rather than HPV infection; however, it only included six women who were HPV-positive (172). The other studies reported that HPV infection had notably adverse impacts, independent of abnormal cytology. Sexual distress was also a theme in nine qualitative studies (87, 89, 200, 201, 203, 204, 206, 208, 209), with HPV-positive women often describing a range of concerns about their sexual relationships, transmission of HPV, and/or impact on their partner. Some women reported anger towards their partner and arguments due to suspected infidelity, or changing their sexual behaviours (e.g. avoiding sex) as a consequence of HPV.

Fear
Quantitative (fear)
Two studies descriptively reported that fear was a common adverse reaction to HPV diagnosis, with 82.4% and 25% of women endorsing it descriptively (128, 199). Similarly, the quantitative component of the mixed-methods study reported >75% endorsed fear; however, the authors categorised their definition of fear as endorsements of “anxious” and “worried” (210). Another study found that cervical cancer worry was higher in HPV-positive women shortly after result notification, but differences disappeared at 6-months (198); and one study reported that worry about developing cervical cancer decreased over time (195). Similarly, during an observational period of 12 months (baseline, 6 months, 12 months) there were no significant differences in fear of disease progression (242).
**Qualitative (fear)**

Fear emerged as a dominant theme in ten qualitative studies (87, 172, 200, 201, 204, 206, 208, 209, 243, 244). Women mainly described fears related to the development of cervical cancer, their future health, and potential infertility. Other women were afraid about the impact of their result or cancer on their family, partner, and/or friends.

**Disgust and Shame**

**Quantitative (disgust and shame)**

Six quantitative studies included measures of HPV-related shame or disgust (195-197, 199, 210, 245): two used the ‘self-image’ domain within a distress measure (223); one adapted an STD-related shame scale (238); and two used non-validated measures. Shame and disgust were higher in women testing positive for HPV with abnormal cytology when compared to normal cytology (196, 197), or HPV-negative with abnormal cytology (197) within 3-months of the result. Statements relating to shame and disgust were descriptively endorsed by the majority (>50%) in a descriptive study (210); and “guilt”, “shame”, and “stigmatisation” were endorsed by 41.1%, 21.5%, and 15.7% respectively in another study (199). HPV-related shame did not change over time (up to 6-months post result) (195), and one correlational study found that higher stigma was significantly associated with utilising fewer coping strategies and reporting less protective behaviour related to cervical cancer (245).

**Qualitative (disgust and shame)**

Shame and/or disgust also emerged as themes in eleven qualitative studies (87, 89, 172, 200, 201, 204-209). These emotions mostly centred round concerns about disclosure of results to partner/family/friends, judgement from others, and/or the belief that negative connotations (such as sexual promiscuity) were associated with HPV, sometimes leading to reports of stigma (89, 172, 207). Some women described feeling ashamed and reported variations of feeling “unclean” or “dirty”. Although shame and disgust appeared to be reported across ethnic groups, these themes seemed more dominant in studies focusing on women from non-white ethnic backgrounds.
Surprise (and Confusion)

Quantitative and Qualitative (surprise)
Despite surprise and/or confusion emerging as themes in ten qualitative studies (87, 201-205, 207, 209, 243, 244), these responses were not measured using validated scales in any of the quantitative studies. One descriptive study reported that 70.1% of HPV-positive women endorsed that they felt ‘shocked’ (210). In qualitative studies, women often expressed surprise as the first emotion experienced after receiving their HPV-positive result. Many reported subsequent confusion about the meaning of HPV and how they had acquired it. Often surprise and confusion appeared to be linked with knowledge that HPV is sexually transmitted, raising questions about its source and concerns about potential infidelity (linking to sexual distress).

Sadness

Quantitative (sadness)
One quantitative study descriptively reported that 14.9% of women who tested HPV-positive had clinically relevant depression scores; however, there was no control group to indicate population norms (195). Another low quality study found that depressive/intrusive thoughts were slightly higher in women who tested HPV-positive compared to HPV-negative (time point not reported) (128). A descriptive study reported that 51.7% of HPV-positive women endorsed that they felt ‘depressed’ (210).

Qualitative (sadness)
Only two out of eleven qualitative studies reported sadness or feelings of depression, and in both they were minor themes (87, 201).
Positive Affect (relief, acceptance)

Quantitative and Qualitative (positive affect)
In the quantitative studies, positive emotional responses, as indicated by improved outcomes following an HPV-positive result, were rarely observed. The only exception was one study where sexual satisfaction was higher in HPV-positive women (84). ‘Relief’ was also endorsed by 27.4%, ‘encouraged’ endorsed by 35.9%, and ‘in control’ endorsed by 68% of HPV-positive women in a descriptive study (210). Ten qualitative studies reported positive emotions such as relief, increased trust, and acceptance, though they were minor themes (87, 200, 202-205, 207, 209, 243, 244). Women who reported positive emotional responses to their HPV results described receiving their test results in person by a healthcare professional, consulting with a healthcare professional after results, having a supportive partner, and/or mobilising social support. Relief that the result was HPV and not cancer was a less common theme.

Apathy

Quantitative (apathy)
One study descriptively measured apathy and found that 38% of women reported no reactive emotion to their HPV diagnosis (128). Although the other quantitative studies did not directly measure indifference or apathy, the lack of observed differences in emotional outcomes between women receiving HPV-positive vs. negative results may be suggestive of apathetic or ambivalent responses, reported across quantitative papers under each individual emotion.

Qualitative (apathy)
Two qualitative studies reported indifference (172, 244), however this was either a minor theme or related more to the HPV testing procedures than response to testing HPV-positive.
Cognitive Behavioural Framework – Interacting Constructs

The emotional response findings for quantitative and qualitative studies were additionally coded to identify related cognitions and behaviours, as a starting point to determine how these three factors interact. Within the eight broad emotion-focused themes, twelve cognitive constructs and ten behavioural constructs were identified (many of which are described in the results under each emotion).

Cognitions Related to Emotional Response

Broadly, adverse emotional response to testing positive for HPV was linked to eight negative cognitions: low perceived control, confusion, stigma, relationship concerns, sexual concerns, cancer-related concerns, lack of trust in others, and uncertainty about meaning of result or future health.

Conversely, neutral or positive emotional responses were linked with high perceived control, trust in others, and acceptance.

Behaviours Related to Emotional Response

Related to behaviours, six areas were linked to adverse emotional response: negative impact on relationships, negative social impact, non-disclosure of results, idiosyncratic prevention, indirect clinical interaction (e.g. results by letter), and changes in sexual behaviour. In brief, negative impact on relationships and negative social impact referred to themes such as reports of arguments with a partner or avoiding contact with others. Non-disclosure of results represented women who expressed that they deliberately concealed their result from others. Idiosyncratic prevention referred to reports of attempts to prevent the spread of HPV through engaging in activities that are not evidence-based, such as washing toilet seats. Indirect clinical interaction referred to receiving results by methods with no personal contact such as a mailed letter, and/or not seeking advice from a healthcare professional. Changes in sexual behaviour described lower sexual activity, avoiding sex, and/or using a condom.
Conversely, four behavioural themes were linked with positive or neutral emotional response: direct clinical interactions; social support; behaviour of others; and future screening attendance. In brief, women who reported speaking to a healthcare professional after their HPV-positive result (direct clinical interactions) or their partner/family/friends (social support) expressed feeling more reassured, less anxious, relieved, and/or more accepting. Helpful behaviours of others related to partners/friends/family sourcing information on HPV or encouraging help-seeking behaviours. Attendance at a screening appointment after receiving an HPV-positive result (future screening attendance) was described by some women as providing reassurance.

According to the cognitive behavioural model, these three constructs of emotions, cognitions, and behaviours are likely to directly influence and/or interact with one another. This formulates a working model of what may influence emotional response to testing positive for HPV. See Figure 2.9 for an overview of emotions, cognitions, and behaviours mapped on to the cognitive behavioural framework.
Figure 2.9 - Emotional response to testing positive for HPV from all studies (quantitative, qualitative, mixed-methods) mapped on to a cognitive behavioural framework. Taken from my published paper (194).
DISCUSSION

Main Findings

This systematic review provides a comprehensive overview of emotional response to HPV diagnosis at cervical cancer screening, as well as a provisional model for understanding how emotions may interact with cognitions and behaviours using the cognitive behavioural framework. Testing positive for HPV at cervical screening appears to be most strongly associated with short-term anxiety, short and long-term psychological distress, and related to feelings of disgust and shame, surprise, and fear about cancer. There was little evidence of sadness or depression and a minority of women reported apathy or relief that they had been diagnosed with HPV rather than cancer.

Anxiety was one of the most common adverse responses reported shortly after women had received their HPV-positive result across all studies. Our meta-analyses revealed higher short-term state anxiety in women testing positive for HPV with abnormal cytology or normal cytology when compared with normal screening results (mean difference on STAI (168) of 7.6 and 6.33, respectively); though high statistical heterogeneity was observed, potentially due to differences in screening contexts and magnitudes of effect sizes ($I^2 >75\%$). These findings are consistent with another systematic review which found elevated anxiety in women with abnormal cytology who were attending for colposcopy (a more advanced stage in the screening process) (180). Interestingly, when comparing our results to this review, anxiety scores observed in colposcopy patients appeared to be descriptively similar to women testing positive for HPV with abnormal cytology (mean STAI score range: 34.0 - 49.0 pre-colposcopy vs. 39.6 - 46.0 after test result). These similarities suggest that anxiety associated with an HPV-positive screening result may be comparable to the anxiety experienced at follow-up investigative procedures (colposcopy); or may persist from the time of result to colposcopy.

Reassuringly, however, the results from our meta-analysis revealed that anxiety did not appear to persist in the long-term (> 2 months after notification), when comparing HPV-positive with abnormal cytology vs. normal/negative result groups. Also, overall, the
mean anxiety scores observed across studies did not exceed thresholds for clinical significance. The anxiety scores associated with a HPV-positive result tended to be higher than expected in the general population but lower than the cut-off for clinically important anxiety. Although, it is worth noting that all quantitative studies assessed anxiety across the whole study sample without conducting subgroup analyses. From a clinical perspective, it is highly unlikely that acute adverse emotional response to HPV would be expected at the population level. It is more likely that certain groups of women would be at higher risk of clinically important anxiety (e.g. low socioeconomic status, ethnic minority groups, low health literacy) who should additionally be studied or analysed separately. Anxiety was a dominant theme in the qualitative literature which, due to the likelihood of self-selection bias in qualitative studies, supports the notion that certain groups of women may be prone to very high anxiety.

HPV positivity was also related to psychological distress in both the short-term and long-term. Our meta-analyses (which combined sexual, test-specific, and general distress) revealed higher distress in women testing HPV-positive with abnormal cytology when compared with normal/negative results, at both result notification to 2-months, and 2-months onwards. Long-term distress (> 2-months), however, seemed to be specific to sexual and test-specific distress, as the studies which measured general distress at this time point found no differences.

Experiencing distress related to sexual relationships, infidelity, and potential transmission of the virus (sexual distress) is consistent with the broader literature on emotional response to other STIs and HPV in non-screening contexts (e.g. genital warts, other cancers) (178, 246). In this review, sexual distress appeared mostly, but not exclusively, limited to women in relationships and/or with current sexual partners in the qualitative literature, which may help explain some heterogeneity in findings. For some women, it was also reported as associated with relationship problems (e.g. arguing over suspected infidelity) and changes in sexual practice (e.g. avoiding sex). Further research could explore whether there are potential mediation or moderation effects between relationship status/sexual activity and sexual distress in HPV-positive women.

Distress related to meaning of screening test results (test-specific distress) was very common in the qualitative literature and was often described as the successor to surprise
and confusion. It was mostly linked to low HPV awareness, not understanding result meaning, confusion about the aetiology of HPV, and concerns about future health. As HPV cannot be cured and there are no clear (practical) prevention methods available (except vaccination prior to exposure), some women reported feeling that they were not in control of their health. Low perceived control appeared related to higher test-specific distress. A small number of women also reported engaging in idiosyncratic prevention methods to help treat or “contain” HPV, such as washing toilet seats or increasing physical activity. As a psychological formulation, these forms of prevention could be interpreted as behavioural attempts to gain control and reduce distress (127). High levels of distress about result also appeared to be closely related to fears about developing cancer which, together, intensified overall adverse emotional response.

Shame and disgust emerged as themes in the qualitative studies and a small number of women also reported feeling that there was stigma attached to HPV, which is consistent with broader STI research (247-249). In line with sexual distress and test-specific distress, shame and disgust seemed to be associated with maladaptive behaviours. Some women reported reluctance to disclose their HPV result to others and/or to seek social support from their partner, family, or peers because of feeling ashamed. To further assess the relevance of shame and disgust in the cervical screening context, future quantitative research should incorporate validated measures which include relevant behavioural impacts.

Relatively few studies measured sadness, depression, or generalised distress. In those studies which did, there was little evidence of adverse (clinically important) effects associated with any HPV-positive result. A small number of qualitative studies reported positive or neutral emotional responses, such as relief that a test result was HPV and not cancer, or indifference. However, these were not common and/or dominant responses.

Across all studies (quantitative and qualitative), adverse emotional response was mainly related to not understanding the meaning of the result, being in a relationship or having a current sexual partner, non-white ethnicity, receiving test result by letter, not discussing the result with a healthcare professional, little social support, and lower levels of education. Adverse emotional response was observed across all studies but appeared most prominent in the qualitative literature. Although fear and surprise/confusion were
common themes in the qualitative studies, they were rarely measured in the quantitative studies, highlighting a gap in quantitative research which warrants further exploration. Overall, our findings suggest that receiving an HPV-positive result at cervical screening can cause significant disturbance for some women, however, likely the minority of the population and/or certain groups.

**Methodological Considerations**

Importantly, this systematic review raises some relevant methodological considerations. Nearly all studies adopted cross-sectional, descriptive, and/or qualitative designs, prohibiting inferences of causality between testing positive for HPV and emotional response. The persistence of HPV infection (and the development of abnormal cells) are closely intertwined with immunological response; and there is a body of literature which suggests that psychological or social stressors can impair immune response (250-252). Therefore, it cannot be ruled out that HPV (re)activation and/or persistence are functions (or sub-functions) of psychological stress (i.e. adverse emotion). Interestingly, the one large RCT study in this review which compared anxiety and general distress between women testing HPV-positive who were told (revealed) vs. not told (concealed) about their HPV status (84), found similarly elevated anxiety scores (no differences). This suggests that elevated levels of anxiety and distress may be present prior to learning HPV-positive screening results, which supports the notion that psychological stress could play a role in HPV (re)activation/persistence. Other research suggesting that anxiety associated with HPV is usually temporary and normalises at 6-month follow-up may provide evidence against this mechanism; although it is worth noting that 41% of HPV cases clear within 6 months (28), meaning effects may be confounded. Further research is needed to test the validity of such psychobiological mechanisms and/or other potential causative pathways.

It is also worth highlighting that very few studies analysed and/or interpreted their data in terms of clinical significance, meaning it was not possible to distinguish between normal and clinically relevant emotional responses for most outcomes. Negative response to adverse information usually a temporary process constituting a normal part of human consciousness. Therefore, studies in this review which drew implicative conclusions based on between-group differences without further interpretation provided little insight
distinguishable from healthy response. To progress this field of psychological research, future studies should be designed and appropriately powered to test for clinical significance rather than between-group differences alone.

Most participants were educated to secondary level or above (where it was reported) and there were relatively few studies from low-and-middle-income countries. The highest quality studies consisted of well-educated (tertiary level) white patients living in high-income-countries which used organised screening programmes. Consequently, the main findings of this review represent relatively homogenous samples and may not be directly translatable to other settings or lower-income-countries. The qualitative studies which were conducted in low-and-middle-income-countries (Brazil, Colombia, Taiwan, and Tanzania) reported stronger adverse emotional impacts (200, 201, 204, 243). Therefore, the findings reported in this review may be conservative compared to other health systems or cultural contexts.

Finally, HPV-positive results in the reviewed studies were usually accompanied by abnormal cytology. This meant that we were unable to determine the relative impact of HPV vs. abnormal cytology for many of the emotions described. However, there were some emotions which seemed inherently related to HPV, such as sexual distress and test-specific distress. Receiving both HPV and cytology results is, nevertheless, reflective of routine screening practice, meaning that the findings of this review should provide valuable and pragmatic insights into receiving results in the context of screening.

Limitations

This timely systematic review benefits from the adoption of a relatively novel and rigorous mixed methods review design. Like most reviews, there are a number of limitations worth considering when interpreting the results. Firstly, although we used a comprehensive search strategy to identify papers across six major databases, the grey literature search was limited to OpenGrey and we did not contact authors or Listservs to identify additional literature. Also, given that there is no clear agreed or distinct theoretical definition for many emotions, emotion categorisations were often based on judgements and interpretations by the review team, especially where data was measured
using non-validated scales or qualitative data. The meta-analyses were performed using small numbers of studies (range: 3 - 6) which can be unreliable and subject to bias, and also prohibited moderator analyses. Therefore, relevant mechanisms could not be explored and caution is warranted in the interpretations. Lastly, whilst we used the cognitive behavioural framework to map our findings, there are several other potentially relevant theoretical models which could be used to structure emotional reactions to HPV; e.g. Williams’ Affect and Health Behavioural Framework (253) (discussed in more detail in the general discussion, Chapter 6) or Leventhal’s Common Sense Model of Self-Regulation (148, 149). Using alternative theoretical frameworks may have led to different formulations but we are confident that our overall conclusions are valid.

**Implications for Policy and Practice**

As HPV primary screening is being implemented around the world, our findings provide rich insight for policymakers and clinicians into women’s experience of receiving HPV-positive results. In attempts to mitigate adverse response, common themes highlighted in this review (e.g. related to confusion around cancer risk or sexual transmission) could be targeted through tailored information in screening result letters or accompanying leaflets. Clinicians working in primary care and cervical screening in areas where HPV-testing is being implemented could also use this information to pre-empt or address women’s questions and concerns, especially in low-and-middle-income countries where adverse emotional response may be greater. Public health or third sector organisations running campaigns on cervical cancer screening could frame their communications to target some of the key areas, e.g. to tackle stigma associated with sexually transmitted aspects. Clinical signposting and pathways could also be embedded within cancer screening programmes to provide support for some of the sub-groups highlighted, who may be at higher risk of clinically important adverse responses (e.g. women from ethnic minority backgrounds, or those with low health literacy or without access to social support).
Conclusion

This systematic review was designed to meet the first aim of my PhD, to synthesise what is currently known about emotional response to testing positive for HPV at cervical screening. Short-term anxiety, distress about test results, distress about sexual relationships, feelings of disgust and shame, surprise, and fear about cancer appear to be the most common emotional responses to testing positive for HPV. Almost exclusive use of observational and qualitative designs, however, limits conclusions regarding clinical significance and prohibits some important causal inferences. This comprehensive review, paired with the provisional framework of relevant emotional, cognitive, and behavioural factors, will act as a springboard for the development of a cogent theoretical literature on this topic. Further, to date, there has been very little research in the context of HPV primary screening where communication of HPV result is routine; hence limited research was identified on the impact of testing HPV positive with normal cytology (the new result group generated from the HPV primary screening algorithm). Future research should aim assess the psychological impact of routine HPV primary screening, in line with the recent or imminent implementation of this method across several countries.
CHAPTER 3 - STUDY 2

Anxiety and distress following receipt of results from routine HPV primary testing in cervical screening: a cross-sectional study in England

Context and Role:

Study 2 presents findings from the psychological evaluation of HPV primary screening which was commissioned by Public Health England in 2015. The grant was awarded to Dr Jo Waller and Dr Laura Marlow in the Department of Behavioural Science and Health at UCL. I was employed to work on this project in January 2016, before starting my PhD in September 2017. I gained the necessary NHS ethics and regulatory approvals, published the protocol, helped develop the measures, managed the multi-site project, and had most of the data collected by the time my PhD commenced. The psychological evaluation assessed outcomes at baseline (shortly after test results), 6-months, and 12-months; primary baseline findings are presented in this PhD.

To gain HRA approvals and recruit participants, I formed positive working relationships with NHS clinical laboratory managers and staff at HPV primary screening pilot sites (Kay Ellis, Christopher Evans, Nicola Fagan, Viki Frew, Miles Holbrook, Janet Parker, David Smith, and Carol Taylor). Policy managers at Public Health England (Ruth Stubbs and Karen Denton) also helped to facilitate public facing aspects of the study, including printing a line about our study in national cervical screening leaflets used in the HPV primary screening pilot areas. Researchers at King’s College London to (Dr Matejka Rebolj and Christopher Matthews) provided me with tabulated data from the wider HPV primary screening pilot to generate statistical weights and apply these weights to our sample. Two researchers (Lauren Rockliffe and Kirsty Bennett) assisted with data collection and data entry.
I also collaborated with a statistician (Dr Deborah Ridout) who, in particular, assisted by performing statistical analysis which combined both multiple imputation and weighted data. I co-developed the analysis plan, generated and applied the statistical weights, and performed the complete case analysis.

The findings of study 2 were published in International Journal of Cancer in April 2020 (see Appendix 3.1 for the full paper):


The protocol was published in BMJ Open in December 2016 (see Appendix 3.2 for the full protocol paper):

INTRODUCTION

Overview

The systematic review, presented in Chapter 2, concluded that testing positive for HPV was associated with adverse emotional response and particularly heightened short-term anxiety and distress. Although an extensive psychological literature on HPV was identified, there had been no research in the context of HPV primary screening, where HPV result communication is routine. Further, we were largely unable to determine the weighted impact of HPV vs. abnormal cytology because traditionally most screening programmes combine these results (i.e. they only test for HPV when abnormal cytology is present). This marks a large gap in the literature, especially as HPV primary screening was recently implemented in England and creates a large new group of women who can test HPV positive with normal cytology.

Background

As described in Chapter 1, over 3 million women take part in the National Health Service Cervical Screening Programme (NHSCSP) in England every year (1). In the UK, cervical screening recently changed to incorporate primary human papillomavirus (HPV) testing at the end of 2019. Testing for the presence of high-risk HPV has been shown to increase sensitivity for the detection of precancerous lesions and is predicted to prevent almost 500 additional cancers per year in England (2-6).

As well as testing far greater numbers of women for HPV, the HPV primary screening algorithm creates groups of women who can test positive for HPV with normal or abnormal cytology. Given these changes to routine protocol for screening and follow-up, it is important that psychological factors are evaluated to prevent unnecessary harm and help determine the information needs and support required for women attending HPV primary screening. Information materials for HPV primary screening have already been developed by NHSCSP (see Appendices 1.1 and 1.2 for the information materials sent to women at the point of invitation). It is unclear whether these are sufficient to ensure that women understand their screening result and cervical cancer risk. Ahead of the full roll-
out of HPV primary screening across England in 2019, the new programme was piloted in six sentinel NHS sites (7). This provided the opportunity to evaluate the psychological impact of HPV primary screening prior to full implementation. It also allowed us to compare the psychological impact of testing HPV positive with normal cytology vs. HPV positive with abnormal cytology, addressing this gap in the literature.

Overall, Study 2 aimed to address objective 2 of my PhD, to compare anxiety and distress between women receiving the different possible test results at routine HPV primary screening in England. The partial conversion of the pilot screening laboratories to HPV screening also allowed the comparison of these women with those receiving a normal cytology result (with no HPV test) as part of the cytology-based programme (16). To our knowledge, and based on the results of the systematic review in Chapter 5, this is the first major study to quantitatively measure the short-term psychological impact of HPV primary testing within a routine programme. Other psychological evaluations have taken place in the context of clinical trials where information on HPV was given to women prior to their result as part of consent procedures.

METHODS

Design

A cross-sectional between-groups design was employed to assess women’s psychological responses to a survey shortly after receiving their cervical screening test results (baseline), as well as 6-months, and 12-months later. This PhD reports baseline findings.

Participants

Participants were women aged 24–65 years who had been screened in one of five NHS sites in England using HPV primary testing as part of the NHSCSP pilot: North West London, Sheffield, Norfolk and Norwich, Liverpool, and Central Manchester. The NHS pilot sites had catchment areas with broad geographical coverage across England. Baseline recruitment to this study commenced on 18/11/2016 and ceased on 14/10/2017
with approximately 3-5 months of active recruitment per site. Health Research Authority (HRA) approval was granted on 26/09/2016 (Research Ethics Committee reference: 16/LO/0902 and Confidentiality Advisory Group reference: 16/CAG/0047). See HRA approval letter (Appendix 3.3).

Women were eligible if they had received one of six possible combinations of HPV and/or cytology test results within the last two weeks, as indicated by their NHS clinical records. The sampling strategy aimed to recruit roughly equal numbers of women from each of the six test result groups. Table 3.1 provides an overview of the six result groups. Five groups were recruited from women included in the HPV primary screening pilot. Three of these groups included women following their first HPV test, who tested HPV-negative, HPV-positive with normal cytology, and HPV-positive with abnormal cytology (Groups 1 to 3 in Table 3.1). The other two groups had initially tested positive for HPV with normal cytology and recently attended their 12 month follow-up appointment, including women who had persistent HPV, and those who had cleared HPV (Groups 4 and 5 in Table 3.1). We also included a control group who had received a normal cytology result (no HPV test) at standard cytology-based screening within the same geographical areas and processed by the same laboratories (Group 6 in Table 3.1).

Table 3.1 - HPV and cytology results for the six groups included in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>HPV result</th>
<th>Cytology result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Negative</td>
<td>Not tested</td>
</tr>
<tr>
<td>Group 2</td>
<td>Positive</td>
<td>Normal</td>
</tr>
<tr>
<td>Group 3</td>
<td>Positive</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Group 4*</td>
<td>Persistent positive at 12 months</td>
<td>Normal</td>
</tr>
<tr>
<td>Group 5*</td>
<td>Negative at 12 months</td>
<td>Not tested</td>
</tr>
<tr>
<td>Group 6 (control)</td>
<td>Not tested</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table 3.1 has been adapted from the protocol paper (170).

*Women in Groups 5 and 6 had all tested HPV positive with normal cytology at their first HPV primary screen and were recruited to the study after their 12-month follow-up test.
Procedures and Clinical Management

To meet CAG Section 251 requirements, prior to participant identification, women were notified about the study via a web link which was printed in NHSCSP HPV primary screening information leaflets and sent alongside their screening invitation letters. The link directed women to our university departmental website which provided study information as well as details of how to opt-out of being approached to take part. No women opted out.

Eligible women were identified by staff in NHS cytology and virology departments at each of the five participating sites. I communicated numbers needed in each group to each laboratory as the study progresses, proportionate to the numbers of results processed at each laboratory. Staff at the NHS sites allocated each potential participant a unique identity number, which they recorded and linked to patient name, address, age, screening history, NHS site, and test result; these outcomes will collectively be referred to as ‘NHS data’. Section 251 approval was granted for the NHS to upload this information to a secure printing and mailing company (CFH Docmail Ltd) for the purposes of contacting participants. Docmail was contractually bound to comply with the Data Protection Act (1998) and securely destroy these data within 30 days of receipt.

Potential participants were mailed invitation packs to their home, which contained an invitation letter, participant information sheet, consent form, questionnaire booklet and prepaid return envelope. To maximise the response rate, a reminder pack containing the same documents was mailed three weeks later.

Women opted to take part by returning their completed consent form and questionnaire to UCL. All documents were pre-printed with unique identity numbers which allowed questionnaire data to be linked with NHS data. At the end of recruitment, UCL received NHS data on all of the women approached (n=5494) in non-identifiable format (name and address removed, and replaced with Index of Multiple Deprivation score and quintile) to allow for demographic comparisons between responders and non-responders.
Outcome Measures

Primary outcomes were state anxiety and general distress (measured using the State Trait Anxiety Inventory (S-STAI-6) (17) and General Health Questionnaire (GHQ-12) (18) respectively). Secondary outcomes included very high anxiety (score >49/80 on S-STAI-6), case-level distress (score >3/12 on GHQ-12), self-reported response to test results (concern and reassurance), and worry about developing cervical cancer. HPV and cytology screening result (Groups 1 to 6 as outlined in Table 3.1) was the independent variable. See Table 3.2 for a more detailed overview of the primary and secondary outcome measures.

Demographic characteristics based on self-report were highest level of education, ethnicity, marital status, and HPV vaccine status. NHS data included information on age, cervical screening history (number of previous screens), NHS site, and Index of Multiple Deprivation score and quintile (IMD; a marker of area-level deprivation, based on residential postcode) (19). Table 3.3 presents an overview of these descriptive outcome measures. See the full questionnaire (Appendix 3.4).

Table 3.2 - A summary of the primary and secondary outcomes measures

<table>
<thead>
<tr>
<th>Description</th>
<th>Scoring and interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong> (S-STAI-6)</td>
<td>The short-form state anxiety inventory (S-STAI-6) is a six-item, validated questionnaire measuring anxiety (169). Cronbach’s alpha was 0.86 across all groups (n= 991), indicating a high level of internal consistency.</td>
</tr>
<tr>
<td></td>
<td>Scores range from 20-80. Normal score expected in the general population at 34-36. Very high anxiety at &gt;49.</td>
</tr>
<tr>
<td><strong>General distress</strong> (GHQ-12)</td>
<td>The General Health Questionnaire (GHQ-12) is a 12-item validated questionnaire used to measure general distress (228). Cronbach’s alpha was 0.91</td>
</tr>
<tr>
<td></td>
<td>Scores range from 0-12. Case-level distress at &gt;3.</td>
</tr>
</tbody>
</table>
Concern about test result* was measured by asking: *How concerned do you feel about your recent screening result?* This question was adapted from the previous NHSCSP psychological evaluation (85).

Reassurance relating to test result was measured by asking: *How reassured do you feel about your recent screening result?* This question was adapted from the previous NHSCSP psychological evaluation (85).

Worry about cervical cancer* was measured by asking: *How worried are you about getting cervical cancer in the next 10 years?* This question was adapted from the previous NHSCSP psychological evaluation (85).

Primary outcomes were anxiety and general distress. Secondary outcomes included concern, reassurance, and worry.*Cut-off points for high/low concern, reassurance, and worry were based on the most stable estimates and distribution of participant responses; sensitivity analyses were performed comparing the different possible cut-off points which revealed consistent finding
Table 3.3 – Descriptive outcome measures.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>Ethnicity, educational attainment, employment and marital status were assessed via questionnaire. Age of participant was communicated to UCL from participating laboratories at pilot sites.</td>
<td>Self-reported in questionnaire. Age at baseline, communicated to UCL from NHS clinical records.</td>
</tr>
<tr>
<td><strong>Index of Multiple Deprivation</strong></td>
<td>Index of Multiple Deprivation score (IMD) was assigned to participants by laboratories and communicated to UCL. The IMD is a measure of area level deprivation which can be derived from a postcode (254). It takes into account: income deprivation; employment deprivation; education, skills and training deprivation; health deprivation and disability; crime; barriers to housing services; and living environment deprivation.</td>
<td>Calculated by the NHS via clinical records and communicated to UCL in score form.</td>
</tr>
<tr>
<td><strong>NHS Site</strong></td>
<td>The NHS site refers to where women were screened and received test results, recorded via communication from participating laboratories.</td>
<td>Communicated to UCL by NHS site.</td>
</tr>
<tr>
<td><strong>HPV vaccine status</strong></td>
<td>Participants were asked to indicate whether they had received the HPV vaccine and how many doses they had.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
</tbody>
</table>
Sample Size and Response Rate

The study was powered to detect a small-to-medium between-group difference (f=0.14) in anxiety (as measured by the S-STAI-6) at the 12-month time-point (10). Based on previous studies (10, 13), we expected anxiety scores across groups to be in the range of 36–40, with a standard deviation (SD) of 12. With an α of 0.05, we calculated that a minimum sample size of 673 in total with roughly 112 per group would give us 80% power to detect between-group differences in anxiety. We therefore initially planned to approach 3415 participants anticipating a baseline response rate of 35%, with 75% of baseline responders returning a 6-month follow-up questionnaire and 75% of 6-month responders returning a 12-month follow questionnaire. However, as the study progressed, our response rate was lower than expected at approximately 22%. In line with our protocol (16), we increased the number of women approached to adjust for this (to n=5494). We estimated that approaching approximately 5500 women would yield a total sample size of 1210 at baseline, 908 at 6-months, and 681 at 12-months. Our baseline sample was 1148 at baseline.

Data Analysis

Ten-percent of data were checked independently for errors by a member of the research team who was not involved in the initial data entry (AF). Error rates were substantially below the pre-specified cut-off for no further action to be taken (<1% error for all outcomes). Demographic characteristics were compared between the six groups using one-way ANOVA and Chi-squared tests as appropriate.

We compared the demographic characteristics of responders and non-responders (including age, test results, number of previous screens, NHS site, and IMD quintile) which revealed small variations. See Table 3.4 for an overview of non-responder demographic characteristics. To adjust for the fact that our approached sample may not have been fully representative of the screening population in the pilot sites, we generated and applied population weights based on age group (24 – 34; 35 – 44; 45 – 54; 55 – 65) and IMD quintile within each test result group. With permission from the Office for Data Release, we used data from 955,387 women who attended HPV primary screening (and
primary cytology for the control group) within the NHSCSP in the five sites included in our study in 2017-8 to calculate the weights.

For each of the primary outcomes (anxiety and distress), we compared the mean scores between the six groups using univariate regression analysis. Further to this, multiple regression analysis was performed to adjust for confounding factors: age, IMD score, ethnicity, marital status, education, number of previous cervical screens, and NHS site. Results are presented as mean difference (MD) compared to the control group, along with 95% confidence intervals. We also present descriptive mean values and standard deviations for each of the six groups. For the secondary outcomes (very high anxiety, case-level distress, worry about cancer, concern and reassurance about results), we fitted both univariate and multiple logistic regression models adjusting for the same confounding factors. Results are presented as odds ratio, indicating the odds of the outcome for each of the groups relative to the control group, with 95% confidence intervals. Due to skewed responses to the concern and reassurance items in the control group, we used the HPV positive with normal cytology group as the reference category for analyses of these outcomes.

Data completeness was >96% for the majority of outcomes and factors, with the exception of anxiety (89%) and IMD (93%). We used multiple imputation assuming data were missing at random to account for missing data. The imputation model included primary outcomes and all socio-demographic factors, which we assumed included all predictors of missingness. The final models were derived by fitting a regression model including all confounders, and estimates were combined using Rubin’s rules (20).

Demographic characteristics have been presented using non-weighted data. All primary and secondary results have been adjusted using the weights described above and using the imputed data. Appendix 3.5 presents the results of the primary and secondary analyses using unweighted data. Analyses were carried out using Stata v15 (21) and SPSS v25 (22), and P value < 0.05 was considered statistically significant.
Table 3.4 - Demographic characteristics of non-responders vs. responders (no weights or adjustments applied)

<table>
<thead>
<tr>
<th></th>
<th>Non-responders</th>
<th>Responders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>4346</td>
<td>1148</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4344</td>
<td>1124</td>
<td>t(5466)=7.7, p=&lt;.001</td>
</tr>
<tr>
<td>Mean years (SD)</td>
<td>38.3 (10.9)</td>
<td>41.2 (11.8)</td>
<td></td>
</tr>
<tr>
<td><strong>IMD Quintile (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>1079 (25.6%)</td>
<td>170 (16.3%)</td>
<td>X²(4)=53.9, p=&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>926 (22.0%)</td>
<td>211 (20.2%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>935 (22.2%)</td>
<td>276 (26.5%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>692 (16.4%)</td>
<td>193 (18.5%)</td>
<td></td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>575 (13.7%)</td>
<td>193 (18.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of previous screens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>4248</td>
<td>1077</td>
<td>t(5323)=8.3, p=&lt;.001</td>
</tr>
<tr>
<td>Mean screens (SD)</td>
<td>5.0 (4.6)</td>
<td>6.3 (4.9)</td>
<td></td>
</tr>
<tr>
<td><strong>NHS site (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liverpool</td>
<td>669 (15.4%)</td>
<td>185 (16.1%)</td>
<td>X²(4)=70.3, p=&lt;.001</td>
</tr>
<tr>
<td>Sheffield</td>
<td>794 (18.3%)</td>
<td>216 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>London North West</td>
<td>789 (18.2%)</td>
<td>150 (13.1%)</td>
<td></td>
</tr>
<tr>
<td>Norfolk &amp; Norwich</td>
<td>425 (9.8%)</td>
<td>205 (17.9%)</td>
<td></td>
</tr>
<tr>
<td>Manchester</td>
<td>1169 (38.4%)</td>
<td>392 (34.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Test Result (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (no HPV test)</td>
<td>1121 (25.8%)</td>
<td>211 (18.4%)</td>
<td></td>
</tr>
<tr>
<td>HPV negative</td>
<td>980 (22.5%)</td>
<td>249 (21.7%)</td>
<td></td>
</tr>
<tr>
<td>HPV positive, normal cytology</td>
<td>935 (21.5%)</td>
<td>263 (22.9%)</td>
<td></td>
</tr>
<tr>
<td>HPV positive, abnormal cytology</td>
<td>639 (14.7%)</td>
<td>171 (14.9%)</td>
<td></td>
</tr>
<tr>
<td>HPV persistent</td>
<td>479 (11.0%)</td>
<td>184 (16.0%)</td>
<td></td>
</tr>
<tr>
<td>HPV cleared</td>
<td>192 (4.4%)</td>
<td>70 (6.1%)</td>
<td></td>
</tr>
</tbody>
</table>

The end column displays the results of Chi-squared analysis and t-tests comparing non-responders to responders.
Patient and Public Involvement (PPI)

At the beginning of the study, we piloted our survey on 10 women of screening age who reported previously having attended cervical screening, recruited via circulation of an institute-wide email at UCL. These women timed completion of the questionnaires and provided feedback on the content and format, which we integrated into the final questionnaire booklet. See the information sheet (Appendix 4.3). We also published a public facing blog on the UCL ‘Health Chatter’ website summarising key study findings: https://blogs.ucl.ac.uk/bsh/2019/07/03/a-new-test-for-cervical-screening-is-being-rolled-out-but-how-do-the-screening-test-results-make-women-feel/.

RESULTS

Five-thousand-four-hundred-ninety-four women were invited to take part and 1148 returned a questionnaire (response rate of 21%). Thirteen participants were excluded from the study due to returning a questionnaire over 90 days after date of identification and eight due to ineligible age (>65); 1127 participants were included in the analyses. See Figure 3.1 for an overview of recruitment.

Demographics

Table 3.5 shows unweighted demographic characteristics across the whole sample and by test result group. Overall, characteristics were similar across each of the test result groups, with some small differences relating to age, number of previous screens, marital status, IMD quintile, and NHS site. These potential confounding variables were adjusted for in the analyses.

Primary outcomes

Anxiety (S-STAI-6)

Regression analysis revealed statistically significant differences in anxiety between test result groups. Women who tested HPV positive with normal cytology or abnormal
cytology had higher mean anxiety scores than women in the control group (no HPV test) (MD=3.5, 95% CI: 0.6 to 6.4, \(p=0.02\), and MD=7.2, 95% CI: 3.7 to 10.6, \(p<0.001\), respectively). There were no differences in mean anxiety scores between the other groups and the control group.

**General Distress (GHQ-12)**

Regression analysis also revealed a higher mean general distress score for the HPV positive with abnormal cytology group compared with the control group (MD=0.9, 95% CI 0.02 to 1.8, \(p<0.04\)). There were no differences in general distress between the other groups and the control group.

Tables 3.6 and 3.7 provide an overview of the results for anxiety and distress.

---

**Figure 3.1 - Overview of recruitment and response.**

- **Approached** \((n=5494)\)
  - Returned Questionnaire \((n=1148)\)
  - **Total Included in Analysis** \((n=1127)\)

**Excluded** \((n=21)\)
- Ineligible age \((n=8)\)
- Returned questionnaire >90 days later \((n=13)\)

- Control \((n=206)\)
- HPV negative \((n=248)\)
- HPV positive with normal cytology \((n=258)\)
- HPV positive with abnormal cytology \((n=170)\)
- HPV persistent at 12-months \((n=179)\)
- HPV cleared at 12-months \((n=66)\)
Table 3.5 - Demographic characteristics of the whole sample (n=1127) and by results group (no weights or adjustments applied).

<table>
<thead>
<tr>
<th></th>
<th>Control (no HPV test)</th>
<th>HPV negative</th>
<th>HPV positive, normal</th>
<th>HPV positive, abnormal</th>
<th>HPV persistent at 12-months</th>
<th>HPV cleared at 12-months</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>206 (18.3%)</td>
<td>248 (22.0%)</td>
<td>258 (22.9%)</td>
<td>170 (15.1%)</td>
<td>179 (15.9%)</td>
<td>66 (5.9%)</td>
<td>1127 (100%)</td>
</tr>
<tr>
<td>Age (n=1125) Mean years (SD)</td>
<td>43.8 (11.0)</td>
<td>43.9 (11.4)</td>
<td>39.9 (12.2)</td>
<td>37.0 (10.6)</td>
<td>40.5 (12.0)</td>
<td>40.6 (11.7)</td>
<td>41.2 (11.8)</td>
</tr>
<tr>
<td>Marital status* n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current partner</td>
<td>164 (80.8%)</td>
<td>214 (87.3%)</td>
<td>184 (72.4%)</td>
<td>111 (66.9%)</td>
<td>131 (74.9%)</td>
<td>51 (78.5%)</td>
<td>855 (77.2%)</td>
</tr>
<tr>
<td>No partner</td>
<td>39 (19.2%)</td>
<td>31 (12.7%)</td>
<td>70 (27.6%)</td>
<td>55 (33.1%)</td>
<td>44 (25.1%)</td>
<td>14 (21.5%)</td>
<td>253 (22.8%)</td>
</tr>
<tr>
<td>Ethnicity n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (British or other)</td>
<td>180 (89.6%)</td>
<td>217 (88.6%)</td>
<td>235 (92.9%)</td>
<td>151 (91.0%)</td>
<td>167 (94.9%)</td>
<td>63 (96.9%)</td>
<td>1013 (91.6%)</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>20 (10.0%)</td>
<td>27 (11.0%)</td>
<td>17 (6.7%)</td>
<td>15 (9.0%)</td>
<td>9 (5.1%)</td>
<td>2 (3.1%)</td>
<td>90 (8.1%)</td>
</tr>
<tr>
<td>Prefer not to say</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>IMD Quintile n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>42 (22.1%)</td>
<td>23 (10.0%)</td>
<td>46 (19.0%)</td>
<td>24 (15.6%)</td>
<td>25 (15.1%)</td>
<td>10 (16.7%)</td>
<td>170 (16.3%)</td>
</tr>
<tr>
<td>2</td>
<td>38 (20.0%)</td>
<td>46 (19.9%)</td>
<td>55 (22.7%)</td>
<td>33 (21.4%)</td>
<td>28 (16.9%)</td>
<td>11 (18.3%)</td>
<td>211 (20.2%)</td>
</tr>
<tr>
<td>3</td>
<td>44 (23.2%)</td>
<td>69 (29.9%)</td>
<td>53 (21.9%)</td>
<td>40 (26.0%)</td>
<td>53 (31.9%)</td>
<td>17 (28.3%)</td>
<td>276 (26.5%)</td>
</tr>
<tr>
<td>4</td>
<td>27 (14.2%)</td>
<td>40 (17.3%)</td>
<td>54 (22.3%)</td>
<td>30 (19.5%)</td>
<td>31 (18.7%)</td>
<td>11 (18.3%)</td>
<td>193 (18.5%)</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>39 (20.5%)</td>
<td>53 (22.9%)</td>
<td>34 (14.0%)</td>
<td>27 (17.5%)</td>
<td>29 (17.5%)</td>
<td>11 (18.3%)</td>
<td>193 (18.5%)</td>
</tr>
<tr>
<td>Education n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree or higher</td>
<td>91 (45.0%)</td>
<td>100 (41.2%)</td>
<td>109 (43.6%)</td>
<td>72 (43.9%)</td>
<td>76 (43.7%)</td>
<td>30 (46.2%)</td>
<td>478 (43.5%)</td>
</tr>
<tr>
<td>Qualification below degree</td>
<td>92 (45.5%)</td>
<td>126 (51.9%)</td>
<td>124 (49.6%)</td>
<td>82 (50.0%)</td>
<td>83 (47.7%)</td>
<td>30 (46.2%)</td>
<td>537 (48.9%)</td>
</tr>
<tr>
<td>No formal qualifications †</td>
<td>19 (9.4%)</td>
<td>17 (7.0%)</td>
<td>17 (6.8%)</td>
<td>10 (6.1%)</td>
<td>15 (8.6%)</td>
<td>5 (7.7%)</td>
<td>83 (7.6%)</td>
</tr>
<tr>
<td>No. of previous screens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 1077) Mean screens (SD)</td>
<td>6.8 (4.7)</td>
<td>6.6 (4.4)</td>
<td>5.9 (5.1)</td>
<td>4.8 (4.7)</td>
<td>7.2 (5.5)</td>
<td>6.9 (5.0)</td>
<td>6.3 (4.9)</td>
</tr>
<tr>
<td></td>
<td>Control (no HPV test)</td>
<td>HPV negative</td>
<td>HPV positive, normal</td>
<td>HPV positive, abnormal</td>
<td>HPV persistent at 12-months</td>
<td>HPV cleared at 12-months</td>
<td>Overall</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
<td>--------------</td>
<td>----------------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>---------</td>
</tr>
<tr>
<td><strong>HPV vaccine status n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 doses</td>
<td>10 (5.0%)</td>
<td>10 (4.1%)</td>
<td>22 (8.9%)</td>
<td>18 (10.8%)</td>
<td>6 (3.5%)</td>
<td>1 (1.5%)</td>
<td>67 (6.1%)</td>
</tr>
<tr>
<td><strong>NHS site n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liverpool</td>
<td>18 (8.7%)</td>
<td>47 (19.0%)</td>
<td>51 (19.8%)</td>
<td>24 (14.1%)</td>
<td>41 (22.9%)</td>
<td>2 (3.0%)</td>
<td>183 (16.2%)</td>
</tr>
<tr>
<td>Sheffield</td>
<td>23 (11.2%)</td>
<td>46 (18.5%)</td>
<td>47 (18.2%)</td>
<td>29 (17.1%)</td>
<td>54 (30.2%)</td>
<td>13 (19.7%)</td>
<td>212 (18.8%)</td>
</tr>
<tr>
<td>London North West</td>
<td>23 (11.2%)</td>
<td>39 (15.7%)</td>
<td>27 (10.5%)</td>
<td>31 (18.2%)</td>
<td>18 (10.1%)</td>
<td>9 (13.6%)</td>
<td>147 (13.0%)</td>
</tr>
<tr>
<td>Norfolk &amp; Norwich</td>
<td>26 (12.6%)</td>
<td>30 (12.1%)</td>
<td>37 (14.3%)</td>
<td>34 (20.0%)</td>
<td>37 (20.7%)</td>
<td>36 (54.5%)</td>
<td>200 (17.7%)</td>
</tr>
<tr>
<td>Manchester</td>
<td>116 (56.3%)</td>
<td>86 (34.7%)</td>
<td>96 (37.2%)</td>
<td>52 (30.6%)</td>
<td>29 (16.2%)</td>
<td>6 (9.1%)</td>
<td>385 (34.2%)</td>
</tr>
</tbody>
</table>

Total N can be found in the end column for the categorical variables. *Marital status: current partner (married, civil partnership, living with partner, in a relationship) and no partner (single, divorced, widowed). †No formal qualifications included those with no qualifications and those who were still studyin.
Table 3.6 - Descriptive characteristics for primary and secondary outcomes by results group (no weights or adjustments applied).

<table>
<thead>
<tr>
<th></th>
<th>Control (no HPV test)</th>
<th>HPV negative</th>
<th>HPV positive, normal</th>
<th>HPV positive, abnormal</th>
<th>HPV persistent at 12-months</th>
<th>HPV cleared at 12-months</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>34.9 (12.5)</td>
<td>32.9 (12.2)</td>
<td>38.3 (14.3)</td>
<td>42.1 (14.9)</td>
<td>36.8 (13.1)</td>
<td>37.0 (12.1)</td>
<td>36.7 (13.6)</td>
</tr>
<tr>
<td>N (%)</td>
<td>185 (18.4%)</td>
<td>232 (23.1%)</td>
<td>224 (22.3%)</td>
<td>148 (14.7%)</td>
<td>157 (15.6%)</td>
<td>60 (6.0%)</td>
<td>1006 (100%)</td>
</tr>
<tr>
<td><strong>Distress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.3 (3.3)</td>
<td>1.9 (3.0)</td>
<td>2.7 (3.6)</td>
<td>3.3 (3.8)</td>
<td>2.5 (3.2)</td>
<td>2.5 (3.7)</td>
<td>2.5 (3.4)</td>
</tr>
<tr>
<td>N (%)</td>
<td>204 (18.3%)</td>
<td>244 (21.9%)</td>
<td>257 (23.1%)</td>
<td>167 (15.0%)</td>
<td>177 (15.9%)</td>
<td>65 (5.8%)</td>
<td>1114 (100%)</td>
</tr>
<tr>
<td><strong>Very high anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score &gt;49</td>
<td>25 (13.5%)</td>
<td>31 (13.4%)</td>
<td>50 (22.3%)</td>
<td>52 (35.1%)</td>
<td>28 (17.8%)</td>
<td>11 (18.3%)</td>
<td>197 (19.6%)</td>
</tr>
<tr>
<td>Score ≤49</td>
<td>160 (86.5%)</td>
<td>201 (86.6%)</td>
<td>174 (77.7%)</td>
<td>96 (64.9%)</td>
<td>129 (82.2%)</td>
<td>49 (81.7%)</td>
<td>809 (80.4%)</td>
</tr>
<tr>
<td><strong>Case-level distress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score &gt;3</td>
<td>49 (24.0%)</td>
<td>53 (21.6%)</td>
<td>71 (27.5%)</td>
<td>53 (31.5%)</td>
<td>50 (28.2%)</td>
<td>16 (24.2%)</td>
<td>292 (26.1%)</td>
</tr>
<tr>
<td>Score ≤3</td>
<td>155 (76.0%)</td>
<td>192 (78.4%)</td>
<td>187 (72.4%)</td>
<td>115 (69.0%)</td>
<td>127 (71.8%)</td>
<td>50 (75.8%)</td>
<td>826 (73.9%)</td>
</tr>
<tr>
<td><strong>Worry about cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher worry</td>
<td>30 (14.7%)</td>
<td>33 (13.4%)</td>
<td>114 (44.4%)</td>
<td>78 (46.2%)</td>
<td>78 (44.1%)</td>
<td>11 (16.7%)</td>
<td>344 (30.7%)</td>
</tr>
<tr>
<td>Lower worry</td>
<td>174 (85.3%)</td>
<td>213 (86.6%)</td>
<td>143 (55.6%)</td>
<td>91 (53.8%)</td>
<td>99 (55.9%)</td>
<td>55 (83.3%)</td>
<td>775 (69.3%)</td>
</tr>
<tr>
<td><strong>Concern</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher concern</td>
<td>7 (3.4%)</td>
<td>7 (2.9%)</td>
<td>84 (32.7%)</td>
<td>79 (46.5%)</td>
<td>56 (31.5%)</td>
<td>3 (4.5%)</td>
<td>236 (21.1%)</td>
</tr>
<tr>
<td>Lower concern</td>
<td>198 (96.6%)</td>
<td>238 (97.1%)</td>
<td>173 (67.3%)</td>
<td>91 (53.5%)</td>
<td>122 (68.5%)</td>
<td>63 (95.5%)</td>
<td>885 (78.9%)</td>
</tr>
<tr>
<td><strong>Reassurance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher reassurance</td>
<td>186 (90.7%)</td>
<td>220 (89.8%)</td>
<td>108 (42.0%)</td>
<td>76 (45.0%)</td>
<td>80 (45.2%)</td>
<td>54 (81.8%)</td>
<td>724 (64.7%)</td>
</tr>
<tr>
<td>Lower reassurance</td>
<td>19 (9.3%)</td>
<td>25 (10.2%)</td>
<td>149 (58.0%)</td>
<td>93 (55.0%)</td>
<td>97 (54.8%)</td>
<td>12 (18.2%)</td>
<td>395 (35.3%)</td>
</tr>
</tbody>
</table>

All binary variables are presented as numbers (%) by test result group. SD = standard deviation.
Table 3.7 - Results for primary and secondary outcomes by test result groups (weighted and adjusted).

<table>
<thead>
<tr>
<th></th>
<th>Control (no HPV test)</th>
<th>HPV negative</th>
<th>HPV positive, normal cytology</th>
<th>HPV positive, abnormal cytology</th>
<th>HPV persistent at 12-months</th>
<th>HPV cleared at 12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety MD (95% CI)</td>
<td>ref</td>
<td>-1.1 (-3.9, 1.8)</td>
<td>3.5 (0.6, 6.4)</td>
<td>7.2 (3.7, 10.6)</td>
<td>2.1 (-1.1, 5.3)</td>
<td>1.0 (-3.3, 5.3)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.45</td>
<td>0.02</td>
<td>&lt;.001</td>
<td>0.21</td>
<td>0.65</td>
</tr>
<tr>
<td>Distress MD (95% CI)</td>
<td>ref</td>
<td>-0.2 (-0.9, 0.4)</td>
<td>0.6 (-0.1, 1.3)</td>
<td>0.9 (0.02, 1.8)</td>
<td>0.1 (-0.7, 0.9)</td>
<td>0.2 (-1.1, 1.6)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.49</td>
<td>0.11</td>
<td>0.04</td>
<td>0.81</td>
<td>0.74</td>
</tr>
<tr>
<td>Very high anxiety</td>
<td>ref</td>
<td>1.3 (0.7, 2.4)</td>
<td>1.9 (1.1, 3.5)</td>
<td>3.5 (1.9, 6.6)</td>
<td>1.4 (0.7, 2.8)</td>
<td>1.2 (0.5, 2.9)</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td>0.43</td>
<td>0.03</td>
<td>&lt;.001</td>
<td>0.31</td>
<td>0.66</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-level distress</td>
<td>ref</td>
<td>1.0 (0.6, 1.7)</td>
<td>1.4 (0.9, 2.3)</td>
<td>1.4 (0.8, 2.4)</td>
<td>1.2 (0.7, 2.1)</td>
<td>1.0 (0.4, 2.3)</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td>0.92</td>
<td>0.17</td>
<td>0.25</td>
<td>0.48</td>
<td>0.99</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worry about cancer</td>
<td>ref</td>
<td>1.1 (0.6, 2.1)</td>
<td>4.8 (2.8, 7.9)</td>
<td>4.9 (2.7, 8.8)</td>
<td>5.0 (2.8, 8.9)</td>
<td>0.90 (0.4, 2.1)</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td>0.67</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High concern</td>
<td>ref</td>
<td>12.0 (6.6, 21.7)</td>
<td>10.9 (6.3, 18.7)</td>
<td>ref*</td>
<td>1.3 (0.8, 2.1)</td>
<td>1.3 (0.8, 2.0)</td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>1.8 (1.2, 2.9)</td>
<td>1.1 (0.7, 1.8)</td>
<td>0.10 (0.02, 0.5)</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
<td>0.60</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>High reassurance</td>
<td>ref</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MD = mean difference; 95% CI = 95% confidence intervals; p= <.05 interpreted as statistically significant. Adjusted for age, marital status, ethnicity, index of multiple deprivation (IMD), education, number of previous screens, and NHS site. Weighted by age group and IMD quintile. Ref = reference group. *The reference group for concern and reassurance is HPV positive with normal cytology due to very low and very high proportions (respectively) of positive responses in the control group for these two outcomes.
Secondary Outcomes

**Very High Anxiety and Case-level General Distress**

Logistic regression was performed to compare the odds of having very high anxiety scores (S-STAI-6 score >49/80) between the results groups. We found significantly increased odds of very high anxiety in the HPV positive with normal cytology group (OR 1.9, 95% CI: 1.1 to 3.5) and HPV positive with abnormal cytology group (OR: 3.5, 95% CI: 1.9 to 6.6), compared with the control group (no HPV test). None of the other groups differed significantly from the control group.

Logistic regression was also performed to determine the effects of test result group on case-level general distress (GHQ-12 score >3/12). None of the groups differed significantly from the control group.

**Worry about Developing Cervical Cancer**

We used logistic regression to ascertain the effects of receiving different test results on the likelihood that women scored highly for worry about developing cervical cancer in the next 10 years (worry score >3; moderately/very worried). After adjusting for potential confounding factors, all three HPV positive groups were found to be at significantly increased odds of high worry when compared with the control group (no HPV test), all with odds ratios over 4 (see Table 3.7).

**Concern and Reassurance Related to Results**

Logistic regression was also performed to ascertain the effects of receiving different test results on the likelihood that women scored highly for concern (score >3; moderately/very concerned) and highly for reassurance (score >2; somewhat/moderately/very reassured). After adjusting for potential confounding factors, the odds of high concern in the HPV positive with abnormal cytology group was 1.8 (95% CI: 1.2 to 2.9) when compared to the HPV positive with normal cytology group. The odds of high concern were significantly lower for the three normal results groups (control, HPV negative, HPV cleared) when compared to the HPV positive with normal cytology group. All three normal results groups had significantly higher odds of high reassurance compared to the HPV positive with normal cytology group. Reassurance was similarly high across these
three normal results groups. Tables 3.6 and 3.7 provide an overview of the results for all secondary outcome measures.

DISCUSSION

Main Findings

Informing women that they test positive for high-risk HPV accompanied by any cytology result appears to be associated with some adverse psychological effects at the population level, at least in the short-term. These findings are consistent with previous studies showing that testing positive for HPV with abnormal cytology is associated with raised anxiety and distress (8-11). However, unique to HPV primary screening and unique to the literature, we also found evidence of raised anxiety, concern about the screening result, and worry about developing cervical cancer in women who tested positive for HPV with normal cytology. These women were more anxious than the control group (normal cytology; no HPV test) and displayed a mean anxiety score slightly above the upper threshold expected in the general population (mean score of 38.3 compared to the normal range of 34-36) (23, 24). They were also 1.9 times more likely to exhibit very high anxiety compared to the control group (indicated by a STAI score >49/80), scoring similarly to individuals with clinically important symptoms or an anxiety disorder (25-27). Women who test positive for HPV with normal cytology carry a very low absolute risk of developing high-grade cervical abnormalities or cancer in the near future (28, 29). Therefore, for many women, informing them of this test result may lead to unnecessary adverse psychological responses. At the population level, it is unlikely that the levels of anxiety observed in our study would cause significant disruptions to women’s daily functioning. This is supported by our small between-group differences for general distress paired with wider evidence indicating that screening-related anxiety is usually temporary (12, 13, 30). However, it is important to remember that 72% of women aged 25-64 living in the UK attend for screening when invited (1), of whom 8.5% are likely to be HPV positive with normal cytology (7). Given the very large numbers of women affected, it is imperative that we do not lose sight of subgroups of individuals who may be more at risk of acute adverse reaction (e.g. very high anxiety). Clinically significant levels of
anxiety may be more common in women who do not understand their result (10, 12, 15); however, research is needed to establish the risk factors and trajectory of high anxiety following an HPV positive result to inform efforts to mitigate this adverse response.

Reassuringly, women with persistent HPV and normal cytology at 12 months did not have significantly higher anxiety than the control group, although descriptively they displayed slightly higher anxiety than would be expected in the general population (mean score of 36.8 compared to normal range of 34-36). This suggests that raised levels of anxiety and distress associated with an initial HPV positive result may normalise with repeated exposure to the result and/or over time, which is consistent with previous research (13, 30). Our findings suggest that efforts to reduce anxiety should therefore primarily focus on women who test HPV positive with normal cytology for the first time.

HPV primary screening has a high negative predictive value and therefore has the potential to reassure the majority of women who are at extremely low immediate risk of cervical cancer. Our findings indicate that testing HPV negative at any point (including 12 months after an HPV positive result) is associated with high levels of reassurance. However, although an HPV negative result offers better protection from cervical cancer than normal cytology (6, 31, 32), women in our study felt similarly reassured after receiving an HPV negative result compared to normal cytology. Low knowledge of HPV and the benefits associated with an HPV negative result may partially account for this (33). Normal or ‘good’ results may also demand little cognitive attention and therefore reduce the likelihood of differentiation (34, 35).

The main findings are broadly consistent with the NHSCSP HPV triage psychological evaluation (85) and other screening studies (83, 86) which also found that testing HPV positive with abnormal cytology was associated with higher anxiety and distress; however, there are small differences in anxiety scores associated with some test result groups. In our study, the control group (normal cytology with no HPV test) scored slightly lower for anxiety than observed in the NHSCSP HPV triage evaluation (mean difference of -2.3 on the S-STAI-6); and the group testing HPV positive with abnormal cytology scored slightly higher (mean difference of 3.3 on the S-STAI-6). Given that over a decade has passed between the two evaluations, it is possible that differences in public awareness and/or screening information materials could account for slightly lower anxiety in our
control group. Knowledge of HPV and its links with cervical cancer may also have risen, in part due to the introduction of the HPV vaccine in the UK in 2008, which may partially account for the higher anxiety in our HPV with abnormal cytology group.

**Strengths and Limitations**

To my knowledge, this is the first major study to evaluate the short-term psychological impact of primary HPV testing within a routine national programme. Participant recruitment linked to routine clinical management through the NHSCSP HPV primary screening pilot ensured accurate data collection and broad geographical coverage across England. A control group with primary cytology allowed additional between-group comparisons, strengthening our cross-sectional design. The sample size was smaller than we anticipated for the group who cleared HPV at 12-months (n=66); however this group had similar scores to the other normal and HPV negative groups. Our response rate was 21% (ranging from 16% in the control group to 27% in the HPV persistent group) which raises uncertainty regarding the extent to which our sample is representative of the wider screening population. We were however able to statistically weight our data to the wider screening population for age and IMD quintile as well as compare demographic characteristics between responders and non-responders. For consistency with the previous NHSCSP evaluation of HPV triage methods (10, 13), some of our secondary outcomes were single-item, non-validated measures (concern, worry, reassurance) which limits interpretations for these outcomes. There was also a 90 day window for women to return their survey and did not measure time (days) from result to survey completion, which may have introduced heterogeneity regarding sensitivity to result exposure (particularly relevant for state anxiety), as well as differences in help-seeking behaviour (e.g. some women may have visited a GP). Like many cross-sectional survey studies, we had an underrepresentation of participants from ethnic backgrounds other than White. Linked to this, the paper-based surveys were only available in English which likely excluded women from non-English speaking backgrounds. Self-selection bias may have also resulted in an overrepresentation of the most anxious women taking part in the survey and we did not measure potentially relevant clinical factors, such as current mental health diagnoses, to help adjust for this. Lastly, our data from non-responders suggests that
younger women and those from more deprived areas of England (lower IMD quintiles) were less likely to take part, which should be factored into interpretations.

**Implications**

Cervical screening programmes should aim to mitigate unnecessary anxiety, worry, and concern in women testing positive for HPV with any cytology result. Use of clear, evidence-based communication in test result letters and information materials will help ensure that women understand their results and the implications for cancer risk. Provision of communication skills training for sample takers related to areas which are anticipated to increase women’s anxiety (e.g. fear of cancer, sexual implications, transmission) should help minimise adverse psychological responses. Reasons for the switch to HPV primary screening should also be clearly communicated to the public ahead of implementation, to reduce the risk of a public backlash like the one recently observed in Australia (36), where a minority of individuals believed that switching to HPV primary screening would miss some cervical cancers. So far, there does not seem to have been any opposition to HPV primary screening in the English pilot sites, suggesting that current communication efforts are working effectively and/or that women are unaware there has been a change to screening methods. The findings of this study should help to inform national screening implementation policies and evaluations in other countries where HPV primary screening is being implemented. Future research should explore what makes women most anxious and determine the strongest modifiable predictors of anxiety (and very high anxiety) in women testing HPV positive, to inform the development of interventions and communication materials.

**Conclusion**

This study addressed aim 2 of my PhD, to compare anxiety and distress between test result groups at HPV primary screening. Testing positive for HPV with normal or abnormal cytology was associated with short-term adverse psychological effects in routine HPV primary screening, although it appears unlikely that this will lead to significant disruption of daily functioning for most women, supported by the small
between-group differences observed for general distress. Our cross-sectional comparison of women receiving their first vs. second HPV positive with normal cytology test result suggests that anxiety is likely to be short-lived and does not persist for women on 12-month early recall. However, nearly a quarter of women receiving their first HPV positive with normal cytology result experienced very high anxiety. This suggests that subgroups of women may experience clinically meaningful adverse impacts despite their very low absolute cervical cancer risk. Further research is needed to understand the sources of anxiety in women testing HPV positive with normal cytology at HPV primary screening.
CHAPTER 4 - STUDY 3

Illness Representation Profiles and their Associations with Anxiety in Women Testing Positive for Human Papillomavirus with Normal Cytology

Context and Role:

Study 3 presents findings from a second cross-sectional survey directly funded by my NIHR Doctoral Research Fellowship. I wrote the proposal, gained necessary NHS ethics / regulatory approvals and contracts, designed the methods and measures, managed the project, and recruited researchers to help with data collection. Following successful recruitment in Study 2, I continued to collaborate with two NHS sites in the North and South of England with whom I had formed positive working relationships.

Two researchers (Lauren Rockliffe and Hanna Skrobanski) helped to identify eligible participants and managed the mailing of surveys from the NHS sites. A research assistant (Selma Stearns) helped enter questionnaire data. I recruited, trained, and managed these part-time researchers as part of my fellowship training and development plan.

Further, I invited a collaborator from King’s College London (Dr Joseph Chilcot) to be involved in the analysis stage of this study. Originally, I had planned to perform structural equation or longitudinal modelling to examine the relationship between illness representations, anxiety, and prospective re-attendance at 12-month cervical screening. However, COVID-19 meant that cervical screening services were suspended through the time window where the majority of study participants were due to attend their 12-month screen, invalidating the re-attendance data. It was also no longer practicable for me to collect this data from NHS clinical records due to workplace restrictions. Therefore, we decided to proceed with latent profile analysis using the cross-sectional sample, to explore the relationship between illness representation profiles and anxiety. Joe Chilcot holds expertise in the application of latent profile analysis for illness representations and
physical health conditions. He conducted the latent profile analysis in this study (profile solution and model fit statistics) and I conducted all other analyses including the latent profiles for illness perceptions and anxiety, as well as interpreting the data. I also performed multiple imputation.
INTRODUCTION

Overview

Study 2 indicated that, despite the low cancer risk associated with testing positive for HPV with normal cytology (HPV+/normal), these women experienced higher short-term anxiety than those with normal results (normal cytology with no HPV test or HPV negative). For most, anxiety was in the normal range, but nearly a quarter experienced clinically significant anxiety for reasons that remain largely unclear. As previously highlighted in my literature review and systematic review (Chapters 1 and 2), there has been no psychological research in women testing HPV-positive with normal cytology at routine HPV primary screening. There has also been almost no theoretically driven work in the HPV psychological literature in the context of cervical screening.

To address these gaps, the overarching aim of Study 3 was therefore to identify psychological factors associated with high anxiety among women testing HPV+ with normal cytology, using Leventhal’s Common-Sense Model of Self-Regulation as a theoretical framework (122, 153). Anxiety was chosen as the main outcome variable because this was statistically significantly higher for women testing HPV+/normal than the control group in Study 2 (whereas there were no differences found for general distress).

Background

Around 270,000 women in England (8.5% of those attending screening) are expected to receive a HPV+/normal cytology result each year (51). Due to the absence of cytological abnormalities, an HPV+/normal result carries a very low absolute risk of cervical cancer; however, given that HPV has been detected, relative risk is higher and women are recalled early for repeat screening at 12-months. Most HPV infections clear naturally within 18-months (65%) (27), and women are only referred to colposcopy after they test HPV+/normal three consecutive times at 12-month intervals (51).
Psychological responses have been well documented in women testing HPV-positive with abnormal cytology (where cancer risk is greater) but have been less well explored in women testing HPV+/normal at routine screening (194). Misinterpreting an HPV+/normal result could cause unnecessary anxiety if women overestimate their risk of cervical cancer. The positive (HPV) and negative (cytology) terminology may also evoke confusion. In the absence of abnormal cytology, some women may focus more on the sexually transmitted aspects of HPV which could lead to concerns about sex/relationships. Importantly, the 12-month follow-up interval means no routine clinical contact in the interim, which could cause and/or intensify psychological consequences.

Leventhal’s Common-Sense Model of Illness Representations (CSM) aims to explain variations in adaptation to illness and health outcomes, based on a dual model of cognitive and affective processes (CSM) (122, 148, 149). Illness representations, which underpin the cognitive pathway, refer to beliefs and expectations about an illness or somatic symptom (see Chapter 1 or further details). To date, the majority of studies focussing on illness representations across conditions have treated each dimension as a separate variable and assessed the influence of individual perceptions on health outcomes. Five meta-analyses of studies measuring individual illness perceptions found that each of the dimensions were differentially related to psychological and behavioural outcomes (154, 159-162). Concerns have been raised about lack of reproducibility of findings for the CSM (255). Across health conditions including cancer, perceptions about illness consequences, concern, identity, and emotional response have been found to be most associated with anxiety; however, high heterogeneity has been identified in systematic reviews and meta-analyses (161, 162, 256).

Given that illness perceptions, as originally conceived by Leventhal et al. (1984) and Meyer et al. (1985), are thought to form overarching representations, treating them as separate perceptions oversimplifies the intended theoretical pathways within the CSM (122, 149, 150). Adoption of individual illness perceptions in previous studies may, in part, explain inconsistencies in findings and heterogeneity. In an attempt to address this, some recent studies have adopted analytic clustering approaches to identify subgroups within a sample with shared patterns of illness perceptions, e.g. (257-260). Unlike the traditional approach of examining individual illness perceptions, clustering approaches make it possible to identify distinct groups of illness perception profiles that are more typical of representations (261). These latent illness representations can be examined to
assess their relation to health outcomes and psychological adjustment. An advantage of adopting a clustering approach is that interventions can be tailored to specific high-risk groups within a population, targeting sets of beliefs known to contribute to adverse outcomes (262).

A recent systematic review explored studies adopting analytic clustering approaches for illness representations in chronic health conditions, and identified only 12 studies by February 2019 in areas such as hypertension, diabetes, and breast cancer (263). The illness representation clusters associated with favourable health-related outcomes across conditions included perceptions of lower consequences, fewer symptoms, lower negative emotion, and more stable disease patterns. It was concluded that the relationship between illness representation patterns and health outcomes appeared to transcend individual health conditions. However, this review identified no studies adopting this approach in HPV, cervical cancer, or cervical screening; therefore, it is unknown whether the same patterns would be observed in this population.

Despite a significant body of psychological research in HPV and cervical screening, to the best of my knowledge, there have been no studies examining individual illness perceptions or overarching illness representations associated with testing HPV-positive. The primary objective of this study was to investigate whether women testing HPV+/normal shared similar or diverse patterns of illness perceptions, to identify illness representation profiles. The secondary objective was to determine the extent to which each illness representation profile was associated with anxiety after controlling for relevant demographic and clinical characteristics.
METHOD

Participants and Design

Women aged 24-65 who had tested positive for HPV with normal cytology for the first time, or second or third consecutive time at 12-month follow-up screen, were recruited through two NHSCSP HPV primary screening sites in England (North West London and Central Manchester). They were sent a cross-sectional survey shortly after they had received their cervical screening result. Health Research Authority (HRA) approval was granted on 09/01/2019 (Research Ethics Committee reference: 18/EM/0227 and Confidentiality Advisory Group reference: 18/CAG/0118). Cervical Screening Research Advisory Committee approval was granted on 15/03/2019 (ODR1819_005). Recruitment commenced on 05/04/19 and ended on 21/04/20. See Appendix 4.1 for the HRA approval letter.

Sample Size

The study was powered to detect an association between health locus of control (controllability) and anxiety ($r=0.08$), which was chosen based on where we anticipated the weakest association in a regression model might lie based on a previous cervical screening study (264). With an $\alpha$ of 0.05, we estimated that a sample size of 295 would provide 80% power to detect a relationship between anxiety and perceived control. Assuming a response rate of 20% (based on the Study 2 response rate), at least 1,475 participants had to be approached to achieve the minimum sample. However, given there is no recommended or standardised sample size calculation for latent profile analysis or structural equation modelling, in practice the sample size target was treated as a minimum guide. Beyond the 295 target, additional recruitment was driven pragmatically by resource (budget and staff) and screening site capacity within the allocated timeframe.

Procedures

Potential participants were identified by NHS staff and researchers on honorary contracts at the two clinical sites. The recruitment procedures were largely designed to replicate
those in Study 2, given they had been successful and positive working relationships had
been established with the NHS laboratory staff. Women were mailed a study invite letter,
information sheet, survey, and pre-paid return envelope. A reminder pack containing the
same information was posted 3-weeks later. A mailing company (CFH Docmail Ltd)
completed printing and postage. Consent was implied by completion of a survey mailed
to UCL, as recommended by UCL Research and Development.

UCL received non-identifiable (pseudonymised) information from NHS laboratories on
all approached participants for age, index of multiple deprivation score, screening test
result, anticipated date of test result delivery, and date of last cervical screen. This data
could only be linked to individual participants if they returned their questionnaire pack
which contained a unique study ID.

Measures

The outcome (dependent) measure was state anxiety (S-STAI-6) (169)). Predictor
(independent) variables included eight illness perceptions (B-IPQ) (265). Covariates
included demographic and clinical variables. See Appendix 4.2 for the full questionnaire.

Anxiety (S-STAI-6)
The short-form state anxiety inventory (S-STAI-6) is a six-item, validated questionnaire
measuring anxiety (169)). Scores range from 20 to 80 and a higher score indicates higher
anxiety. The normal score in the general population ranges between 34 and 36. In Study
2, women testing HPV+/normal displayed a mean score of 39.9 (SD=12.2). Cronbach's
alpha was 0.89 (n = 560) indicating a high level of internal consistency.

Illness Perceptions (BIPQ)
The eight-item Brief Illness Perception Questionnaire (BIPQ) was used to measure
cognitive and emotional representations relating to HPV diagnosis (265). Each item
represented one illness perception and was assessed on a rating scale from 0 – 10. The
eight items included: consequences (how much does your HPV affect your life?), timeline
(how long do you think your HPV will last?), personal control (how much control do you
feel you have over your HPV?), treatment control (how much do you think cervical
screening can help your HPV?), identity (how much do you experience symptoms from your HPV?), coherence (how well do you feel you understand your HPV?), emotional representation (how much does your HPV affect you emotionally?) and illness concern (how concerned are you about your HPV?). Higher scores indicated more negative views towards HPV for most dimensions, with the exception of personal control and treatment control where higher score represented more adaptive views. The BIPQ has been shown to be a valid and reliable measure across a variety of health conditions (161).

**HPV-related Symptom Attributions (IPQ-R subscale)**

The Illness Perception Questionnaire-Revised (IPQ-R) symptom subscale (known as illness identity) was used to measure a more detailed list of HPV-related symptom attributions (266). The IPQ-R symptom subscale asks participants whether they have experienced a list of fifteen general symptoms within the last 4-weeks which they think are related to their HPV. Response options of ‘yes’ or ‘no’ are offered. To make the subscale more relevant to the symptomatic profile of HPV, we also used three additional symptoms: unusual bleeding, pain from sex, and vaginal discharge.

**Demographics**

Demographic characteristics based on self-report included highest level of education, ethnicity, marital status, age, area-level deprivation, and NHS site.

Highest level of education was grouped as degree level or higher (degree or higher degree) and qualification below degree (no formal qualification, O-Levels, CSE, ONC/BTEC, A-Level, higher education qualification). Ethnicity was grouped as White (British or other), other ethnic group (Black/African/Caribbean/Black British; Asian/Asian British; Mixed/Multiple ethnic groups; and other ethnic group), and prefer not to say. Marital status was grouped as current partner (married, cohabiting with a partner), no partner (single, divorced, separated and widowed), and other.

Age (years), index of multiple deprivation (IMD score and quintile; a multidimensional marker of area-level deprivation, based on residential postcode), and NHS site (North West London or Greater Manchester) were recorded from clinical records.
Clinical characteristics

Clinical characteristics based on self-report included a non-validated measure of clinical diagnosis of a current anxiety disorder (yes, no, prefer not to say) and current depression (yes, no, prefer not to say). NHS data from clinical records provided information on test result, including whether women had received their first HPV+/positive test result; or second or third consecutive HPV+/positive result at 12 month or 24 month follow-up screen, respectively. Test result was grouped as 1st vs. 2nd or 3rd HPV+/normal result.

Analysis

Data were entered by Selma Stearns and Hanna Skrobanski; and I checked ten percent of data for errors. Error rates were substantially below the pre-specified cut-off for no further action to be taken (<1% error for all outcomes). Statistical analyses were performed using IBM SPSS v25 and MPlus v7.3 and a p-value < 0.05 was considered statistically significant. Demographic and clinical characteristics were descriptively assessed using one-way ANOVAs and Chi-squared tests, as appropriate.

Latent profile analysis (LPA) is a method used to identify underlying subgroups in a population across a set of theoretically selected variables (267). In this study, LPA was used to assess the primary aim and evaluate whether underlying subgroups shared similar or diverse illness perceptions about HPV. LPA is a model-fitting method which uses probabilistic clustering and generates several model fit statistics, providing a process for comparing the number of profiles. To select the most parsimonious number of profiles and maximise the model fit, a series of latent profile models were fitted to the data. Firstly, a single-profile model (based on the assumption that all participants had the same pattern of illness perceptions) was fitted. This was followed by successive models which increased by the unit of latent profiles until the results were no longer interpretable. In order to determine the best-fitting model, the interpretability of the model, sample size of each latent profile, and model fit statistics including Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), adjusted BIC (ABIC), Bootstrapped likelihood ratio test (BLR test), Lo-Mendell-Rubin likelihood ratio test (LMR LR test), and adjusted LMR LR test (ALMR LR test) were considered. Classification uncertainty was assessed by model entropy based on the posterior probabilities of latent profile membership. For
the LMR LR test, ALMR LR test, and BLR test, a significant p-value indicated that the k profiles model fitted to the data better than the k – 1 profile model. Once the best-fitting model was determined, women in our sample were assigned their most likely latent profile membership which denoted their illness representation profile. Following latent profile membership assignment, MANOVA and post-hoc tests were performed to examine differences in individual illness perceptions between latent profiles.

Hierarchical multiple linear regression was used to assess the secondary aim to assess the extent to which anxiety was associated with illness representations when controlling for relevant demographic and clinical characteristics. Anxiety acted as the outcome (dependent) variable. Demographic and clinical characteristics were entered in Model 1 as covariates (age, IMD score, ethnicity, education, test result, NHS site, current anxiety diagnosis, current depression diagnosis). Illness representation profile was entered in model two as the predictor (independent) variable to determine the extent to which each group contributed to a significant percentage of the variance in anxiety, when controlling for demographic and clinical characteristics. These models included inverse-probability sample weight to account for measurement error from the determination of most likely latent class membership.

Data completeness was >95% for the majority of outcomes and factors, with the exception of anxiety (87%), IMD (94%), current depression (87%), current anxiety (87%), and the BIPQ items timeline (92%) and symptoms (93%). We used multiple imputation to account for missing data and the model included the main outcomes and all socio-demographic factors, which we assumed included all predictors of missingness. Demographic variables where participants had indicated ‘prefer not to say’ or ‘other’ were treated as missing in the multiple imputation model and analyses. The final models were derived by fitting a regression model including all confounders, and estimates were combined using Rubin’s rules (268). A sensitivity analysis was conducted comparing completer data with multiple imputed data, and no substantive differences were found. All results have been presented using imputed data.

The LPA solution with model fit statistics was conducted by an external researcher (JC) as this analysis required familiarity with MPlus. All other analyses, including multiple imputation, and the LPA interpretations were conducted by me.
Patient and Public Involvement (PPI)

Two women who had tested HPV+/normal were recruited as PPI representatives and were managed in accordance with NIHR INVOLVE guidelines (https://www.invo.org.uk/). Both of these women were originally participants in Study 2 and contacted us during the recruitment process using details provided in the information sheet, expressing an interest in the research topic. Given that they were actively engaged in the topic, these women were invited to be PPI representatives in Studies 3 and 4. As part of their PPI role, they reviewed the research protocol, NHS ethics application, all patient-facing materials (information sheet, survey questions, and cover letter), and provided feedback on acceptability and structure of the content and design, which was integrated into final documents. They also participated in stakeholder engagement meetings and 1-to-1 briefings as necessary. All contact with the PPI representatives was via telephone and email, given they lived in geographical areas outside London. See the final cover letter and information sheet (Appendices 4.3 and 4.4).

Further, a public facing Public Health England (PHE) blog was published online outlining research plans and encouraging members of the public to get in contact with feedback. The blog featured on the PHE website and was circulated via PHE and NHS mailing lists and social media (see: https://phescreening.blog.gov.uk/2019/02/05/cervical-screening-hpv-test-result-research/).
RESULTS

We invited 2,702 women to take part; the majority from NHS Greater Manchester (N=2,090; 77.4%) as this was the largest HPV primary screening site with large geographical coverage across North England. The remainder (N=612; 21.6%) were invited from NHS North West London which was a small screening site with rich ethnic diversity in its catchment area. Overall, 646 women returned a questionnaire (N= 513, Manchester; N= 133 London) and were included in the analysis, generating 23.9% response rate (24.5% Manchester; 21.7% London).

Demographics and Sample Characteristics

Table 4.1 shows demographic and clinical sample characteristics. On average, women were 38.3 years (SD=11.9) and completed the survey 21.5 days (SD=16.1) after receiving their test result. They were predominantly White (British or other) (81.4%), had a current partner (73.1%), and received their first HPV+/normal test result (78.2%). Educational attainment was roughly equally split between qualifications above and below degree level (52.2% lower-than-degree). Mean anxiety score was 47.2 (SD=16.4), and 18.4% and 16.3% reported a current anxiety disorder and current depression diagnosis, respectively. Illness perception scores ranged from the lowest value for personal control (M=1.3 out of 10, SD=2.1) to highest value for treatment control (M=8.1 out of 10, SD=2.6). Relatively small proportions of women reported attributing specific symptoms to their HPV (most symptoms reported by <5%); however, the three most common were discharge (18.9%), unusual bleeding (12.4%), and pain during sex (10.4%). Table 4.2 provides the full list of HPV-related symptom attributions.

Identifying Illness Representations

LPA estimated model fit statistics for 1 to 6 profiles, and allocated participants to each BIPQ profile. Three distinct groups of illness representations were identified. Whilst a four-profile solution had the best model fit as determined by the BIC and entropy values,
the VLMR LR and ALMR LR tests were non-significant, suggesting it did not improve above a three-profile model. Consequently, a three-profile model was selected since it was a significant improvement over a two-profile model (VLMR LR, ALMR LR, and BLRT all p < 0.001) had reasonable sample sizes within each latent profile which allowed the patterns to be interpreted. See Table 4.3 for an overview of the model fit statistics.
Table 4.1 - Demographic and clinical characteristics (N=646)

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (M, SD)</td>
<td>38.26 (11.86)</td>
</tr>
<tr>
<td>Ethnicity (N, %)</td>
<td></td>
</tr>
<tr>
<td>White (British or other)</td>
<td>526 (81.42)</td>
</tr>
<tr>
<td>Other ethnic group</td>
<td>96 (14.86)</td>
</tr>
<tr>
<td>Prefer not to say</td>
<td>24 (3.72)</td>
</tr>
<tr>
<td>Education (N, %)</td>
<td></td>
</tr>
<tr>
<td>Qualification below degree</td>
<td>337 (52.17)</td>
</tr>
<tr>
<td>Degree level or higher</td>
<td>309 (47.83)</td>
</tr>
<tr>
<td>Marital Status (N, %)</td>
<td></td>
</tr>
<tr>
<td>Current partner</td>
<td>472 (73.07)</td>
</tr>
<tr>
<td>No current partner</td>
<td>174 (26.93)</td>
</tr>
<tr>
<td>Other</td>
<td>-</td>
</tr>
<tr>
<td>IMD Quintile (N, %)</td>
<td></td>
</tr>
<tr>
<td>Quintile 1 (most deprived)</td>
<td>156 (25.70)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>176 (28.99)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>128 (21.09)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>88 (14.50)</td>
</tr>
<tr>
<td>Quintile 5 (least deprived)</td>
<td>59 (9.72)</td>
</tr>
<tr>
<td>NHS site (N, %)</td>
<td></td>
</tr>
<tr>
<td>North West London</td>
<td>133 (20.59)</td>
</tr>
<tr>
<td>Greater Manchester</td>
<td>513 (79.41)</td>
</tr>
<tr>
<td>Current depression diagnosis (N, %)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>105 (16.25)</td>
</tr>
<tr>
<td>No</td>
<td>541 (83.75)</td>
</tr>
<tr>
<td>Prefer not to say</td>
<td>-</td>
</tr>
<tr>
<td>Current anxiety diagnosis (N, %)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>119 (18.42)</td>
</tr>
<tr>
<td>No</td>
<td>527 (81.58)</td>
</tr>
<tr>
<td>Prefer not to say</td>
<td>-</td>
</tr>
<tr>
<td>Test Result (N, %)</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; HPV+/norm result</td>
<td>505 (78.17)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; or 3&lt;sup&gt;rd&lt;/sup&gt; HPV+/norm result</td>
<td>141 (21.83)</td>
</tr>
</tbody>
</table>
### Demographics

| Days to response (M, SD, N) | 21.47 (16.06), 645 |

### Outcome and Predictor Variables

<table>
<thead>
<tr>
<th>Illness Perceptions (M, SD)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequences</td>
<td>4.06 (2.94)</td>
</tr>
<tr>
<td>Timeline</td>
<td>5.96 (2.86)</td>
</tr>
<tr>
<td>Personal control</td>
<td>1.31 (2.13)</td>
</tr>
<tr>
<td>Treatment control</td>
<td>8.06 (2.55)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>1.45 (2.86)</td>
</tr>
<tr>
<td>Concern</td>
<td>7.05 (2.79)</td>
</tr>
<tr>
<td>Understanding</td>
<td>4.03 (3.01)</td>
</tr>
<tr>
<td>Emotion</td>
<td>5.40 (3.11)</td>
</tr>
</tbody>
</table>

*Note. M = mean, SD = standard deviation, N = number of participants, % = percentage. Education was dichotomised to represent below degree level (no formal qualification, O-Levels, CSE, ONC/BTEC, A-Level, higher education qualification) vs. degree level or higher (degree or higher degree). Ethnicity was dichotomised as White (British or Other) vs. other (Black/African/Caribbean/Black British; Asian/Asian British; Mixed/Multiple ethnic groups; and other ethnic group). Marital status was dichotomised as partner (married and cohabiting with a partner) vs. no partner (single, divorced, separated and widowed). Anxiety score could range from 20-80 and illness perceptions from 0-10.*
Table 4.2 - List of individual HPV-related symptom attributions.

<table>
<thead>
<tr>
<th>HPV-related symptom attributions</th>
<th>(N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>122 (18.89)</td>
</tr>
<tr>
<td>Unusual bleeding</td>
<td>80 (12.38)</td>
</tr>
<tr>
<td>Pain during sex</td>
<td>67 (10.37)</td>
</tr>
<tr>
<td>Pain</td>
<td>55 (8.51)</td>
</tr>
<tr>
<td>Sleeping difficulties</td>
<td>43 (6.66)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (5.88)</td>
</tr>
<tr>
<td>Loss of strength</td>
<td>21 (3.25)</td>
</tr>
<tr>
<td>Upset stomach</td>
<td>21 (3.30)</td>
</tr>
<tr>
<td>Stiff joints</td>
<td>18 (2.79)</td>
</tr>
<tr>
<td>Headaches</td>
<td>18 (2.79)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (2.48)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (2.32)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>14 (2.17)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>13 (2.01)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>10 (1.55)</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>9 (1.39)</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>8 (1.24)</td>
</tr>
<tr>
<td>Wheeziness</td>
<td>3 (0.46)</td>
</tr>
</tbody>
</table>

The statistics represent the number (N) and percentage (%) of the sample who endorsed that they experienced a symptom and then endorsed ‘yes’ they believed this symptom was related to their HPV.
Table 4.3 – Model fit statistics for latent profile analysis of illness perceptions

<table>
<thead>
<tr>
<th>Profile</th>
<th>AIC</th>
<th>BIC</th>
<th>ABIC</th>
<th>LLMR LR test p-value</th>
<th>ALMR LR test p-value</th>
<th>BLRT p-value</th>
<th>Entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24253.19</td>
<td>24324.72</td>
<td>24273.92</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>23355.52</td>
<td>23467.29</td>
<td>23387.92</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.834</td>
</tr>
<tr>
<td>3</td>
<td>22903.32</td>
<td>23055.33</td>
<td>22947.38</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.871</td>
</tr>
<tr>
<td>4</td>
<td>22684.11</td>
<td>22876.35</td>
<td>22739.83</td>
<td>0.158</td>
<td>0.161</td>
<td>&lt;0.001</td>
<td>0.839</td>
</tr>
<tr>
<td>5</td>
<td>22589.33</td>
<td>22821.81</td>
<td>22656.72</td>
<td>0.692</td>
<td>0.695</td>
<td>&lt;0.001</td>
<td>0.858</td>
</tr>
<tr>
<td>6</td>
<td>22439.51</td>
<td>22712.29</td>
<td>22518.57</td>
<td>0.396</td>
<td>0.402</td>
<td>&lt;0.001</td>
<td>0.865</td>
</tr>
</tbody>
</table>

AIC: Akaike; BIC: Bayesian
ABIC: Sample size adjusted BIC
VLMR LR: Vuong-Lo-Mendell-Rubin Likelihood Ratio Test K-1 Profiles
ALMR LR: Adjusted Lo-Mendell-Rubin Likelihood Ratio Test
BLRT: Parametric Bootstrapped Likelihood Ratio Test For K-1 Profiles

Table 4.4 presents the estimated mean BIPQ scores (and 95% confidence intervals) generated from the LPA 3-profile model. Profile-1 \((n=248, 38.4\%)\) was labelled ‘adaptive representations’ as it was characterised by: low consequences, moderate timeline, low personal control, high treatment control, almost no symptoms, moderate concern, moderate understanding, and low emotional response. Profile-2 \((n=293, 45.4\%)\) was labelled ‘maladaptive representations’, as participants displayed moderate consequences, high timeline, low personal control, high treatment control, almost no symptoms, high concern, low understanding, and high emotional response. Profile-3 \((n=105, 16.2\%)\) was labelled ‘maladaptive somatic representations’ as it consisted of moderate consequences, high timeline, low personal control, high treatment control, moderate-high symptoms, high concern, moderate understanding, and high emotional response.

Profile-1 (adaptive representations) was used as the reference group in the subsequent analyses as it was anticipated that this profile represented a baseline response most indicative of likely low-to-normal affective response.
Table 4.4 – Estimated means (95% confidence intervals) of illness perceptions for the 3-profile LPA solution (N=646).

<table>
<thead>
<tr>
<th>Illness Perception</th>
<th>Profile-1 (n=248) Adaptive Representations</th>
<th>Profile-2 (n=293) Maladaptive Representations</th>
<th>Profile-3 (n=105) Maladaptive Somatic Representations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequences</td>
<td>1.72 (1.47-1.96)</td>
<td>5.43 (4.89-5.98)</td>
<td>5.93 (5.34-6.52)</td>
</tr>
<tr>
<td>Personal control</td>
<td>1.57 (1.26-1.88)</td>
<td>1.08 (0.83-1.34)</td>
<td>1.18 (0.82-1.53)</td>
</tr>
<tr>
<td>Treatment control</td>
<td>8.17 (7.87-8.48)</td>
<td>8.09 (7.77-8.42)</td>
<td>7.75 (7.20-8.29)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.44 (0.28-0.59)</td>
<td>0.49 (0.36-0.61)</td>
<td>6.11 (5.79-6.43)</td>
</tr>
<tr>
<td>Concern</td>
<td>4.53 (4.00-5.07)</td>
<td>8.73 (8.47-9.00)</td>
<td>8.55 (8.14-8.96)</td>
</tr>
<tr>
<td>Understanding</td>
<td>4.34 (3.94-4.75)</td>
<td>3.64 (3.26-4.01)</td>
<td>4.28 (3.66-4.90)</td>
</tr>
<tr>
<td>Emotion</td>
<td>2.48 (2.06-2.89)</td>
<td>7.37 (6.93-7.80)</td>
<td>7.07 (6.57-7.57)</td>
</tr>
</tbody>
</table>

*Note.* $M$ = estimated mean, $CI$ = 95% confidence interval, $N$ = number of participants. All illness perceptions are scored out of 10.
One-way multivariate analysis of variance revealed significant differences in illness perceptions between the three profiles (observed means), $F(16, 1270)=157.78$, $p<.001$; Wilk’s $\Lambda=.11$. Follow-up univariate analysis of variance revealed that perceived consequences ($F(2, 642)=206.03$, $p<.001$), timeline ($F(2, 642)=69.40$, $p<.001$), personal control ($F(2, 57)=4.51$, $p<.05$), symptoms ($F(2, 642)=782.01$, $p<.001$), concern ($F(2, 642)=303.45$, $p<.001$), understanding ($F(2, 642)=7.98$, $p<.001$), and emotion ($F(2, 642)=312.02$, $p<.001$) differed significantly between the three latent profiles, using Bonferroni adjustment to account for multiple comparisons. Tukey post-hoc tests showed that when compared with Profile-1 (adaptive representations), Profile-2 (maladaptive representations) displayed higher consequences (MD=3.6, 95% CI=3.1-4.1, $p<.001$), higher timeline (MD=2.1, CI=1.6-2.7, $p<.001$), higher concern (MD=3.9, CI=3.5-4.3, $p<.001$), lower understanding (MD= -0.7, CI= -1.4 - -0.1, $p<.01$), and higher emotional response (MD=4.7, CI: 4.3-5.2, $p<.001$). When compared with Profile-1, Profile-3 (maladaptive somatic representations) showed higher consequences (MD=4.0, CI= 3.4-4.6, $p<.001$), higher timeline (MD=3.1, CI=2.4-3.8, $p<.001$), higher symptoms (MD=5.2, CI=4.8-5.5, $p<.001$), higher concern (MD=3.7, CI=3.2-4.3, $p<.001$), and higher emotion (MD=3.4, CI=2.8-4.0, $p<.001$). Profile-3 displayed higher symptoms (MD=4.9, CI=4.6-5.2, $p<.001$), higher timeline (MD=1.0, CI=0.3-1.7, $p<.01$), and lower emotion (MD= -1.4, CI= -0.8 - -1.9, $p<.001$) when compared with Profile-2. See Table 4.5.

Post-hoc chi-square analyses were performed to compare the proportions attributing specific symptoms to having HPV between the three latent profiles, and a p-value <.003 was considered significant to account for multiple tests (0.05/18 tests). Overall, the maladaptive somatic illness representation profile endorsed nearly all symptoms most frequently. The most commonly endorsed were discharge (49.5%), unusual bleeding (32.4%), pain during sex (28.6%), pain (24.8%), fatigue (13.3%), and sleeping difficulties (11.4%). See Table 4.6 for the full results.

Table 4.7 displays demographic and clinical characteristics between each of the three profiles. Only age, days to response to the survey, education, the proportion with a current anxiety disorder, and the proportion with a current depression differed significantly across the three profiles (all $p<.05$).
Table 4.5 – Illness perceptions by latent profile (N=646).

<table>
<thead>
<tr>
<th>Illness Perception</th>
<th>Profile-1 (n=248)</th>
<th>Profile-2 (n=293)</th>
<th>Profile-3 (n=105)</th>
<th>F</th>
<th>Post-hoc Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>1.71 (1.67)</td>
<td>5.30 (2.79)</td>
<td>5.67 (2.52)</td>
<td>206.03***</td>
<td>1&lt; 2, 3</td>
</tr>
<tr>
<td>Timeline</td>
<td>4.59 (2.69)</td>
<td>6.74 (2.84)</td>
<td>7.72 (3.00)</td>
<td>69.40***</td>
<td>1&lt; 2, 3; 2&lt;3</td>
</tr>
<tr>
<td>Personal control</td>
<td>1.57 (2.35)</td>
<td>1.13 (2.17)</td>
<td>0.94 (2.04)</td>
<td>4.51</td>
<td>-</td>
</tr>
<tr>
<td>Treatment control</td>
<td>8.21 (2.42)</td>
<td>7.99 (2.79)</td>
<td>8.35 (2.95)</td>
<td>1.06</td>
<td>-</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.43 (1.00)</td>
<td>0.71 (1.42)</td>
<td>5.62 (1.80)</td>
<td>782.01***</td>
<td>1, 2&lt; 3</td>
</tr>
<tr>
<td>Concern</td>
<td>4.64 (2.46)</td>
<td>8.56 (1.72)</td>
<td>8.38 (1.78)</td>
<td>303.45***</td>
<td>1&lt; 2, 3</td>
</tr>
<tr>
<td>Understanding</td>
<td>4.33 (2.98)</td>
<td>3.59 (3.19)</td>
<td>4.73 (3.27)</td>
<td>7.98***</td>
<td>1, 3 &gt; 2</td>
</tr>
<tr>
<td>Emotion</td>
<td>2.50 (1.94)</td>
<td>7.25 (2.18)</td>
<td>5.87 (3.34)</td>
<td>312.02***</td>
<td>1&lt; 2, 3; 3&lt;2</td>
</tr>
</tbody>
</table>

*Note. M = mean, SD = standard deviation, F = F-test. **p < 0.01; ***p<.001. All illness perceptions are scored out of 10.*
Table 4.6 – HPV-related symptom attributions by the latent profile (N=646).

<table>
<thead>
<tr>
<th>HPV-related symptom attribution</th>
<th>Profile-1 (n=248)</th>
<th>Profile-2 (n=293)</th>
<th>Profile-3 (n=105)</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adaptive</td>
<td>Maladaptive</td>
<td>Maladaptive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Representations</td>
<td>Representations</td>
<td>Somatic</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>21 (8.47)</td>
<td>49 (16.72)</td>
<td>52 (49.52)</td>
<td>82.81***</td>
</tr>
<tr>
<td>Unusual bleeding</td>
<td>12 (4.84)</td>
<td>34 (11.60)</td>
<td>34 (32.38)</td>
<td>51.87***</td>
</tr>
<tr>
<td>Pain during sex</td>
<td>12 (4.84)</td>
<td>25 (8.53)</td>
<td>30 (28.57)</td>
<td>46.65***</td>
</tr>
<tr>
<td>Sleep difficulties</td>
<td>2 (0.81)</td>
<td>29 (9.90)</td>
<td>12 (11.43)</td>
<td>22.46***</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (0.81)</td>
<td>22 (7.51)</td>
<td>14 (13.33)</td>
<td>23.47***</td>
</tr>
<tr>
<td>Loss of strength</td>
<td>0 (0)</td>
<td>13 (4.44)</td>
<td>8 (7.62)</td>
<td>16.01***</td>
</tr>
<tr>
<td>Upset stomach</td>
<td>3 (1.21)</td>
<td>10 (3.41)</td>
<td>8 (7.62)</td>
<td>9.68</td>
</tr>
<tr>
<td>Stiff joints</td>
<td>1 (0.40)</td>
<td>10 (3.41)</td>
<td>7 (6.67)</td>
<td>11.46**</td>
</tr>
<tr>
<td>Headaches</td>
<td>3 (1.21)</td>
<td>8 (2.73)</td>
<td>7 (6.67)</td>
<td>8.12</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>10 (3.41)</td>
<td>6 (5.71)</td>
<td>11.92**</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (0.40)</td>
<td>9 (3.07)</td>
<td>5 (4.76)</td>
<td>7.51</td>
</tr>
<tr>
<td>Weight gain</td>
<td>0 (0)</td>
<td>10 (3.41)</td>
<td>4 (3.81)</td>
<td>8.97</td>
</tr>
<tr>
<td>Sore throat</td>
<td>0 (0)</td>
<td>6 (2.05)</td>
<td>7 (6.67)</td>
<td>16.63***</td>
</tr>
<tr>
<td>Weight loss</td>
<td>0 (0)</td>
<td>6 (2.05)</td>
<td>4 (3.81)</td>
<td>7.90</td>
</tr>
<tr>
<td>Sore eyes</td>
<td>1 (0.40)</td>
<td>5 (1.71)</td>
<td>3 (2.86)</td>
<td>3.62</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>0 (0)</td>
<td>5 (1.71)</td>
<td>3 (2.86)</td>
<td>5.88</td>
</tr>
<tr>
<td>Wheeziness</td>
<td>0 (0)</td>
<td>3 (1.02)</td>
<td>0 (0)</td>
<td>3.63</td>
</tr>
</tbody>
</table>

Note. N = number of participants. % = percentage. X² = Pearson’s Chi-Square statistic.

**p < .003 to account for multiple tests; ***p < .001.
Table 4.7 – Descriptive and clinical characteristics by latent profile (N=646).

<table>
<thead>
<tr>
<th></th>
<th>Profile-1 (n=248) Adaptive Representations</th>
<th>Profile-2 (n=293) Maladaptive Representations</th>
<th>Profile-3 (n=105) Maladaptive Somatic Representations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>F</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.48 (13.06)</td>
<td>38.25 (12.16)</td>
<td>41.31 (13.74)</td>
</tr>
<tr>
<td>IMD Score</td>
<td>26.14 (15.06)</td>
<td>25.20 (17.94)</td>
<td>23.90 (19.03)</td>
</tr>
<tr>
<td>Days to Respond (N=644)</td>
<td>22.17 (17.08)</td>
<td>19.44 (14.88)</td>
<td>25.07 (18.97)</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
<td>6.05**</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree or higher</td>
<td>132 (53.23)</td>
<td>141 (48.12)</td>
<td>36 (34.29)</td>
</tr>
<tr>
<td>Below degree</td>
<td>116 (46.77)</td>
<td>152 (51.88)</td>
<td>69 (65.71)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>206 (86.19)</td>
<td>237 (84.34)</td>
<td>83 (81.37)</td>
</tr>
<tr>
<td>Other ethnic group</td>
<td>33 (13.81)</td>
<td>44 (15.76)</td>
<td>19 (18.63)</td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Partner</td>
<td>62 (25.00)</td>
<td>79 (26.96)</td>
<td>34 (32.38)</td>
</tr>
<tr>
<td>Partner</td>
<td>186 (75.00)</td>
<td>214 (73.04)</td>
<td>71 (68.62)</td>
</tr>
<tr>
<td>NHS Site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester</td>
<td>197 (79.44)</td>
<td>237 (80.89)</td>
<td>79 (75.24)</td>
</tr>
<tr>
<td>London</td>
<td>51 (20.56)</td>
<td>56 (19.11)</td>
<td>26 (24.76)</td>
</tr>
<tr>
<td>Test Result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st result</td>
<td>185 (74.60)</td>
<td>237 (80.89)</td>
<td>83 (79.05)</td>
</tr>
<tr>
<td>2nd or 3rd result</td>
<td>63 (25.40)</td>
<td>56 (19.11)</td>
<td>22 (20.95)</td>
</tr>
<tr>
<td></td>
<td>Profile-1 (n=248) Adaptive Representations</td>
<td>Profile-2 (n=293) Maladaptive Representations</td>
<td>Profile-3 (n=105) Maladaptive Somatic Representations</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Current Anxiety Disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (14.11)</td>
<td>53 (18.09)</td>
<td>32 (30.48)</td>
</tr>
<tr>
<td>No</td>
<td>213 (85.89)</td>
<td>240 (81.91)</td>
<td>73 (69.52)</td>
</tr>
<tr>
<td><strong>Current Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (10.08)</td>
<td>50 (17.06)</td>
<td>30 (28.57)</td>
</tr>
<tr>
<td>No</td>
<td>223 (89.92)</td>
<td>243 (83.94)</td>
<td>75 (71.43)</td>
</tr>
</tbody>
</table>

M= mean; SD= standard deviation; $F$= F-value; $X^2$= chi-squared value.

*p < 0.05; **p < 0.01; ***p < 0.001.
Associations Between Anxiety and Illness Representations

Univariate analyses revealed that women who had lower education, a current diagnosis of anxiety, a current diagnosis of depression, and had received their first HPV+/norm test result displayed significantly higher anxiety scores (all \(p<.05\)). There were also significant differences in anxiety between the three latent profiles, \(F(2, 642)=100.87, p<.001\). Post-hoc tests using Bonferroni adjustment showed that when compared with Profile-1 (adaptive representations), Profile-2 (maladaptive representations) and Profile-3 (maladaptive somatic representations) had significantly higher anxiety scores (MD=17.3, CI=14.3-20.2, \(p<.001\); and MD=13.2, CI=9.4-17.0, \(p<.001\), respectively). Profile-2 had significantly higher anxiety than Profile-3 (MD=4.1, CI=0.5-7.7, \(p<.05\)).

Table 4.8 displays descriptive statistics for anxiety.

Table 4.9 displays the standardised regression coefficients (\(\beta\)), R, adjusted R\(^2\) and change in R\(^2\) after entering all variables into the multiple hierarchal linear regression model. Model 1 included demographic and clinical variables and statistically significantly explained 3.7% of the variance (adjusted R\(^2\)) in anxiety scores, \(F(9, 620)=3.63, p<.001\). Model 2 additionally included the three illness representation profiles and explained an additional 21.8% of the variance in anxiety, with the overall model explaining 25.6%, \(F(11,620)=20.4 \ p<.001\). IMD score and test result were significantly associated with anxiety (\(B=-.09\), \(t=-2.5\), \(p<.05\) and \(B=-.11\), \(t=-2.8\), \(p<.01\), respectively). Maladaptive representations (Profile-2) and maladaptive somatic representations (Profile-3) were also significantly associated with higher anxiety, when compared with adaptive representations (Profile-1) (\(B=.51\), \(t=12.4\), \(p<.001\) and \(B=.34\), \(t=8.3\), \(p<.001\), respectively). In summary, the final model found that lower socioeconomic status, receiving a first HPV+/normal test result, and having maladaptive or maladaptive somatic representations were significantly associated with higher anxiety.
Table 4.8 – Univariate analysis of demographics and outcomes variables for anxiety (N=646).

<table>
<thead>
<tr>
<th></th>
<th>Anxiety (S-STAI-6)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years (n=646)</td>
<td>-.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMD Score (n=646)</td>
<td>.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to Respond (n=645)</td>
<td>-.38</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>M (SE)</th>
<th></th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree or higher (n=309)</td>
<td>45.69 (1.01)</td>
<td></td>
<td>5.11*</td>
</tr>
<tr>
<td>Below degree (n=337)</td>
<td>48.54 (0.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (n=526)</td>
<td>47.02 (0.73)</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Other ethnic group (n=96)</td>
<td>47.11 (0.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Marital Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner (n=472)</td>
<td>46.20 (0.77)</td>
<td></td>
<td>1.11</td>
</tr>
<tr>
<td>No partner (n=174)</td>
<td>48.29 (1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NHS Site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manchester (n=513)</td>
<td>47.18 (0.72)</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>London (n=133)</td>
<td>47.16 (1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test Result</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; HPV+/normal result (n=505)</td>
<td>47.89 (0.74)</td>
<td></td>
<td>4.48*</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; or 3&lt;sup&gt;rd&lt;/sup&gt; HPV+/normal result (n=141)</td>
<td>44.62 (1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current Anxiety Disorder</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=119)</td>
<td>51.91 (1.71)</td>
<td></td>
<td>14.87***</td>
</tr>
<tr>
<td>No (n=526)</td>
<td>45.59 (0.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Current Depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=105)</td>
<td>51.85 (1.75)</td>
<td></td>
<td>12.59**</td>
</tr>
<tr>
<td>No (n=541)</td>
<td>45.79 (0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Illness Representations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Anxiety (S-STAI-6)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adaptive (n=248)</td>
<td>36.48</td>
<td>(0.94)</td>
</tr>
<tr>
<td>Maladaptive (n=293)</td>
<td>53.74</td>
<td>(0.87)</td>
</tr>
<tr>
<td>Maladaptive Somatic (n=105)</td>
<td>49.68</td>
<td>(1.30)</td>
</tr>
</tbody>
</table>

r= Pearson’s correlation; M= mean; SE= standard error; F= F-value.
*p < 0.05; **p < 0.01; ***p < 0.001.

Table 4.9 - Multiple hierarchical linear regression for anxiety (n=646)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standardised coefficients</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Demographics and Clinical Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-.04</td>
<td>-.04</td>
<td></td>
</tr>
<tr>
<td>IMD Score</td>
<td>.07</td>
<td>.09*</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>.03</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>.07</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>-.03</td>
<td>-.02</td>
<td></td>
</tr>
<tr>
<td>Test result</td>
<td>-.12**</td>
<td>-.11**</td>
<td></td>
</tr>
<tr>
<td>NHS site</td>
<td>-.03</td>
<td>-.01</td>
<td></td>
</tr>
<tr>
<td>Current anxiety disorder</td>
<td>.08</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Current depression</td>
<td>.06</td>
<td>-.01</td>
<td></td>
</tr>
<tr>
<td>2. Illness Representations</td>
<td></td>
<td>.518</td>
<td>.256</td>
</tr>
<tr>
<td>Adaptive</td>
<td>ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maladaptive</td>
<td>.51***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maladaptive somatic</td>
<td>.34***</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. *:0.05, **0.01, ***0.001. R = correlation coefficient. Demographic and characteristic variables coded as follows: ethnicity (1=white; 2=other ethnicity), education (1=Degree or Higher; 2=Below Degree-Level), marital status (1=no partner, 2=partner), test result (1=1st result, 2=2nd or 3rd result), NHS site (1=Greater Manchester, 2=North West London).
DISCUSSION

Main Findings

To the best of my knowledge, this is the first study to identify illness representation profiles following an HPV+/normal result, and to explore their associations with anxiety. The study demonstrated, first, that different groups of women testing HPV+/normal have different illness representations profiles, coherent with the theoretical construct originally proposed by Leventhal and colleagues (149, 150). In our sample, three distinct profiles of illness representations were identified (termed ‘adaptive’, ‘maladaptive’, and ‘maladaptive somatic’) which differed significantly in their patterns of illness perceptions. Secondly, we found that these illness representation profiles accounted for 21.8% of the variance in anxiety, after adjusting for relevant demographic and clinical characteristics. When compared with adaptive representations (Profile-1), women with maladaptive representations (Profile-2) and maladaptive somatic representations (Profile-3) displayed statistically significantly higher anxiety, with potentially clinically meaningful differences (mean differences of >13 on S-STAI-6 and scores >49 for Profiles 2 and 3). Our identified latent profile structure of illness representations may, therefore, provide important insights for targeting maladaptive beliefs in interventions or patient communications, potentially helping to reduce anxiety within subgroups of highly anxious women following an HPV+/normal result.

Interpretation of Illness Representation Profiles and Anxiety

Women with adaptive representations (Profile-1) accounted for around 38% of our sample, and displayed the lowest anxiety score which sat in the normal population range (mean S-STAI-6 of 36.5; normal range 36-38). In fact, their anxiety score was almost identical to that observed following a normal screening result in Study 2 (normal cytology or HPV-negative) (240). Notably, this group was characterised by low perceived consequences of HPV, suggesting that fear of cervical cancer and/or sexual distress were unlikely to be concerns. Despite suboptimal understanding of HPV (mean understanding score of 4.3/10), their wider representation profile appeared to reflect a relatively accurate
account of their result. They perceived a moderate HPV timeline when HPV usually clears within 1-2 years; almost no symptoms when HPV is asymptomatic; and low-moderate concern when their relative risk of cervical cancer is higher-than-average but their absolute risk is very low. The overall patterns of illness perceptions observed in Profile-1 may, therefore, act as a baseline reference characterising healthy affective response to testing HPV+/normal.

Since this study was cross-sectional, we were unable to determine whether the ‘adaptive’ representations in Profile-1 could also be associated with maladaptive behavioural impacts in the long-term. If some women were in fact apathetic or avoidant, they may be less likely to re-attend their 12 month cervical screen, which would reduce the mortality-reduction benefit of HPV primary screening. For example, emotional detachment has been associated with favourable cognitive-affective outcomes by initially reducing distress in patients with chronic illness and disability (269, 270); but could also potentially lead to maladaptive behaviours through disengagement (271-273). An argument supportive of potential apathy or avoidance in Profile-1 is that their relatively acute anxiety score (average of 22 days after result) is almost identical to women receiving a normal cytology or HPV negative screening result up to 3 months later in previous studies, including Study 2 (194, 240). Future research should explore the interplays between longer-term adjustment and behavioural impacts for women with low affective response following an HPV+/normal result.

Women with maladaptive representations (Profile-2) accounted for the majority of the sample (around 45%) and, in contrast with Profile-1, were characterised by higher perceived consequences, concern, and emotional response; as well as lower understanding. Consistent with the wider HPV literature, these women appeared focused on the timeline of HPV and its potential consequences, and reported high emotional impact and concern related to HPV (85, 87, 89, 104). Unsurprisingly, when compared with the adaptive representation group (Profile-1), they had markedly higher anxiety (mean difference of 17.3), as well as displayed descriptively clinically significant anxiety (mean of 53.7; >49). Even after adjustment for demographic and clinical characteristics, including a current anxiety disorder, this profile explained the most variance in anxiety of all outcomes entered (standardised coefficient of 0.5). In keeping, some systematic reviews of illness representations across other conditions have found that perceived
consequences and emotion are among the most important drivers of health-related outcomes (154, 263). Our findings therefore appear to support the central role of illness representations in highly anxious women following HPV diagnosis; as well as the CSM as a useful cognitive-affective framework more broadly.

Lastly, women with maladaptive somatic representations (Profile-3) accounted for the minority of the sample (16%). Interestingly, this profile presented with descriptively very similar individual illness perceptions as maladaptive representations (Profile-2), but with the exception of notably higher perceived HPV-related symptoms (mean difference of 4.9 on the BIPQ). HPV is an asymptomatic infection; the only evidenced reason for related symptoms is early stage cervical cancer (e.g. abnormal bleeding or discharge). Given that women in this study had tested normal for cytology, cancer is extremely unlikely unless they had received a false-negative cytology result, which is rare. Therefore, symptom perceptions associated with HPV in this group are almost certainly due to misattributions or psychosomatic. On descriptive examination of individual symptoms reported for maladaptive somatic representations (Profile-3), the three most commonly endorsed symptoms were discharge (50%), unusual bleeding (32%), and pain during sex (29%), which are the three items we added to the BIPQ measure to match a similar symptomatic profile of cervical cancer. Discharge and unusual bleeding were also symptoms listed as symptoms of cervical cancer in the information leaflets sent alongside screening invitation letters (see Appendix 1.2). This suggests that, for most, misattribution of conceivable HPV-related symptoms was more likely than common everyday generic symptoms (e.g. fatigue).

In terms of anxiety levels, women with maladaptive somatic representations displayed clinically significant anxiety (mean of 49.7); and had higher anxiety than those with adaptive representations (Profile-1), but lower than those with maladaptive representations (Profile-2). Lower anxiety observed for maladaptive somatic vs. maladaptive representations (mean difference of -4.1) appears to contradict some of the wider psychological literature. Several studies have demonstrated that negative affect plays a central role in health complaints and somatic symptom reporting (e.g., (274, 275)), and especially misattribution of common symptoms to specific causes (e.g., vaccination, (276)). Our findings could simply depict that, in the context of an HPV+/normal result, some highly anxious women attribute symptoms to HPV whilst others do not.
Alternatively, discrepancies relative to the wider literature could be due to a number of explanations. For example it could be that women who perceived high symptoms initially had higher anxiety than those with maladaptive representations (Profile-2), which led them to book a GP appointment or seek social support, resolving some of their anxiety before they took part in our survey. Alternatively, nuanced meanings behind certain illness perceptions may have varied to differentially influence anxiety (e.g. perceived consequences could be related to cervical cancer vs. sex/relationships). If these underlying meanings were disproportionately distributed between Profile-2 and Profile-3, these profiles would not be directly comparable despite presenting similar illness perception profiles. Further, it is possible that women in Profile-3 were highly anxious for reasons other than their HPV result, which is supported by them showing the highest rates of current anxiety disorders and current depression (around 30%). Mood disorders characteristic of negative affect are well-established markers of symptom reporting and misattribution (277). Lastly, it could be that Profile-3 presents potentially unreliable findings for anxiety score due to its relatively small sample size (n=105).

Across all three illness representation profiles, perceived understanding, personal control, and treatment control were very similar, suggesting that these beliefs are unlikely to contribute to anxiety for women testing HPV+/normal. The importance of understanding (coherence), personal control, and treatment control in influencing emotional and behavioural outcomes have been mixed across systematic reviews (154, 160, 263). Interestingly, the HPV qualitative literature has suggested that women reporting lower perceived understanding of HPV and lower control have expressed higher distress (194). Coherent with Leventhal’s portrayal of illness representations as interacting and dynamic mental models (122), our findings may highlight that beliefs about understanding and control co-exist or interact with other perceptions to produce combined differential effects (e.g. affective impact of low control alone vs. low control paired with high consequences). It is also possible that similar illness perceptions are expressed through alternative affective pathways (e.g. low understanding leading to shame as opposed to anxiety) or through behavioural pathways (e.g. avoiding sex), which we did not measure but could cause specific forms of distress (194).

Demographic and clinical characteristics only accounted for 5.1% of the variance in anxiety, even when adjusting for a current anxiety disorder and depression, which are
inherently highly correlated with anxiety. Further, neither a current anxiety disorder nor depression significantly contributed to the explained variance in anxiety. In England, around 19% of women have a common mental health disorder (largely comprising anxiety and depression), which is roughly similar to the reports of current anxiety disorders and depression observed in this study (16% and 18%, respectively) (278). Hence, this may provide preliminary support for a causal mechanism whereby receiving an HPV+/normal result directly leads to high anxiety (as opposed to already highly anxious women experiencing adverse reactions), given that the sample does not appear to over-represent women with an anxiety disorder or depression. Alternatively, these findings could reflect issues with using non-validated self-report measures of current anxiety and depression, and/or not detecting undiagnosed cases which are estimated to be common in the UK (279).

**Limitations**

Our cross-sectional design may be particularly problematic when interpreting illness representations, which are dynamic mental models which evolve over time, e.g. (280, 281). Illness representations can change over the trajectory of a condition (282, 283). Whilst we likely captured relatively acute response for the majority of women as supported by our 21-day average from HPV result to survey completion, some responded up to 111 days later. This introduces the possibility that some illness representations may have evolved to a more chronic or different state. Further, almost a fifth of our sample had tested HPV+/positive for the 2nd and 3rd consecutive time, which although were controlled for in analyses, may have integrated chronic or cyclical representations. Some women may also have visited a GP or attended colposcopy (colposcopy is recommended after a 3rd consecutive result) before completing our survey, which could have modified their illness representations following acquisition of new information (153). Overall, high sample heterogeneity could have been an issue when measuring illness representation in this study. Future research should adopt longitudinal designs with distinct specified time points following an HPV+/normal result.

We also had a low postal response rate (24%), therefore, the sample may not represent the wider HPV+/normal population; especially given that nearly half were educated to
degree-level or above. Although the majority of the sample were White British (82%), it was more representative of other ethnicities than the national average in England and Wales (86% White British) (284). Mean anxiety score was also substantially higher than Study 2 which adopted similar recruitment methods in the same population (M=47.2 vs. M=38.3, respectively) (240). This likely reflects higher sensitivity to result exposure in this study (Study 2 took longer to mail women), but could represent an opt-in bias of the most anxious women taking part in this psychological survey (which asked more obvious psychological questions than Study 2). In addition, it is worth noting that some women may have struggled to complete the IPQ-R symptom subscale (266). There were several cases where data were missing for the first IPQ-R question asking about women’s perception of general symptoms experienced in the past 4 weeks; but endorsements had been completed for the follow-up question asking about HPV-related symptom perceptions. For this reason, the data presented in this study included the percentage of HPV-related endorsements in the whole sample, rather than calculating the percentage of HPV-related endorsements in those who reported general symptoms.

Lastly, adopting a clustering analytic approach for identifying illness representations could be considered a crude operationalisation of Leventhal’s dynamic and time-specific mental model (122). It could also have reduced our statistical power for detecting relationships due to grouping women into subsamples. Nevertheless, we believe that this analytical method is still superior to the traditional approach of assessing illness perceptions individually, and allowed us to identify latent cognitive profiles specific to women experiencing varying levels of anxiety after their HPV+/normal result.

Conclusion

This study identified three distinct illness representation profiles of women shortly following an HPV+/normal result at cervical cancer screening, which explained 21.8% of the variance in anxiety after controlling demographic and clinical characteristics. These illness representation profiles corresponded to women displaying normal and clinically significant levels of anxiety, with between-group differences suggesting that perceived consequences, timeline, concern, emotion, and symptoms related to HPV may be the most important drivers of anxiety. Future research should adopt longitudinal designs to understand the trajectory of illness representations from HPV diagnosis through to
clearance vs. persistence, which would also allow for inferences of casualty to be drawn. Other known affective and behavioural outcomes related to HPV should be incorporated into analyses. While it is a novel strength that the questionnaire used in this study assessed psychological aspects expected to influence anxiety on the basis of CSM, there may be other important constructs which have not yet been identified. Exploratory research is needed to unpick the meaning behind illness representations profiles identified in this study; and understand the wider, more holistic, picture of psychological response to testing HPV+/normal.
Exploring Reasons for Variations in Anxiety after Testing Positive for Human Papillomavirus with Normal Cytology: A Comparative Qualitative Study

Context and Role:

Study 4 presents the qualitative findings from my NIHR Doctoral Research Fellowship. Recruitment was informed by Study 3, using survey answers to purposively sample women for interviews. I developed the methodology and interview topic guide, performed all the in-person interviews, and analysed and interpreted the data. I recruited a research assistant (Selma Stearns) to help identify participants and assist with arranging the time and location of interviews. Another researcher (Kirsty Bennett) read the transcripts and second-coded 10% of the data.

The findings of Study 4 were published in Psycho-Oncology in September 2020 (see Appendix 5.1 for full paper):

INTRODUCTION

Overview

Study 2 found that women testing HPV-positive with normal cytology (HPV+/normal) displayed heightened anxiety shortly after receiving their result. Then, Study 3 adopted a theoretical approach to better understand and explain possible reasons for the observed anxiety associated with this low risk result. Study 3 concluded that illness representations may play a key role in anxiety for women testing HPV+/normal, even after adjusting for relevant demographic and clinical characteristics. It was noted, however, that nuanced meanings behind illness representation profiles were not accounted for which could differentially influence anxiety (e.g. perceived consequences related to cervical cancer vs. sex/relationships). Further, in line with the findings from Study 1, as well as the CSM and CBT, it was anticipated that there may be behavioural, emotional, and/or physiological factors associated with an HPV+/normal result which had not yet been captured or measured.

Building on Studies 1-3, the aim of Study 4 was therefore to explore reasons for variations in anxiety in women testing HPV+/normal at routine HPV primary screening. An overarching explanatory sequential mixed methods design was adopted where qualitative research methods were used to help explain and augment the findings from the prior quantitative studies (Studies 2 and 3) (182, 285). Using a mixed sampling method (182), pre-planned in-depth interviews were conducted with women who were purposively sampled from Study 3 to compare and contrast the experiences of those scoring low-to-normal vs. very high for anxiety. It was hoped that using an additional qualitative approach would help to contextualise HPV-related illness representations identified in Study 3, and elicit potential wider impacts which were not measured in the prior quantitative work.
METHODS

Participants and Design

Women aged 24-63 who had tested HPV+/normal were recruited to take part through two NHSCSP HPV primary screening sites in England. The in-depth interviews were conducted with women who had taken part in the survey in Study 3 assessing their anxiety scores (see: doi.org/10.1186/ISRCTN15113095), who did not report a current anxiety disorder or depression. Women were purposively sampled to compare the experiences of those with low-to-normal vs. high anxiety (indicated by a score of ≤38 vs. >49 on the S-STAI-6 (169), respectively). Health Research Authority (HRA) approval was granted on 09/01/2019 (Research Ethics Committee reference: 18/EM/0227 and Confidentiality Advisory Group reference: 18/CAG/0118). Cervical Screening Research Advisory Committee approval was granted on 15/03/2019 (ODR1819_005). See Appendix 4.1 for the HRA approval letter.

Procedures

Potential participants were identified by NHS staff at two large cervical screening sites in England (North West London and Greater Manchester NHS Foundation Trusts). Eligible women were mailed a study information pack to their home address shortly after receiving their result letter, which contained a questionnaire assessing state-anxiety (using the S-STAI-6) as part of the larger cross-sectional survey (Study 3, Chapter 4). If women completed the survey, they could opt-in to be considered for an interview. Interview participants were purposively sampled to represent 15 women with low-to-normal anxiety and 15 women with high anxiety. Where possible, women were also sampled to include a range of ages, ethnicities, educational attainment, and marital statuses. In practice, this meant iteratively revisiting the list of interviewed women with high vs. low anxiety, to select new participants based on underrepresented demographics and balance these across groups. Participants were selected on a first-come-first-serve basis and were provided with further information (verbal information, information sheet, written consent form) and offered a £40 gift voucher, plus reimbursement for travel expenses.
The in-depth semi-structured interviews followed a topic guide (see Appendix 5.2) developed using the existing literature and grounded in relevant psychology theory, including Leventhal’s Common-Sense Model of Self-Regulation (148, 149) and Cognitive Behavioural Theory (127, 134). For example, the topic guide reflected an assessment of emotions, cognitions, behaviours and physiological responses, in line with Cognitive Behavioural Theory (see Appendix 5.2; questions 5a-d). It also covered Leventhal’s illness perceptions by including questions on perceived cause, controllability (personal and treatment control), consequences, and symptoms of HPV (see Appendix 5.2; questions 12a-d and 13). The areas covered in the topic guide were piloted with members of the project steering group and feedback was integrated from two Patient and Public Involvement (PPI) representatives (see Study 3 statement on PPI; and Appendices 5.3 and 5.4 for the consent form and information sheet). The interviews began with questions about the participant's experience of cervical screening and receiving their test result. The rest of the interview was driven by responses to this question, and included questions about emotional and physiological response, cognitions, behaviours, perceived understanding, and disclosure of result. Interviews took place face-to-face between 28th June 2019 and 31st August 2019 and were audio-recorded and transcribed verbatim with participant identifiers removed by an external transcription company. Emerging themes from the transcripts were noted whilst conducting the interviews, and some additional questions were iteratively incorporated as the interviews progressed. All women provided written informed consent before the start of the interview and were debriefed at the end.

In addition to demographic information provided by participants in the survey in Study 3 (age, ethnicity, educational attainment, marital status, mental health diagnoses), some data was obtained from their clinical records (test result, deprivation score, NHS site, date of screen, and anticipated date of test result delivery).

Analysis

Data were coded using the qualitative data analysis software NVivo 12 (286). To become familiar with the data, Kirsty Bennett and I read all the transcripts; and Jo Waller and Laura Marlow read 3-5 transcripts each. I made notes about the transcripts and used segments of text from each to form initial codes. New codes from each transcript were
iteratively compared with those from previous transcripts, with additional codes created where there were deviations. Themes and subthemes were interpreted from the coded data and developed into a preliminary thematic framework. Then Kirsty Bennett, Laura Marlow and Jo Waller independently reviewed the transcripts, codes, and preliminary thematic framework. All codes were discussed until there was consensus on the final thematic framework, which was refined iteratively. The interview transcripts and participant details were uploaded to NVivo and I coded all transcripts. Kirsty Bennett independently coded 10% of the transcripts (n = 3) to check the inter-rater reliability of the framework which was good (Kappa = 0.91).

Once all the data had been coded in NVivo, it was then summarised in a framework matrix to allow for thematic comparisons between participants who had scored low-to-normal vs. high for anxiety. The framework matrix used rows for participants and columns for themes. NVivo auto-generated verbatim quotations under each of the themes in the framework matrix, and data were exported to excel sheets for ease of interpretation.

Framework Analysis (287) was chosen because it facilitates comparisons within and between cases (288).

Rigour

Trustworthiness refers to the level of confidence that can be inferred in qualitative data and interpretations, as well as in the quality of the methods adopted (289, 290). Four criteria are recommended to guide trustworthiness in qualitative research: credibility, transferability, dependability, and confirmability (291). Our credibility was maximised by involving four researchers in the discussions and interpretations of the data (289). Transcripts were also iteratively visited throughout the analysis process to ensure that themes remained grounded in the data, and several quotes are provided to allow the reader to draw their own conclusions (292). Transferability was addressed by providing detailed descriptions of the sample and highlighting relevant contextual factors throughout. Dependability was ensured by providing a detailed description of the methodology to allow for replication of the procedures (293). Confirmability was addressed by using open questions and reflecting back participant’s own words in interviews, to minimise transference of bias from the interviewer to participants. Further, an audit trail of notes
were kept after each interview detailing emerging themes, which were reflected upon before the start of each subsequent interview (293).

RESULTS

Interviews were conducted with 30 women, including 15 with low-to-normal anxiety (median score of 26.7, range: 20.0-36.7) and 15 with high anxiety (median score of 63.3, range: 53.3-80.0). Table 5.1 displays a summary of participant characteristics.

Interviews lasted on average 46 minutes (range: 24–75 minutes). Women completed their anxiety questionnaire on average 11.5 days (range: 6-53 days) after receiving their test result and attended the interview on average 35.5 days after their result (range: 22-76 days).
Table 5.1 – Participant characteristics and demographics overall and by anxiety group.

<table>
<thead>
<tr>
<th></th>
<th>Overall Sample (N=30)</th>
<th>Low Anxiety (N=15)</th>
<th>High Anxiety (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety score (Median, Range)</strong></td>
<td>45.0 (20.0-80.0)</td>
<td>26.7 (20.0-36.7)</td>
<td>63.3 (53.3-80.0)</td>
</tr>
<tr>
<td><strong>Age in years (Median, Range)</strong></td>
<td>37.5 (24.0-63.0)</td>
<td>48.0 (26.0-63.0)</td>
<td>33.0 (24.0-63.0)</td>
</tr>
<tr>
<td><strong>Education (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below Degree</td>
<td>15</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Degree or Higher</td>
<td>15</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td><strong>Ethnicity (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mixed/multiple</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Relationship status (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>23</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>No partner</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>Index of Multiple Deprivation† (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most deprived (Deciles 1-5)</td>
<td>19</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Least deprived (Deciles 6-10)</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td><strong>HPV with normal cytology result (N)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st result</td>
<td>21</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>2nd or 3rd result ‡</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

† Index of multiple deprivation is a multidimensional marker of area-level deprivation, based on residential postcode. ‡ Women had tested HPV+/normal for a 2nd or 3rd consecutive time at their 12-month recall at HPV primary screening.
Summary of Themes

Women’s reactions to receiving test results covered six themes: 1) emotional response; 2) cognitions related to HPV; 3) behaviours; 4) disclosure of result and social influence; 5) physiological response; and 6) interactions of stressful life events or health conditions. Differences between low and high anxiety groups are highlighted throughout. Quotes are reported with participant number (P) and by anxiety group (low as LA; high as HA).

See Figure 4.1 for an overview of the thematic comparisons between low vs. high anxiety.
Figure 4.1 - Thematic comparisons between women with low vs. high anxiety.

- **Experience of High Anxiety**
  - Anxiety “up and down”
  - Linked to external triggers & distraction
  - Lasted around a few days to 2 months
  - Shifted from fear to background worry

- **High Anxiety**
  - Fear
  - Worry/anxiety

- **Low Anxiety**
  - Apathy
  - Relief

**Emotion**

- **Shared Themes**
  - Shock
  - Embarrassment or shame

**Cognition**

- **High Anxiety**
  - Consequences of cancer: thoughts about death or impact on loved ones
  - Higher perceived risk of cancer
  - Prolonged infidelity concerns
  - HPV-related symptom attributions
  - 12 month wait for screen is too long
  - Low personal control (internal locus)
  - Fertility cognitions (younger women)

- **Shared Themes**
  - Questions about cancer timeline
  - Sexual cognitions and questions:
    - Source of HPV
    - Transmission of HPV
    - STI label and stigma
    - Questioned relationship infidelity
    - Mortgage/insurance concerns
    - Confused about result meaning
    - Majority perceived no symptoms
    - Low control over HPV

- **Low Anxiety**
  - Acceptance
  - 12 month wait for repeat screen means it can’t be serious
  - HPV is normal and common
  - Low control (external locus)
  - Normal cytology means no cancer
  - Immune system clears HPV naturally

**Environment & Social Context**

- **High Anxiety**
  - Stressful/trumatic event
  - Works in healthcare
  - Cancer in media

- **Low Anxiety**
  - Other health conditions
  - Knows people with cancer

**Physiology**

- **High Anxiety Only**
  - Cried
  - Increased heart rate
  - Stomach sensations
  - Experienced “shakes”
  - Sleep disruption
  - Nocturia

- **High Anxiety**
  - Avoided or stopped sex
  - Healthy diet to boost immunity
  - Skipped meals due to anxiety
  - Increased physical activity
  - Smoked fewer cigarettes
  - Spoke to health professional
  - Disclosed result to more people
  - Kept result letter for reference

- **Shared Themes**
  - Searched the internet for information
  - Disclosed result to selected individuals

- **Low Anxiety**
  - Carried on as normal
  - Reluctance to disclose result due to STI stigma
  - Disposed of result letter
Emotional Response

Adverse emotional responses were described mainly by women with high anxiety. Many described experiencing fear or worry shortly after receiving their results, which often related to the development of cervical cancer and/or its potential impact on their family.

*It creates a worry that wasn’t there before. Obviously, you worry about illnesses and death and things like that when you’ve got, especially when you’ve got children anyway.* (P5, HA)

*It’s that panic. You think, oh my goodness. You don’t want it [cancer] to happen to you and your family. You want - you want that bubble, you want… to be able to protect - protect it and protect them.* (P25, HA)

The period between receiving a result and attending the interview was described as "up and down" (P7, HA), sometimes linked to external triggers (e.g. cancer on TV) or lack of distraction. The period of highest anxiety was reported as lasting between a few days and a couple of months. However, for some, the result remained an “underlying anxiety” (P2, HA).

*The first couple of months it was there. Um then it sort of faded…* (P20, HA)

*It comes and goes. Um, I tend to just put it out of my mind the majority of the time ‘cause, you know, I’ve got a busy life and things. So… You forget about things like that. But it, it comes back every now and again.* (P5, HA)

Both anxiety groups described ‘shock’ or ‘surprise’ immediately after their result because they had no symptoms, had been vaccinated, or were unaware they were being tested for HPV. After the initial shock, some women in the low anxiety group reported little concern or “relief and reassurance” (P6, LA).

*I was just a bit surprised ’cause obviously there’s no symptoms and I kind of felt like everything was fine.* (P23, HA)

*I was very surprised because I knew I had the vaccination, so I did not expect that at all.* (P13, HA)

*It was a bit of a shock um so I thought it was just testing cervical cancer. I didn’t know that it was testing these other elements or things.* (P24, HA)
Some women receiving an HPV+/normal result for the second or third time were ‘more relaxed’ because they knew what to expect, whilst others felt worse because their body was not successfully fighting HPV. After a third result, two women felt ‘reassured’ to be offered further investigation (colposcopy).

I more, was more relaxed that I had it this time, even though I didn’t like having it, still having it. (P15, LA)

So I was obviously shocked when I got the letter to say it was still there. Because I think I’d, I’d, in my mind I thought oh well, I had it last year, it’s probably gone away now. (P14, HA)

Cognitions About HPV

Cognitions about HPV covered six subthemes: 1) understanding of result; 2) cervical cancer and the aetiology of HPV; 3) 12-month screening interval; 4) sexual impact; 5) symptom attributions; and 6) other HPV-related cognitions.

Understanding of Result

Few women were aware they had been tested for HPV prior to receiving their result. Many were ‘confused’, ‘perplexed’ or ‘uncertain’ about its meaning.

I think the more you read into it, the more confusing it gets. (P16, LA)

I was not aware that they’re testing for HPV as well. I was, just thought it was just a smear for the cells itself. (P29, HA)

There was particular confusion around the combined positive (for HPV) and negative (for cytology) aspect, as well as what ‘cytology’ or having an ‘infection’ meant.

So you’re thinking well I’ve not got cancerous cells, I’m okay for three years, so you think yeah, thumbs up. But then, but you’ve got HPV so you might get cancerous cells. Do you understand what I mean? (P14, HA)
Shared questions across anxiety groups related to the cause of HPV, how it develops, and/or its timeline. Most women were aware that sexual activity caused HPV. Others guessed that HPV was caused by poor hygiene or was a symptom of another condition. A minority of women reported that they did not know the cause.

*I’d say, casual sex, unprotected sex, also just sexual contact, um, it’s probably increased my chances of HPV.* (P12, HA)

*I have no idea. Literally no idea. Absolutely none. I have found no information on where it could come from at all.* (P28, LA)

Most women believed that HPV lasted 1-2 years; though a minority believed HPV would stay ‘forever’ or had been there ‘since birth’.

*I’m assuming it could last up to a year or go before that or it could still be there, which makes me think that it may have been something that had already been in my system for up to two years.* (P8, LA)

*Well, I think probably for... forever because I... from what I understand there’s no cure and um if it’s something that has been dormant and there then it will probably stay there for life.* (P22, LA)

Some women wanted to know whether they had ‘high-risk’ HPV in order to assess their cancer risk. Highly anxious women viewed themselves as medium-to-high risk of cervical cancer.

*In the letter they obviously tell you that - that 50 per cent of the women carry the virus, but only 70 per cent of those women develop cervical cancer... so you’re thinking to yourself... basically I’ve got 70 per cent chance of developing cervical cancer.* (P1, HA)

In contrast, most women in the low anxiety group reported feeling at ‘low’ risk of cancer and that their result was ‘not serious’. Low perceived risk related to not having abnormal cells; HPV not being the direct cause of cancer; and HPV not causing problems when dormant or detected early.
At the moment I’m probably low risk because yes, it’s come back HPV positive, but it says there are no abnormal cells. (P18, LA)

I know it’s nothing serious. Um, and your immune system apparently, um, can cope with it sometimes, um, until it- it- it becomes a negative result. (P11, LA)

Consequences related to developing cancer and its future impact were shared subthemes for both groups; however, these cognitions were prominent in highly anxious women. Some described thoughts about death and cancer treatment.

Because you start thinking, “Is my life sort of coming to…” because I don’t know, if I do get it, will my body be able to err, go through the therapy and will I be, will I survive or not survive? (P26, HA)

Several highly anxious women discussed the potential impact of cancer on their children or partner. In contrast, women in the low anxiety group explained that there was no point focussing on cancer or worrying about it.

When the kids do something that makes me proud or, or something like that. And then I’ll think oh, what if I wasn’t here to see it. (P5, HA)

We’re like a team, me and him [partner]. It’s just us, so… So if I went, it’d just be him on his own [tearful]. (P7, HA)

Things happen and yes, it’s come back positive and I don’t really understand why, but that’s the way it is and worrying about it isn’t going to help. (P18, LA)

Many women in the low and high anxiety group wanted to find a cure for HPV and some had thought about treatments they could undergo to avoid cancer (e.g. hysterectomy).

Normally you have a virus, you take some medication and you kill the bloody thing. Why am I not being given any medication? (P1, HA)

Maybe I have to think about surgery or something like that. (P6, LA)

Actually I just prefer the treatment, just to get rid of it. Me friend did say she’d read somewhere that you could pay £600 for a treatment to get rid of it and she said she was gonna do that. (P15, LA)

Regardless of anxiety group, nearly all women reported ‘no control’ or a lack of control over HPV. Women with low anxiety expressed that they did not need to exert control because HPV clearance and transmission depended on external factors, so they were
‘accepting’ or ‘calm’ about it. Some of these women suggested that viral infections were inevitable or they took the fatalistic view, “if your time’s up, your times up” (P28, LA).

At the moment I don’t really feel like I’ve got any particular control. Um I don’t really feel like I need to have control of it. It just exists. (P21, LA)

In contrast, highly anxious women reported unease about their lack of control and described feeling ‘lost’. One woman described HPV as a “ticking time bomb” because she could not control its progression to cancer (P14, HA).

I also feel like it gives you that feeling of helplessness that you can’t do anything to make it better. I don’t really like that feeling. (P24, HA)

Most highly anxious women sought ways to exert control. Some searched for treatments or changed their behaviours (described under ‘behaviours’). One woman highlighted that there was merit in “trying to do something, regardless of whether it actually does anything” (P5, HA). A minority of women across both groups believed that they had ‘a lot’ of control over HPV via attending their follow-up screen, monitoring themselves for cancer symptoms, and controlling the transmission of HPV to others. A couple were ‘confident’ their body would fight HPV.

I think pretty much… a lot [of control] really because it… it’s my body and I think I… I’ll… if I notice s- a slight change then it is down to me to make sure that I get it looked at, seen to. (P22, LA)

I think I have control…whether I pass it on to anyone. (P12, HA)

If it grows, it grows within you. If my body fights it, I’m confident my body will fight it because I strong within myself, err, but otherwise I don’t have control of the virus. (P27, LA)

12-month screening interval

In the UK, women who receive an HPV+/normal result for the first or second time at HPV primary screening are recalled for a 12-month follow-up screen. Whereas many women in the low anxiety group believed the 12-month wait was ‘normal’, nearly all highly anxious women wanted to re-attend earlier.
I think it’s a long time to wait, twelve months. Yeah, maybe six months or three months, but I think twelve months is a long time to wait. (P4, HA)

I think it’s normal. I think yeah, I think when it comes up next year, that’s fine. (P27, LA)

Some wanted more information on the rationale for the interval and questioned the decision-making of doctors/policymakers, with suggestions it could be a ‘financial’ decision. Many highly anxious women questioned whether cancer might develop before their next screen. In contrast, a few women in the low anxiety group believed the 12-month interval implied that HPV was not serious.

I feel like I’ve got the you know, sort of sword of Damocles on top of my head. I’m waiting for 12 months to know if something wrong is happening or not so it’s all a bit...I find the 12 month wait, that’s gonna be horrendous. (P1, HA)

I thought, “If it’s anything more serious than that, they won’t, they’d invite me in sooner.” (P9, LA)

A year, um, seems like outrageous, really. ...You know, things like that, like what can happen within that year? Can it develop into something more? Can it, you know, like what’s your, what’s your pros and cons, what are the risk factors? Is there a positive in having another screening in three months. (P2, HA)

One woman feared she and her cohort could be research guinea pigs until the scientists and policymakers understood the timeframe for progression to cervical cancer.

‘Cause what’s gonna happen in ten years? Are they gonna turn round and say HPV is the new cervical cancer and all those women that have been just having roll-on smears every year, um, are we like the guinea pigs, see what happens? See how long it develops for before it’s taken, perhaps, seriously. (P19, HA)

A few women had already requested an earlier screen from their GP or were considering getting screened privately. The preferred screening interval was most commonly reported as 6-months, with some stating 3-months as ideal. One explained that she was more ‘accepting’ of the wait after she was informed her body can take up to 2-years to clear HPV.

You know, when she explained and said that it was err, it was something that people naturally have in their system and, and it can take up to two years to erm, you know,
for people to get rid of it, if you like, if they can get rid of it, then I kind of understood.
(P7, HA)

**Sexual Impact**

Cognitions about the sexual impact of HPV mainly centred round the source of infection and timeline, transmission, the STI label, and relationships/infidelity.

Several women reported being “in a fog” (P6, LA) about who had given them HPV and when. Some were confident HPV was from their current partner whilst others were unsure.

> I still don’t really understand how on earth I’ve got HPV having been with my husband a lot of years, very careful, we are not planning on any more babies so there’s always... where it goes there’s protection in the way so I... yes, confused. (P20, HA)

> Well, it- it must- it must be - it must be [partner’s name] if it is a transmitted disease. It must have come from- from him because prior to me, er, going out with [partner’s name], I’ve not been out with anybody for about fifteen years. (P11, LA)

Many questioned whether HPV was definitely an STI, whilst some believed HPV was “not an actual STI” (P30, LA). Others wanted to know whether HPV could be passed on; condoms are needed; re-infection can occur between partners; and whether the act of sex as opposed to sexual contact caused HPV.

> And is it definitely sexually transmitted? (P4, HA)

> Should I be wearing protection? Can I pass it on to another partner? None of that is answered, nothing. (P9, LA)

> If my infection clears up, does he have, does he still have residual infection? In which case, can he re-infect me? Does, does having the infection and recovering mean that I’ve then got immunity? (P17, LA)

The STI label was reported as ‘dirty’ by some women, as well as “oppressive” (P4, HA) and “nasty” (P28, LA). Some associated HPV with sexual promiscuity.
You always almost don’t want to see anybody and you almost feel that you’re here because you know, you’ve done something wrong, which you shouldn’t, but you do, you know. (P22, LA)

There is this sort of stigma around it like, ‘Oh well, they must sleep around or they must be dirty,’ (P23, HA)

It was like one route you can get it is from having lots of sexual partners and I was like, oh god, he’s gonna think this, but it was fine. (P24, HA)

Thoughts about potential infidelity were common among both groups but appeared pronounced in highly anxious women. Many women reported believing that their (ex)partner may have been unfaithful; though, most no longer believed this at the time of interview.

My first thought was oh my god, he’s cheated and I’m gonna marry him in a few months’ time. (P25, HA)

I think I know that he hasn’t been unfaithful. I think I do know that. I now appreciate this can happen and be in my body. I could have done this to myself 20 years ago. (P20, HA)

Infidelity continued to be an issue for some highly anxious women by adding an element of mistrust or disruption to their relationship. A couple thought that their partner may not want to engage in sex if they knew HPV was an STI.

If he thinks that I could give him something then he’s... he can rightly not want to do it [sex], which is completely fine but then obviously that would affect our relationship. (P24, HA)

I think it put, like, a bit of a downer on the relationship then, because then I thought well if he’s up to something else behind my back... it planted the seed of doubt then, err, in the back of my mind. And we’ve not been together now for ten weeks. (P14, HA)

So now I’m obviously looking at all my exes going, ‘You... you bastard!’ and thinking, it was you! (P20, HA)
Symptom Attributions

HPV was widely reported as asymptomatic but some highly anxious women attributed symptoms to the virus, including: the development of a fibroid in the womb; a urinary tract infection; breast milk production; previous genital warts; and thrush. One woman with low anxiety attributed flu-like symptoms and weight gain to HPV.

_They found quite a large fibroid going through the wall of my womb, so then you think, “Well is that a cancer from HPV?” (P4, HA)_

Some women across both groups mentioned symptoms but were unsure if they were connected to HPV, including irregular bleeding, cramp pain, cold sores, fallopian tube pain, cystitis, bleeding after sex, and bladder leaks.

_I’ve had bleeding after sex once and I have painful sex but I don’t know whether that’s anything to do with that or menopause. (P16, LA)_

_I have had bl- bladder leaks just lately but whether that’s connected or not. (P11, LA)_

Other HPV-related Cognitions

Fertility-related consequences were mentioned by younger women in the high anxiety group.

_It came to my mind like the worst, like I will never be able to have kids. (P13, HA)_

_Well you can pass it on to the baby as well. So if you google it, you can pass it on to the partner and the baby. (P14, HA)_

Across both anxiety groups, some women spoke about HPV being linked to poor personal hygiene, oral cancer, and sounding like human immunodeficiency virus (HIV). A minority expressed immune-deficiency related cognitions.

_You always think, well, is it in terms of hygiene, is it in terms of you know... I don’t know, not wearing cotton or all kinds of things, you know. (P8, LA)_
I just try and block it out ’cause I just don’t like to think oh, I’ve got HPV. It just sounds really, sounds like HIV, it just sounds like a bit of, um, it’s not a very nice disease. *(P15, LA)*

That’s another thing as well because I do know my body immune system is quite low. *(P26, HA)*

The HPV vaccine was also discussed and was linked with annoyance about not being offered it by those with high anxiety.

*So there is a vaccine available, I wasn’t offered it and now I’ve developed the fucking virus.* *(P1, HA)*

Two women discussed the consequences of HPV on their health and mortgage insurance. One had been advised by her insurer that she needed to formally declare her second HPV+/normal result on her mortgage.

*And so he went back to the insurance company and said should she put this down... and their answer was if it was the first one, no - but now she’s had two, yes. And we will not cover her for any treatment.* *(P28, LA)*

*When you go into a new mortgage they ask you all about medical history and I will have to now tell them about the HPV. So they’ll put some clause in my insurance cover so that, if anything further down the line, um, happens to me because of HPV, they’ll void that out of me insurance. That’s, that’s what worries me.* *(P14, HA)*

**Behaviours**

Only women with high anxiety reported changing their behaviour due to HPV. Some reported avoiding sexual intercourse or using condoms.

*We’ve not had any sexual intercourse since I got the letter.* *(P18, HA)*

*I just think that, I think in my mind, I thought to myself if I keep having sex it’s never going to get, it’s never going to go away.* *(P14, HA)*

A few attempted to boost their immune system with vitamin supplements, changes to diet, and exercise.
I’m more conscious about... It sounds stupid, doesn’t it? Taking um multivitamins. (P20, HA)

For like the first month I was on this really healthy exercise and eating hype to boost my immune system! That was purely the h- HPV because I thought, oh, my immune system needs to fight it. (P24, HA)

One woman reported reducing smoking and another described vaping more to deal with the stress of HPV.

Maybe that cheeky cigarette that I would probably have on a night out, I don’t. I just stay away from that... little conscious things like that I’ve just decided that I’ll just stay clear of that. (P12, HA)

I probably vaped a little bit more. (P25, HA)

Women were also asked what they did immediately after they received their result. Many reported using the internet to search for information on HPV; and highly anxious women described this most extensively, stating it was often ‘unhelpful’. Women with low anxiety usually reported putting their result letter to one side, “skim reading” it (P2, LA), or getting on with their day. Some women described using distraction (e.g. activities or work) to avoid thinking about their result.

I found that what I was reading online was so unhelpful. (P2, HA)

Um I actually got on the phone to my daughter... (P22, HA)

I probably cooked tea for the kids [laughter]. I would have just put the letter to one side. (P9, LA)

### Disclosure of Result and Social Influence

Seeking social support was described as a coping strategy to help deal with HPV. Nearly all highly anxious women reported disclosing their result to at least one person; though some delayed disclosure or did not tell certain individuals. Non-disclosure in this context was often because women did not want to burden loved ones.

I just don’t really want to worry her [sister] about this kind of thing. (P1, HA)
Because then, essentially, I’m just passing my anxiety on to him [partner], you know, so... (P2, HA)

In the low anxiety group, the decision to disclose was mixed. A few women stated that they did not tell anyone because they were not concerned. Those who did disclose sometimes omitted certain information (e.g. the sexually transmitted aspect) due to embarrassment, not wanting to be viewed as “promiscuous” (P22, LA), or viewing their result as “personal” (P8, LA). Two women were contemplating whether to disclose their result to a partner.

I think I just tried to put it out of my head and I was a bit embarrassed so I never even discussed it with anyone. (P15, LA)

Do I have to have that horrible... ‘cause I’m not with him now, so do I have to have that horrible conversation with him, or can I just leave it...? (P9, LA)

Several women also mentioned other people they knew who had cancer and a few worked in healthcare, where cancer was prominent in their daily lives. The celebrity Jade Goody’s battle with cervical cancer, as well as cancer in the media, was discussed by a minority.

I’m at the stage of my life where quite a few of my peers have had it and died. And so I understand what that means and it is nasty... (P28, LA)

I think obviously because I work in... in the nature of my job, I work with a lot of cancer patients, um, I think seeing them... in my experience of seeing them, it makes me... it just makes me worried of what it could be. (P12, HA)

Physiological Response

Physiological responses were exclusive to highly anxious women. Soon after their result, some reported crying, sensations in their stomach, and/or sleepless nights. Others described bodily sensations such as shaking and increased heart rate, and nocturia. One reported that she lost her appetite due to her anxiety.

I don’t usually cry that often so... but off of that I just like burst into tears. (P24, HA)

I had the shakes. (P14, HA)

I definitely didn’t eat for the rest of the day. (P2, HA)
Interactions of Stressful Life Events or Health Conditions

Whereas only one woman reported an acutely stressful life event in the low anxiety group, around half of women in the high anxiety group reported significant adverse events (e.g. death of a loved one, ongoing clinical treatments, a partner leaving them). Several women also reported having other health conditions to manage alongside HPV; however, there were no obvious differences in existing conditions between the high and low anxiety groups. Supporting quotes have not been included for this theme to ensure participant identity remains anonymised.

DISCUSSION

Main findings

The findings from this study advance the qualitative literature by exploring psychological response to testing HPV positive with normal cytology at routine HPV primary screening and identifying themes which may be specific to women with high anxiety. Only highly anxious women expressed fear and worry, fatalistic cognitions about cancer, fertility-related cognitions, adverse physiological responses, and changes in behaviour(s). In comparison to those with low anxiety, they more strongly voiced cognitions about relationship infidelity, the 12-month wait for follow-up screening, a low internal locus of control, and HPV-related symptom attributions.

Similar to other studies (as identified in Study 1), we found that testing positive for HPV was linked to concerns about cervical cancer and feelings of fear and worry (194). In this study, cancer-related cognitions appeared to be the most dominant theme and were the primary concern for highly anxious women. In particular, these women often focussed on the consequences of cancer and expressed cognitions about undergoing cancer treatments or leaving loved ones behind. Further, many highly anxious women considered themselves to be at medium-to-high risk of cervical cancer. In particular, the normal cytology aspect of an HPV+/normal result indicates very low short-term cancer risk and should therefore offer reassurance. However, nearly all women focussed on the HPV-
positive aspect of their result and gave little or no attention to the normal cytology part of their result. Instead, some incorrectly believed that HPV was the direct precursor to advanced cervical cancer. These findings help to interpret Study 2 in this PhD which found heightened anxiety associated with an HPV+/normal result at HPV primary-screening. Targeted information in HPV+/normal result letters emphasising the very low short-term cancer risk and explaining the relevance of normal cytology could improve women’s understanding and help prevent unnecessary anxiety.

Linked to cancer-related cognitions, many highly anxious women voiced concerns about the 12-month wait for routine follow-up, questioning whether cancer may develop in the interim. Given that 12-month recall is specific to HPV primary screening, it is also important for screening policymakers to communicate the rationale for this interval in HPV+/normal result letters to help reassure women. Further, addressing this concern from the outset may prevent unintended additional healthcare system costs, given that many women expressed contacting their GP at least once to request an earlier screen.

The sexually transmitted nature of HPV has previously been linked to feelings of stigma, shame, and embarrassment (86, 89, 194). To date, most studies have assumed that sexual concerns play a central role in the development of anxiety following an HPV-positive result. Interestingly, however, we found that most sexual cognitions and related feelings of embarrassment were common to both anxiety groups. Relationship infidelity was the only subtheme which was more pronounced in women with high anxiety. Although not a distinctive finding in the previous qualitative literature, Study 1 revealed that relationship infidelity concerns have presented as themes more generally, with confusion about the cause or source of HPV linked to reports of anxiety. It is also worth noting, that even though several women in our study expressed cognitions related to sexual impact, they rarely reported these as primary concerns. Although they require confirmation using quantitative studies, our findings help tease out nuances pertaining to cognitive vs. emotional responses to HPV. Longitudinal studies also support this notion given that psychosexual distress remains elevated for up to 12-months, whereas general anxiety normalises within 3-months, indicating two distinct psychological pathways (demonstrated through the meta-analysis findings in Study 1) (194, 294).

Low perceived control can be associated with poor health outcomes including adverse emotional response (161). In line with the systematic review evidence from Study 1, nearly all women in our study reported feeling that they had little or no control due to a
lack of treatment or practical prevention methods for HPV. A novel finding was that highly anxious women appeared to focus on internal factors they could use to gain control (e.g. consuming multivitamins), in contrast to women with low anxiety who linked external factors (e.g. fate) to acceptance of HPV. These findings point to individual differences in the interaction between locus of control and coping styles which, in the absence of a viable solution for HPV, may drive feelings of anxiety. Further research is needed to explore potential mechanisms between control beliefs and coping mechanisms or behaviours in HPV.

HPV is asymptomatic, yet some highly anxious women believed or questioned whether certain idiosyncratic symptoms may be HPV-related. This is in line with Leventhal’s CSM and the wider psychological literature, where negative affect is known to play a central role in somatic symptoms and perceived symptom attribution (274-276). Further, these findings are consistent with Study 3 which found that a subgroup of highly anxious women with maladaptive somatic representations perceived symptoms related to HPV. Healthcare professionals and screening information materials should therefore emphasise the asymptomatic nature of HPV, while also encouraging women to monitor and/or seek further investigation for specific cervical cancer symptoms (e.g. unusual bleeding, pain from sex).

Fertility-related cognitions associated with an HPV-positive result have also been identified in previous studies (86, 89). In this study, although a relatively minor theme, this was specific to younger women with high anxiety. General practitioners could provide reassurance about fertility to younger women who have received an HPV+/normal result, emphasising that a HPV-positive result alone is not known to affect fertility.

Few studies have explored physiological and behavioural responses to HPV, with the exception of some general sexual behaviours (196, 197, 295). We incorporated these constructs into our topic guide, and several anxious women reported experiencing physiological sensations shortly after receiving their result (e.g. crying, shaking, stomach sensations), as well as changing their behaviour(s) due to HPV (e.g. stopping sex, vitamin consumption, avoiding cigarettes). Behavioural and physiological factors should be incorporated into future cervical screening evaluations to assess their relevance and the full psychological impact of receiving HPV-positive results.
Finally, there is a paucity of HPV-related research grounded in psychological theory, which also differentiates between normal responses vs. potentially clinically meaningful anxiety. Adoption of Cognitive Behavioural Theory and Leventhal’s Common-Sense Model to develop our topic guide and drive interview questions, which proved useful for eliciting beliefs and facilitating the emergence of a comprehensive thematic framework. This study highlights the merit in integrating established psychological theory into qualitative methodologies in the field of HPV, which will be discussed further in Chapter 6 (general discussion).

**Strengths and Limitations**

To my knowledge, this is the first qualitative study to explore reasons for anxiety in women testing HPV+/norm at routine HPV primary screening. The comparative qualitative design paired with the use of a theoretically informed interview schedule facilitated a rich account of women’s experiences and allowed thematic nuances to emerge between anxiety groups. Recruitment was linked to routine clinical management at HPV primary screening, ensuring a diverse and well-characterised sample. However, due to the relatively small numbers within each demographic group, we were unable to explore intersections between demographics and anxiety. We were able to calculate the time (days) between women receiving their result and attending interview, which ranged from 22 - 76 days. It is possible that this wide range in time from result may have introduced heterogeneity for women’s recall of events and/or experiences of anxiety. Although we excluded women who reported a current anxiety disorder, we did not measure anxiety scores prior to HPV primary screening, meaning we could not determine whether receiving an HPV+/normal result was the primary source of their anxiety. Further, this sample did not include women with mid-range anxiety (S-STAI-6 scores between 39 and 48) as the aim was to explore very high anxiety; therefore, there may be unidentified themes relevant or distinct to moderately anxious women. Finally, like most research studies, self-selection bias may have meant that the identified themes are not transferable to other highly anxious women attending cervical screening.
Implications

To date, cervical screening patient communications and public health campaigns aimed at minimising adverse psychological impacts have wholly based their content on population level research without stratification by result group or anxiety level. The findings of this study begin to build an evidence-base for the development of specific messages targeting the concerns of highly anxious women, which could be included in standard HPV-positive results letters, or covered in training for sample-takers or GPs who might discuss HPV results with women.

Conclusion

Receiving an HPV-positive with normal cytology result related to emotional, cognitive, behavioural, and physiological responses; some of which were specific to, or more pronounced in, women with high anxiety. These findings support and augment those in Study 3, which identified distinct illness representation profiles associated with low-to-normal vs. very high anxiety. To avoid unintended consequences for women attending HPV primary screening (e.g. unnecessary anxiety and/or adverse behavioural impacts), these distinct themes should be used in tandem with the findings from Study 3 to guide the development of evidence-based patient communications and screening implementation policy.
Overall, this thesis aimed to explore psychological response to testing positive for HPV at cervical cancer screening, with a particular focus on HPV primary testing and the new test result group (HPV-positive with normal cytology). Four original research studies were conducted which, together, have markedly advanced the psychological literature in cervical cancer screening. The adoption of timely policy-relevant questions paired with the use of rigorous methodologies and relevant evidence-based theory facilitated the identification of novel insights into emotional, cognitive, and behavioural aspects of receiving an HPV-positive result.

In this last chapter, I will summarise the key findings of Studies 1–4 and discuss their strengths and limitations, whilst proposing future directions for research, policy, and practice.

**Summary of PhD Findings**

**Overview of Study 1**

Firstly, Study 1 aimed to address Objective 1 of this PhD, to describe and synthesise emotional response to testing HPV-positive at cervical screening. A mixed method systematic review was conducted, using a results-based convergent synthesis design, and findings were also mapped on to the cognitive behavioural model. Random-effects meta-analyses revealed that women testing HPV-positive with abnormal or normal cytology displayed higher short-term anxiety than those with normal results (up to 2 months after result); however, there were no long-term differences (up to 12 months after result). Psychological distress (general/sexual/test-specific) was higher in HPV-positive women with abnormal cytology in the short-term and long-term.
The synthesised narrative quantitative and qualitative results indicated that testing HPV-positive was also related to disgust/shame, surprise, and fear about cancer. After formulation using the CBT model, adverse response broadly related to eight cognitive constructs (low control; confusion; cancer-related concerns; relationship concerns; sexual concerns; uncertainty; stigma; low trust) and six behavioural constructs (relationship problems; social impact; non-disclosure of results; idiosyncratic prevention; indirect clinical interaction; changes to sexual practice). Almost exclusive use of observational and qualitative designs limited inferences of causality and conclusions regarding clinical significance. There were also no studies which examined short-term emotional response in the context of HPV primary screening, marking a large gap in the literature given the recent policy shift to adopt these methods in England and internationally.

**Overview of Study 2**

Building on findings from Study 1, Study 2 was then used to narrow the focus and examine short-term anxiety and distress in women receiving different test results at routine HPV primary screening (Objective 2). In the adjusted analyses which accounted for sociodemographic characteristics, anxiety was statistically significantly higher in women testing HPV-positive with either normal cytology or abnormal cytology, compared with the control group (normal cytology, no HPV test). Distress was slightly higher in women who tested HPV-positive with abnormal cytology (but not HPV-positive with normal cytology) compared with the control group. Increased odds of very high anxiety were found in women who had tested HPV-positive with normal or abnormal cytology, compared with the control group. Overall, this pattern of results was only observed among women receiving their first HPV-positive result; not among women who had tested HPV-positive with normal cytology at 12-month follow-up screen.

It was concluded that testing HPV-positive with normal cytology for the first time was associated with elevated anxiety despite carrying very low immediate cervical cancer risk. However, receiving the same test result at 12-month early recall did not appear to be associated with higher anxiety, suggesting anxiety may normalise with repeated exposure and/or over time. Overall, Study 2 provided a robust descriptive overview of the trends of anxiety and distress associated with the different possible test results at NHSCSP HPV primary screening. It was noted that further work was needed to provide insight into
reasons for the observed associations, especially for women experiencing very high anxiety who had received the new test result generated from the HPV primary screening algorithm (HPV-positive with normal cytology).

**Overview of Study 3**

Following evidence from Study 2 that women testing HPV-positive with normal cytology displayed heightened short-term anxiety at HPV primary screening, Study 3 then attempted to identify psychological (cognitive) factors which could help to explain reasons for anxiety. Leventhal’s Common Sense Model of Self-Regulation was used to provide theoretical grounding in the methodology given that this theory had been widely tested across other health conditions and operated on a dual cognitive-emotion pathway. Study 3 aimed to identify latent profiles of women who shared similar or diverse patterns of illness perceptions about testing positive for HPV with normal cytology; and to examine the relationships between illness representation profiles and anxiety (Objective 3).

Latent Profile Analysis identified three distinct profiles of illness representations (termed ‘adaptive’, ‘maladaptive’, and ‘maladaptive somatic’) which differed significantly in their patterns of illness perceptions. Hierarchal linear regression revealed that these latent illness representation profiles accounted for 21.8% of the variance in anxiety, after adjusting for relevant demographic and clinical characteristics. When compared with adaptive representations (Profile-1), women with maladaptive representations (Profile-2) and maladaptive somatic representations (Profile-3) had significantly higher anxiety, displaying potentially clinically meaningful differences. It was concluded that the identified latent illness representation profiles could play an important role in anxiety, providing new insights for targeting maladaptive beliefs within subgroups of highly anxious women following an HPV-positive with normal cytology result. Further research was recommended which focussed on unpicking the meaning behind illness representations, and explored wider cognitive, behavioural, and emotional experiences associated with very high anxiety.
Overview of Study 4

Lastly, building on Studies 1-3, Study 4 was a comparative qualitative interview study to help further disentangle experiences and beliefs specific to women with low vs. very high anxiety. In particular, addressing Objective 4, this study aimed to explore reasons for variations in anxiety in women testing HPV-positive with normal cytology at routine HPV primary screening.

Several HPV-related themes were shared across the high and low anxiety groups, but only highly anxious women expressed fear and worry, fatalistic cognitions about cancer, fertility-related cognitions, adverse physiological responses, and changes to their health behaviour(s). In comparison with those with low anxiety, highly anxious women also more strongly voiced cognitions about the 12-month wait for follow-up screening, relationship infidelity, a lower internal locus of control, and HPV-related symptom attributions. It was concluded that receiving an HPV-positive with normal cytology result related to various emotional, cognitive, behavioural, and physiological responses; some of which were specific to, or more pronounced in, women with high anxiety. Paired with the findings of Study 3, it was argued that distinct illness representations and themes relevant to women experiencing high anxiety (clinically significant levels) could be used to inform targeted patient communications and HPV primary screening implementation policy.

Novel Contributions

Taken independently and together, the four studies presented in this PhD showcase original research contributions and provide novel insights within the HPV and cervical screening domain. Prior to this PhD, there had been no systematic review assessing emotional response to HPV at cervical screening, despite a relatively comprehensive existing literature. Emotional response had never been meta-analysed or isolated from important potential confounders (e.g. cancer diagnosis or genital warts). Internationally, there had been no formal psychological evaluation assessing anxiety and distress at routine HPV primary screening, despite the shift in policy to promote this screening
method and several countries implementing it. Linked to this, there had been no research exploring anxiety in the new (and common) group of women receiving HPV-positive with normal cytology results at routine HPV primary screening. Overall, this body of work was also the first to add a theoretical lens to psychological aspects of HPV at cervical screening and appraise findings on the basis of clinical significance, facilitating the provision of a preliminary evidence base for policymakers to test and develop communication materials.
PSYCHOLOGICAL IMPLICATIONS AND FUTURE CONSIDERATIONS AT CERVICAL CANCER SCREENING

A number of academic considerations have already been raised throughout this thesis outlining specific findings worthy of contention, as well as critical suggestions for future research. Here, cross-cutting issues will be discussed which I believe warrant further investigation and wider debate in the cervical screening domain.

High-Risk Groups and Adverse Psychological Impacts

Overall, the findings of this PhD suggest that receiving an HPV-positive result at cervical screening is associated with short-term anxiety and some other adverse emotional, cognitive, behavioural, and physiological impacts. Clinically significant anxiety, however, appears to affect a minority of women and may be concentrated within certain high-risk groups. In support of this, Study 2 demonstrated that anxiety and distress were raised at population level shortly after an HPV-positive result, but mean scores did not exceed the threshold for clinical significance. The odds of clinically significant anxiety, however, were significantly higher in women testing HPV-positive for the first time (regardless of their cytology result) compared with the control group. Hence, some women did appear to experience notable adverse impacts. Similarly, Study 3 found that women who had tested HPV-positive with normal cytology and had maladaptive or maladaptive somatic illness representations, displayed mean anxiety scores above the threshold for clinical significance.

To progress the field, research emphasis should be now placed on further characterising subgroups of women who may be at higher risk of clinically significant anxiety and/or adverse behavioural outcomes (e.g. avoiding sexual activity). In doing so, targeted strategies can begin to be developed to minimise unnecessary burden. As a starting point, Study 1 identified key characteristics associated with adverse emotional response from the previous literature. Broadly, adverse response was related to: not understanding result meaning; having a current (sexual) partner; an ethnicity other than White; receiving a test result by letter; not discussing a result with a healthcare professional; little social support; and lower education. In line with some of the findings in Studies 3 and 4, it is also possible
that women who are already anxious due to an existing mental health diagnosis or adverse life event may experience interaction effects, and respond acutely to an HPV-positive result. Future research should aim to build on these preliminary indications, and clearly distinguish between the needs of the general population and high-risk groups. Concerted efforts should be placed on developing mitigation strategies for groups most likely to experience clinically significant adverse impacts.

Linked to this, importantly, this PhD builds an evidence base reflecting key beliefs and illness representations associated with clinically significant anxiety. Study 3 found that women who had maladaptive or maladaptive somatic illness representations held shared patterns of illness perceptions, which were associated with clinically significant anxiety. Higher perceived consequences, concern, and emotional representations (and symptoms for the maladaptive somatic group), as well as lower personal control and understanding, were common to both. Further, Study 4 provided rich insights into the distinct beliefs held by women with clinically significant anxiety, when compared with those with low anxiety. Together, these findings provide evidence-based foundations upon which explanatory mechanisms can be explored and tailored interventions can be developed and tested in high-risk groups.

Anxiety, Fear, and Worry Associated with HPV: Are They Distinct Or All One And The Same?

Early on in this PhD, it became apparent that distinguishing between negative affective states would be challenging. Negative affect is described as broadly encompassing “aversive mood states, including anger, contempt, disgust, guilt, fear, and nervousness” (296), and was a core theme throughout. Negative affect is weighted heavier than positive affect in terms of its ability to influence health outcomes, and operates largely independently from positive affect (297-299). However, given the lack of scientific consensus on the nuanced definitions of different mood states within negative affect (touched on in Chapter 2, Study 1), emotion categorisation was largely defined by a combination of existing validated outcomes (e.g. anxiety or distress measure) and women’s qualitative accounts. In the systematic review (Study 1), the American Psychological Association emotion definitions were also used to guide informed judgement in terms of emotion synthesis categorisation (see Table 2.4).
The most common types of negative affect measured or reported following an HPV-positive result were anxiety, fear, and worry (across Studies 1–4). However, similar to much of the psychological literature on other cancers, these three constructs were referred to interchangeably by both researchers and study participants. For example, in the qualitative research (Studies 1 and 4), women sometimes referred to fear/worry/anxiety more than once in the same sentence, making them seemingly indistinguishable. Similar experiences which used different semantics were difficult to categorise (e.g. “I was so worried that I cried” vs. “I felt anxious… I just burst into tears”). To some extent, this also carried through to the previous quantitative literature where different studies used the same validated measure but reported the outcome differently; e.g. the PEAPS-Q (226) was used to measure ‘distress’ (241) vs. ‘worry’ (88). As outlined in Study 1, a study also measured fear as a quantitative endorsement of both “I feel worried” and “I feel anxious” (210).

Although fear, worry, and anxiety are inherently linked, they are conceptually distinct and can differentially relate to affective, cognitive, behavioural, and physiological outcomes in cancer (300). In psycho-evolutionary terms, fear is usually defined as a negative affective response to a perceived threat characterised primarily by physiological arousal (301). Whereas, worry is defined as a parallel cognitive and affective state which is often specific to an event, and can be characterised by intrusive or avoidant thoughts or feelings in the context of cancer screening (119). Anxiety as measured in most cervical screening studies, on the other hand, is usually characterised by short-term apprehension, nervousness, and uncertainty related to specific or a number of future events (168). Importantly, these three forms of negative affect can be distinct in how they predict or relate to important health outcomes. For example, in breast cancer screening, worry about breast cancer has been shown to predict higher screening uptake (118). Similarly, moderate levels of anxiety may predict higher uptake at screening (273), but anxiety can also carry adverse symptoms such as disrupted sleep or lack of concentration, sometimes interfering with everyday functioning (302, 303). Generalised fear of cancer has been found to be positively associated with screening uptake (119); however, specific forms of fear have been associated with avoidance behaviours, including fear of cancer diagnosis, treatment, or test procedures (273, 304, 305).

As a reflexive point, fear, worry, and anxiety were listed as distinct psychological responses in this thesis. However, I cannot be confident that they always reflected their
formal meanings beyond the methodological steps taken to maximise rigour, as outlined within each Chapter. Like many other areas of health, it is apparent that the field of cervical screening is in its infancy in terms of refinement and measurement of emotion. Consensus is needed regarding the operationalisation of common affective responses related to HPV, and greater care needs to be taken to employ psychometrically valid and reliable measures. More broadly, there is also a need for the field of psychology to develop formalised procedures for describing and categorising emotional constructs when analysing and reporting qualitative data.

**What Constitutes Adverse Psychological Impact And Where Does The Ethical Threshold Lie?**

To date, there appears to be no clear consensus around what constitutes adverse psychological response at cervical cancer screening. Over the past two decades, psychological evaluations or trials at cervical screening in England have been conducted as adjuncts to clinical trials and health economic evaluations. These psychological studies in large have indicated some short-term psychological impacts associated with HPV-positive or abnormal screening results (*e.g.* raised anxiety and distress). Yet, the accepted stance is usually that cervical screening is safe with minimal psychological burden (84, 85, 88, 170, 240). There appears to be an unspoken assumption that ‘short-term’ impact is acceptable whilst ‘long-term’ is not, without pre-specified definitions of what these durations mean or whether intensity of response should be an equal consideration.

While not intending to question the conclusions drawn in the HPV literature (which extends to my own work), I raise the apparent ambiguity underpinning some of these definitions with hope that future studies may consider refining them. In part, the lack of clarity may link to some of the points raised in Study 1 arising from little attention given to the clinical significance of findings in previous work. Building on the findings from the systematic review, Study 2 (the commissioned NHSCSP psychological evaluation) was the first to expressly discuss the results in terms of clinical significance in addition to outlining observed trends. Following suit, the other three studies in this PhD also differentiated between normal and clinically significant anxiety. Though this does not explicitly address the issue of what constitutes adverse response, these shifts in reporting and interpretation are positive steps towards determining clinical relevance. It is
important that future research continues this build on this work, adopting methodologies which reflect clinical significance as well as refinement of pre-specified definitions and rationales.

Equally, as a broader policy consideration, it is unclear whether indeed an ethical threshold exists based on the results of psychological studies in HPV, which if crossed could have the potential to meaningfully alter cervical screening implementation (beyond routine patient communication). The findings from Study 2 in this PhD aimed to directly guide implementation of NHSCSP HPV primary screening in England. Without an agreed benchmark of what ‘bad’ or ‘unethical’ psychological impact denotes at cervical screening however, clinical interpretations and implications for policy and practice remain restricted. Some studies have incorporated health-related quality of life measures into cervical screening evaluations in attempt to provide a metric by which psychological harm could weighted against (physical) health benefits; e.g. (88, 295). Such measures, however, may be considered a crude marker of psychological harm.

Policy-driven discussions are seldom centred on psychological impacts as an independent weighted consideration at cervical screening. NHSCSP clinical and cost-effectiveness evaluations are usually of primary interest; reflected via substantially higher allocated funding to them, and the comparative adjunct nature of most psychological studies. While not within the scope of this PhD to discuss whether this is approach suitable or not, I hope that by highlighting some of these uncertainties, this may encourage future dialogues aimed at more concretely establishing the role of psychological research at cervical screening.

**HPV Positivity and Psychological Impact: Correlation, Causation, or Interaction?**

Another important consideration for interpreting the implications of this work, most often neglected in previous research, is that nearly all HPV-related psychological studies have adopted observational or qualitative designs. This was one of the key methodological findings highlighted in Study 1 (systematic review) and also extends to the designs used in this PhD. Literature from the last three decades has been largely rooted in the assumption that HPV-positivity and cervical abnormalities directly lead to adverse psychological responses; i.e. causality has been inferred mostly from observational data.
This limitation has been rarely discussed or acknowledged in the literature. Therefore, whilst not a primary finding from my PhD, I want to flag this as an area worthy of wider academic discussion.

Establishing the causal nature and pathways of the relationships between testing HPV-positive and adverse psychological outcomes should help to determine the relevance and importance of research in this area. It will also help to inform future cervical screening evaluations and policy decisions. Crucially, if adverse psychological responses are not largely due to receiving an HPV result, but instead due to non-screening-related confounding characteristics, then this reduces the likelihood of targeted efforts being effective at mitigating or preventing these outcomes via cervical screening pathways. Not intending to detract from the adverse experiences reported by women in the qualitative literature (including Study 4), quantitative causal mechanisms are necessary to assess the clinical significance of findings and the scale of the issue. They help to further establish the ethical responsibilities which fall under the remit of the NHS cervical screening programme. Three areas, in particular, may be important to consider: i) psychological stress and immunological function; (ii) sexual distress and pre-existing relationship or sexual issues; and (iii) pre-existing mental health conditions.

**HPV and Psychological Stress, Sexual Distress, and Pre-Existing Conditions**

As touched on in Study 1 relating to anxiety and general distress, the (re)activation, persistence, and clearance of HPV infection are closely intertwined with immunological factors; and psychological or social stressors are known to impair immune response (250-252). Some evidence has supported a mechanism whereby stressful life events can negatively affect immune function, leading to higher risk of infections (306-308). In the context of HPV, this poses the question of whether some women who are already anxious or distressed have lower immune function, which could lead to an increased likelihood of HPV (re)activating and persisting (not clearing).

Psychobiology studies in HPV are scarce and the few that exist have had mixed findings. For example, higher perceived stress has been associated with impaired HPV-related immune response in women with cervical abnormalities (252). However, another study suggested that although psychological stressors could influence relevant immune
parameters, there was no evidence to suggest that they affected clinical manifestations of HPV infection (309). Limitations of these studies include cross-sectional designs (rather than prospective designs following the course of HPV infections) and small sample sizes, without sufficiently controlling for possible confounders. Therefore, overall, there is inconclusive evidence. It cannot be ruled out that activation and/or persistence of HPV are, in fact, possible markers of pre-existing psychological stress. Further research is needed to explore such psychobiological mechanisms.

Similarly, with regard to sexual distress, the risk of HPV infection is greater in those who are currently sexually active and have had a higher number of sexual partners. Again, it is possible that sexual distress associated with an HPV result could be characteristic of inherent sexual issues or behaviours resulting from higher sexual activity, as opposed to solely a causative effect via HPV diagnosis. As indicated in Study 1 (systematic review), some of the evidence has been mixed for sexual distress, depending on whether an observational vs. RCT design has been employed (84). It is possible that differences between studies could be partly due to confounding psychosexual factors not accounted for in observational designs. There could also be moderation effects or interactions at play whereby women who have already experienced relationship infidelity issues or have trust issues may (exclusively) experience the greatest psychosexual impacts (as was sometimes expressed in Study 4). Therefore, again, the weighting and degree to which HPV-positive results may directly vs. indirectly contribute to sexual distress is not fully understood.

Further, mediation or interaction effects may also be at play between psychological outcomes and pre-existing mental health conditions, whereby those women with a current mental health condition (e.g. anxiety disorder) may experience the most adverse impacts following an HPV-positive result. Efforts were made to statistically adjust or exclude women with a self-reported current anxiety disorder or current depression in Studies 3 and 4 to minimise confounding; however, as anxiety score was not measured prior to HPV primary screening, we were unable to determine whether receiving an HPV+/normal result was the primary source of women’s anxiety. Again, this reinforces uncertainties regarding causal mechanisms and identification of high-risk groups. Some broader research has found that (severe) mental illness is predictive of lower cervical screening attendance (310-313). Women with mental illness may also differentially engage with screening information materials (313, 314), and experience distinct barriers at cervical screening (315). To date, there does not appear to be any research which exclusively
explores psychological response to testing HPV-positive in women with mental illness. Future research should aim to compare the responses of women with current mental health diagnoses to those without no diagnosis, as well as incorporate validated diagnostic tools to highlight potentially relevant undiagnosed cases.

Overall, speculatively drawing on the studies in this PhD and from the theories embedded, it seems most probable that bidirectional and interacting relationships may interplay between HPV positivity and adverse psychological response. In Study 3, HPV-related illness representations accounted for 22% of the variance in anxiety when controlling for self-reported clinical anxiety and depression, suggesting that maladaptive beliefs about HPV can play a central role (though this study was cross-sectional). Further, Study 4 presented reports of highly anxious women’s concerns and experiences which seemed largely specific to HPV and cervical cancer; though several of these women also described unrelated ongoing adverse life events. Therefore, it seems unlikely that immunological function, inherent sexual activity, or pre-existing mental health conditions would fully account for the observational findings in literature. The more likely question is whether they partially contribute and to what degree.

Overall, research is needed to explore and test these potential causal pathways. To do this, randomised controlled designs with baseline measures of anxiety and sexual distress (pre-results) should be adopted wherever possible. Psychological evaluations should be embedded within primary clinical trials as opposed being commissioned as standalone cross-sectional adjunct studies. Clinical data from patient records could also be incorporated, including mental health history (e.g. current anxiety disorder, depression, mood disorder), as well as statistically adjusting for validated measures of current sexual behaviours. Psychobiological studies using prospective longitudinal designs could be conducted to explore relationships between known psychological and social stressors/markers (e.g. chronic psychological stress, social isolation, adverse life events, cortisol levels), HPV biological markers (e.g. viral load, onset, clearance rate, recurrence), and immune parameters (e.g. leukocytes, alpha2-globulins, beta-globulins). Together, this would provide clarification and inform the relevance of cervical screening policy interventions.
IMPLICATIONS FOR PSYCHOLOGY THEORY

The Utility of the CSM and CBT

As highlighted throughout this thesis, attempts to explain psychological response to HPV at cervical screening had been largely atheoretical prior to my research. Only two theory-based studies were identified which used Leventhal’s Common Sense Model of Self-Regulation (148, 149) and Cognitive Behavioural Theory (127, 134) to guide interview or survey questions, reportedly proving to be useful frameworks (104, 128). Both of these theories were embedded in the overarching methodology of this thesis for reasons described in Chapter 1, and were the first to add a comprehensive theoretical lens to HPV in the cervical screening context.

First and foremost, before commenting on the theoretical application used, it is worth emphasising that I did not perform formal validity testing on the CSM or CBT; therefore, the comments and formulations made in relation to these theories are methodologically cognisant but nonetheless conjectural. Observations described in this section are largely reflexive and attempt to provide overviews relating mainly to utility and face validity.

Part of the rationale for embedding the CSM and CBT in the overarching methodology was that they both incorporated dynamic emotion pathways/constructs, and were aimed at complementing each other at different stages of the PhD. Overall, the encompassing framework of CBT was used to facilitate preliminary but comprehensive formulations, and was especially useful when assessing the previous literature and helping to formulate qualitative data (Studies 1 and 4). Then, the more focussed health-specific CSM successfully helped to identify HPV-related illness representations and pathways/processes (Studies 3 and 4).

Both of these theories introduced slightly different nuances and came with their own merits and limitations. Given that it was never an aim of this PhD to directly juxtapose the CSM and CBT, a comparative critique will not be performed in detail. As an overarching point, however, CBT appeared to summarise a broader set of psychological responses than the CSM; and more explicitly captured relevant behavioural and physiological factors associated with testing HPV-positive. In terms of utility, CBT facilitated the production of a relatively straightforward but helpful framework, which
assisted with the identification and collation of wide-ranging relevant constructs; but offered very little insight into pathways and specific interactions. In Studies 1 and 4, theoretical formulations were proposed based on CBT (see Figures 2.9 and 4.1) which helped to capture rich accounts of women’s experiences. In Study 4, the use of CBT to formulate comparisons between low and high anxiety groups undoubtedly enhanced my findings by facilitating the emergence of thematic nuances specific to each group.

In contrast, the CSM offered a narrower focus on key constructs allowing for more precise categorisations of HPV-related cognitions. The CSM’s dual cognitive-emotion pathway and its links with coping and self-management behaviours, facilitate the formulation of explicit hypotheses which could be tested in future research by building on the findings of Study 3. For example, exploring predictive relationships between (mal)adaptive illness representations, anxiety, and cervical screening re-attendance. However, the emotion pathway was far less developed which is largely reflective of the fact that illness representations (i.e. the cognitive pathway) have gained the most traction in the health psychology literature to date (316). Compared with CBT, the CSM also failed to clearly incorporate physiological responses; though certain constructs are inherent of physiological factors (e.g. disrupted sleep with general distress or increased heart rate with fear-based emotional outcomes).

Common to both the CSM and CBT is that they do not explicitly incorporate sociodemographic characteristics. Rather, the models are said to be embedded within environmental or cultural contexts. Lack of weighted consideration given to known socioeconomic factors within psychological formulations may miss important interactions or moderation/mediation effects. For example, emotion and affect regulation have been found to differ systematically across ethnic groups, which may carry important implications for explaining differences in cancer screening behaviours (273). Directly relevant to the CSM and CBT, for example, women from ethnic minority groups in the UK have described more extreme emotional experiences associated with cervical screening than those of White ethnicity (British or other) (317). More broadly, African Americans have been found to report lower negative affect and lower stress compared with European Americans, and may be less emotionally expressive during conflict than European groups (318). Lower socioeconomic status may also be related to adopting more emotion-focussed coping strategies (319); and affect regulation has been found to be associated with lower depression in lower (vs. higher) socioeconomic groups (320).
To enhance the findings of this PhD and complement the CBT formulations already performed (Figures 2.9 and 4.1), the overarching results from Studies 1-4 have been speculatively formulated using the CSM. See Figure 5.1, which is intended to illustrate how potential constructs could interact, but needs formal testing in future research. In brief, women’s representations and emotional response to an HPV-positive result may depend on: how they process information in their test result letter; conversations they may have had with a screening healthcare professional; their existing knowledge of HPV and cervical cancer; their perceptions of pre-existing HPV/cancer related symptoms; and environmental triggers such as cancer in the media. As illustrated in Studies 1, 3, and 4, women’s emotional representations may include worry about HPV, potential infidelity, or future impacts on loved ones. Fear of cervical cancer and concerns about test result meaning or fertility may also be present; as well as shock at the result, embarrassment about the STI aspect, and loss of trust or anger towards partner. Equally, some women may express little emotion related to their HPV-positive result.

In terms of illness representations, perceived consequences may relate to the potential impact of cancer; of cancer treatment; on family or loved ones; on relationships or sex life; or on fertility. Timeline could link to women’s questions about: the progression of HPV or cancer; timing of infection to determine the source or person responsible for transmission (linking to potential infidelity); and the 12-month wait for re-screen for women testing HPV-positive with normal cytology. Low personal control over HPV and high treatment control (via cervical screening) were expressed, and a subgroup of women may perceive HPV-related symptoms, as identified in Studies 3 and 4. Coherence may also be important and relate to perceived understanding of an HPV test result and risk of cervical cancer.

Together, these cognitive illness representations and emotional representations may interact to regulate coping strategies and behaviours such as: cognitive reappraisal (e.g. ‘HPV is common’ or ‘HPV is nothing to worry about’); problem-focussed coping (e.g. healthy eating, discussing worries with a GP, avoiding sex); emotion venting (e.g. crying); seeking social support (e.g. discussing result with friends/family/partner); and avoidance (e.g. distraction or non-disclosure of result). Overall, these pathways may differentially relate to emotional outcomes (e.g. anxiety and distress) or health-related
outcomes (e.g. sexual or general functioning). In line with the CSM, coping strategies or behaviours are then likely to be appraised in relation to whether they have had a successful impact on relevant health-related and emotional outcomes.

Overall, the CSM seemed to provide a useful account of psychological response to testing HPV-positive. The formulated model highlights relevant mechanistic pathways which can be further explored and tested in future research. However, it is worth noting that the emotional pathway was difficult to formulate due to its lack of development in the wider CSM literature; therefore, the categorisation of emotional illness representations vs. emotional outcomes likely warrant additional caution in the interpretations.
Figure 5.1 - Overarching findings formulated using Leventhal’s Common Sense Model of Self-Regulation; model adapted from (154).
Alternative Theoretical Formulations and Relevant Constructs

Williams’ Affect and Behavioural Framework

Whilst CBT and the CSM were used to map and formulate findings, there are several other potentially relevant theoretical models which could be used to understand psychological response to HPV. For example, Williams’ Affect and Health Behavioural Framework (253) has been recently proposed as a dual-processing framework of pathways through which affect-related concepts may interrelate to influence health behaviour. Building on previous research, Williams and colleagues distinguish between affect-related concepts which are categorised as: “(a) affective response to the target behaviour; (b) incidental affect: affect that is not caused by the target behaviour but may influence the target behaviour; (c) affect processing: cognitive processing of previous or anticipated affective responses to the target behaviour, including anticipated affective response, affective attitude, affective association, and implicit attitude; and (d) affectively charged motivation: motivational states that include an affective component, including fear, and intrinsic motivation” (321).

In the context of HPV, these four forms of affect could have been applied to some of the themes in this thesis. This may have led to more nuanced formulations of negative affect and its influence on relevant behaviours (e.g. cancer screening re-attendance, sexual activity, dietary habits, engagement with health services). Given that theory had not been applied to HPV in the cervical screening context previously, however, it would have difficult to foresee some of the focal areas without the work produced as part of this thesis. Therefore, now that relevant cognitive, affective, physiological, and behavioural constructs have been identified using CBT and the CSM, Williams’ Affect and Health Behavioural Framework could be a promising model to further advance the field through application in future research.

Intolerance of Uncertainty

Similarly, on the individual level, certain trait-based constructs are known to influence anxiety within the clinical psychology domain, which could have been incorporated into
the methodologies used in this PhD. For example, ‘intolerance of uncertainty’ is commonly associated with generalised anxiety disorder and mood disorders (322). Intolerance of uncertainty is defined as “a dispositional characteristic that results from a set of negative beliefs about uncertainty and its implications and involves the tendency to react negatively on an emotional, cognitive, and behavioural level to uncertain situations and events” (323). Given that HPV clearance vs. persistence and the development of cervical abnormalities are largely unpredictable with no cure, a diagnosis of HPV inherently generates uncertainty related to its potential progression to cancer. Study 4 (qualitative study) found that highly anxious women expressed fear and worry related to the potential development of cancer, as well as concerns about the 12-month wait to be re-screened, which are potentially indicative of intolerance of uncertainty. Further, uncertainty has been expressed related to the duration of HPV infection, linked to when and from whom women acquired the infection (Studies 1 and 4). It would, therefore, have been beneficial to include a measure of uncertainty in my quantitative research, such as the widely-used validated Intolerance of Uncertainty Scale (324). Again, future research could assess the relevance of this construct for explaining anxiety or other forms of negative affect.

Health Psychology and the Role of Affect Regulation

As highlighted, there are alternative theoretical frameworks which may have led to different formulations for explaining psychological response to HPV. Broadly, this links to a wider discussion point reflecting trends in the application of health psychology in the UK. Most of the traditional or popular health psychology theories tend to either neglect affective response altogether (e.g. Theory of Planned Behaviour; Temporal Self-Regulation Theory; Health Belief Model; Transtheoretical Model (325-328)) or have failed to give it weighted consideration (e.g. COM-B (329)).

Leventhal’s CSM is a health psychology theory which explicitly incorporates a dual-pathway of cognition and emotion, hence why it was chosen for use in this thesis. Despite the CSM incorporating emotion however, this pathway is still far less developed than its cognitive counterpart. As highlighted in a recent commentary by O’Carroll (2020), emotion has been a secondary consideration in health psychology research (316). Attention should be focussed on the role that emotion can play in directly regulating
behaviour, rather than solely acting as a secondary outcome which can be modified via illness perceptions in the CSM. In contrast in clinical psychology, negative affect is usually recognised as a core part of formulations and as having a central role in maladaptive cognitions and behaviours (330). This differs substantially to the formulations typical in health psychology, which tend to be largely focussed on cognitive and environmental triggers of behaviour, with little or no reference given to emotion.

It is possible that health psychology in the UK, as a discipline, has predominantly focussed on cognitive, behavioural, and environmental aspects of health in an attempt to distinguish itself from clinical psychology. A recent oral history of health psychology in the UK reported that during the 1980s, psychologist practitioners working in the area of health often rejected a mental health approach in favour of acquiring ‘academic rigour’. This movement away from abnormal mental health models (which often centre on affect) may have been compounded by the British Psychological Society (BPS) Division of Clinical Psychology opposing one-to-one clinical work by health psychologists in the 90s, when the BPS Division of Health Psychology was first being established (331). It is possible that these series of events may, in part, have meant that health psychology researchers inadvertently neglected the potential central role that affect can play in influencing health behaviour. Only very recently has the potential for independent effects via affect and affect regulation pathways gained traction in health behaviour research (321, 332). It seems likely that upcoming trends will incorporate more explicit integration and testing of emotion in health psychology and behaviour change theory.

**Affect Regulation and Behavioural Response to Testing HPV-Positive**

Relevant to the role of affect when testing HPV-positive, it is worth highlighting that both healthy behaviours and risk behaviours can be used as affect regulation strategies. For example, some women may smoke tobacco following an HPV-positive result to reduce anxiety, whereas others may increase their physical activity to achieve the same outcome (both of these behaviours were expressed by highly anxious women in Study 4). It would be helpful for future research to explore and define what healthy vs. risk behaviours comprise following an HPV-positive result; and determine the mechanisms to these outcomes. Further, negative trait affect has been found to be central in health complaints and symptom reporting, while positive affect appears to be less important (274, 275, 333).
Hence, differences in negative trait affect could potentially help interpret reasons for reported symptom attributions associated with HPV in highly anxious women who had maladaptive somatic representations, as identified in Study 3.

It is also possible that affect could also play a role in determining 12-month re-attendance at cervical screening for women who have already tested HPV-positive with normal cytology. As outlined in Chapter 1, early findings from the English HPV primary screening pilot indicate that around 15% of women who test HPV-positive with normal cytology do not attend their follow-up screen. Sociodemographic inequalities associated with 12-month early recall have so far been found to be minimal (115). Therefore, this could indicate that psychological factors may be central in non-re-attendance at 12-months; consistent with this subgroup having already attended screening, eliminating many of the known sociodemographic and practical barriers initially preventing access. Future research should explore these potential pathways through adopting longitudinal designs and linking baseline psychological outcomes to prospective re-attendance data.

Over the last three decades of cervical screening research more broadly, few studies have quantitatively explored behavioural response to testing HPV-positive, with the exception of some generic sexual behaviours (e.g.,(196, 197, 295)). Behavioural factors should be routinely incorporated into future cervical screening evaluations to assess their relevance at population level and the full psychological impact of receiving HPV-positive results. Longer-term behavioural impacts related to sexual practices may be particularly relevant given that sexual distress has been shown to persist at 12-months post-result (194, 294).
Person-centred care is a term increasingly used by the NHS and health policymakers as the vision for modern optimised healthcare. It can be enacted in many forms and, for those who have attended cancer screening includes ensuring that patients who receive test results are equipped with the information necessary to understand their result meaning, and are not harmed by unnecessary burden. Test results at cervical screening are delivered by letter and HPV primary screening procedures mean that only 4.2% of women are invited back for immediate follow-up in England (51). Thus, the opportunity to engage with patients after they receive their result is extremely limited. The NHSCSP has therefore made concerted efforts to facilitate person-centred care as best they can via screening communication materials (e.g. information in letters and informed choice pamphlets) and training for healthcare professionals delivering care in the screening pathway.

One of the key challenges for the NHSCSP when designing and delivering a population level centralised and computer-based cancer screening service is that all patient communications are standardised with limited opportunity for modification. Tailoring of materials, such as result letters and accompanying information, is only possible by test result group and cannot usually be stratified for subgroups with differing information needs. Further, certain results are indistinguishable in the NHSCSP centralised system and generate the same result letter, when they are often distinct from the patient’s perspective. For example, women who test HPV-positive with normal cytology for the first time receive the same letter when they attend their 12-month follow-up screen and test HPV-positive with normal cytology for a second consecutive time. In Study 4, women who were in this situation expressed frustration at receiving the same letter twice. The result was not the same from their perspective, as their HPV had not cleared and they were unsure whether their cancer risk or subsequent screening procedures would change.
Tailoring Information to Reach High-Risk Subgroups

Given that the implementation of HPV primary testing in England has led to a significant increase in the numbers of women receiving HPV-positive results, emphasis has been placed on the need for targeted public health efforts to improve HPV-related knowledge (101). A recent UK study found that women lacked knowledge about the meaning of HPV-positive results in the context of HPV primary screening (105). Information about HPV which is perceived as unclear has also been linked to misinterpretation of test results and reportedly higher distress (89). Further, there is also potential for inequalities to manifest in terms of psychological burden and informed decision making. As alluded to in Study 1, lower levels of education and having an ethnicity other than white were associated with adverse psychological response. Women with lower educational attainment have also displayed poorer understanding of the NHS cervical screening information leaflet, suggesting that the content may be too complex for some recipients (112).

Therefore, the NHSCSP needs to develop strategies which mean that the same information at population level can be communicated to meet the needs of varying groups, whilst covering essential clinical information. Whilst not the explicit focus of this PhD, pragmatic suggestions for approaches to better deliver information to women receiving HPV-positive results can be generated from the findings. Of those risk factors identified in this PhD which are the most malleable or amenable to screening policy intervention (e.g. information conveying result meaning, mode of delivery), pragmatic and cost-effective strategies could be developed, tested, and implemented at population level. Local NHS policies could then be further refined to target some of the harder-to-reach or high-risk groups (e.g. ethnic minority, low education, or existing mental health diagnosis).

Pragmatic Policy Suggestions

As a starting point, for example, the NHSCSP could focus on improving the clarity of result information, ensuring that recommended health literacy levels are met and common questions or concerns are covered. They could also consider increasing or altering possible channels of result delivery, beyond result letter (e.g. signposting to an NHS or
third-sector support helpline in letters). Localised strategies could be adopted in tandem to provide additional support or tailored information to geographical regions with known groups at greater risk. For instance, NHS Trusts or GP practices in areas with higher proportions of ethnic minority or low socioeconomic populations could adopt policies where follow-up calls from trained screening nurses are delivered to women following an HPV-positive result. Similarly, but allowing for more personalisation, NHS Trusts could also embed automatic system notifications in GP electronic records which flag patients in high-risk groups who have received an HPV-positive result, to encourage GP-initiated conversations in routine practice (e.g. HPV-positive patients with a current mental health issue). Comparable policies have been successfully employed via NHS Digital and form part of the UK Government’s vision for improving future services across the health and care system (334). To be successfully implemented in cervical screening, the NHSCSP would need to recommend clear strategies at the national level; setting direction and outlining plans for local policy uptake in NHS Trusts, Clinical Commissioning Groups, and GP practices.

Tackling pragmatic and knowledge-based outcomes alone, however, are unlikely to fully alleviate the adverse psychological impacts associated with an HPV-positive result. It is well-established that modifying general knowledge on its own is rarely enough to substantively alter psychological or behavioural outcomes (335). Knowledge about HPV and test results are unlikely to fully reflect women’s core health beliefs and illness representations about HPV (as demonstrated in Study 3). Importantly, this PhD starts to build an evidence base reflecting the key beliefs and illness representations associated with clinically significant anxiety and maladaptive outcomes. As previously discussed, potential sociodemographic and psychological characteristics may be specific to highly anxious groups, providing evidence-based foundations upon which tailored interventions could be developed and tested. Thus, targeting sets of beliefs known to contribute to adverse psychological outcomes in highly anxious women via some of the modes of delivery highlighted (e.g. test result letters or clinical conversations) could reduce or prevent adverse psychological outcomes (e.g. anxiety and distress).

In tandem, the wider behavioural science literature could also be used to design behaviourally-enhanced letters and leaflets to optimise re-attendance; e.g. adopting an applied behavioural framework such as MINDSPACE (336). For example, NHS Health Check invitation letters using shortened and simplified text with a clear behavioural
instruction to book an NHS Health Check have been found to improve uptake (337, 338). A colorectal cancer screening trial also found that more people returned their test kit when sent a behaviourally enhanced instruction leaflet (339). Targeting key HPV-related representations whilst adopting behavioural science techniques could be used as the basis for developing evidence-based screening information materials, which aim to minimise unnecessary psychological impacts and maximise screening re-attendance.

Overall, given that population level services offer limited opportunity for personalisation or stratification, it is unlikely that any single strategy would fully mitigate psychological burden or be perceived as helpful for all women. Nevertheless, small changes (with small effect sizes) can still make a meaningful difference to women’s wellbeing at population level when over 450,000 women receive HPV-positive results each year in England (51). HPV self-sampling will also soon be piloted in two areas in North London, where women who do not attend cervical screening will be mailed home-based cervical sample kits to complete and post back for testing (340). If HPV self-sampling is implemented nationally by the NHSCSP, there will be greater reliance on communication via written materials due to no routine in-person clinical contact. Therefore, collaborative efforts between researchers, policymakers, and patient and public representatives should continue to be prioritised to develop and improve written content.

Testing of Materials and Brief Intervention Development

The new NHSCSP HPV primary screening communication materials were launched at beginning of 2020, but to date there has been no formal testing of the updated materials. As an initial step, the NHSCSP should test the efficacy, effectiveness, and acceptability of the content and materials through embedded randomised controlled trials and engagement with patients and the public from diverse groups and backgrounds. Linked to this, policy review of structures and regulatory processes should be considered to ease the ability for researchers to trial communication materials at routine cervical screening. The current NHSCSP system presents significant barriers to accessing routine data, including regulatory sign offs from independent screening-specific committees (e.g. Cervical Screening Programme Research Advisory Committee) in addition to standard HRA and NHS ethics approvals. Office for Data Release Approvals are also required for
accessing routine aggregated screening data. Centralising and/or reducing some of these steps would encourage more ecologically valid research studies at cervical screening (e.g. using routine clinical samples as opposed to population surveys or hypothetical scenarios).

In addition to content, there is also a need to better understand the effectiveness of information provision at different stages of the invitation and screening process. This will help to determine optimal points for information to be communicated to women in the NHSCSP routine pathway. For example, women may not fully engage with or read the information leaflets which accompany cervical screening invitation letters. Supporting this notion, nearly all women in Study 4 reported being unaware that they were being tested for HPV prior to their result, despite routine NHSCSP invite pamphlets detailing this information. It seems unlikely that generic information at the point of invitation will yield as much attention as personally relevant information contained later (e.g. the result letter). Therefore, simple cost-effective modifications to the information delivery points in the cervical screening pathway may yield promising effects. Future research could examine relationships between levels of engagement with cervical screening information, mode of delivery, and psychological (e.g. anxiety, distress, understanding of result) and behavioural outcomes (e.g. screening re-attendance or help-seeking).

Discussions about the use of HPV testing or HPV-positive results could be initiated by health professionals at the start of the screening process (e.g. during a screen or when booking an appointment) or in routine clinical reviews (e.g. colposcopy or GP appointments). To assess the feasibility and acceptability in routine practice, the views of screening nurses and GPs may be important to identify their support needs, as well as to plan for barriers and facilitators to initiating these types of conversations.

Finally, online HPV-focussed self-help interventions could be another possible option to reduce psychological burden and improve behavioural or health-related outcomes, such as sexual functioning. Brief psycho-education interventions could centre on addressing maladaptive illness representations, drawing from the findings in Studies 3 and 4. Cognitive behavioural treatment approaches could also be integrated into these interventions, building on the preliminary theoretical formulations detailed in this thesis. They could be methodologically strengthened by, for example, also applying formal intervention development methods such as Intervention Mapping (341). Although
requiring some initial investment to test and develop brief self-help interventions, once available, these could easily be embedded digitally via NHS and third sector websites, and signposted to in test result letters using Quick Response (QR) codes.

**Other Health Services and Unknown Policy Impacts**

Limited data exists on behavioural impacts associated with an HPV-positive result. Several women in the qualitative literature (Studies 1 and 4) reported making an appointment(s) with their GP following an HPV-positive result to request an earlier screen, due to worry about the timeline for progression to cancer. Some also reported seeking medical advice or treatments to reduce symptoms of distress (e.g. medication for disrupted sleep). More generally, many reported speaking to a healthcare professional for clarification and reassurance. If some of these themes held true for even a small proportion at population level, there could be substantive knock-on effects for the health and care system which have not been factored into NHSCSP cost-effectiveness analyses.

At population level, these extra primary care visits could yield large financial costs if even only a minority of women altered their help seeking behaviours. In England, the average GP appointment costs the health and care system around £30 (342). Therefore, if, say, even 10% of HPV-positive women in England attended their GP to discuss their result or to request an earlier screen, this would cost the NHS approximately £1.25mn each year (£30 x 41,500; see Chapter 1, Table 1.3). This figure does not factor in wider indirect costs relating to, for example, lost salary from women taking time out of work to attend GP appointments. It also further adds strain to an overburdened NHS system and offsets the national agenda to increase capacity at primary care in England (343, 344).

Given the vast majority of HPV-positive results carry a very low absolute risk of cervical cancer, GP visits should be largely preventable if clear evidence-based information is conveyed in result letters and delivered optimally via routine channels (as detailed in Chapter 1). Focus should be placed on determining the patterns of help-seeking behaviour after an HPV-positive result from aggregated national health records; and quantifying costs through health economic analysis. In light of the arguments previously outlined, investment into rigorous development and testing of routine NHSCSP communication
materials (and/or alternative approaches) could also be a cost-effective strategy to prevent unnecessary health service engagement in the long-term.

Policy Impact of the Research in this PhD

In addition to the traditional academic aims of this PhD, more broadly, my NIHR fellowship sought to inform national policy decisions relating to the content of routine patient communications at NHS cervical screening. The research findings (mainly from Studies 1 and 2), as well as my personal contributions from attending national committee meetings, successfully informed the content of NHSCSP national invite letters, test result letters, and information booklets sent to >3mn women per year in England.

Notably, the findings from Study 2 directly led to the NHSCSP agreeing to include additional information for women testing HPV-positive with normal cytology, in the form of Frequently Asked Questions (FAQs) aimed at addressing women’s common concerns. Prior to this, no additional information was given to these women explaining what their HPV-positive with normal cytology test result meant or its potential implications. Figure 5.3 displays the FAQs sent to women (details on the development process will be expanded on later).

The FAQs are now included on the flip-side of NHSCSP HPV-positive with normal cytology result letters which are routinely sent to around 277,000 women per year. In line with the policy rationale for this PhD, it is anticipated that the narrowed findings from Studies 3 and 4 will help to refine the content of the FAQs. Targeting those factors which were identified as distinctly relevant to highly anxious women (e.g. cervical cancer risk, 12-month screening interval rationale, and relationship infidelity issues) may offer a cost-effective approach to helping reduce unnecessary psychological burden.

Stakeholder Engagement

Overall, my successful policy impact was achieved through extensive involvement with key stakeholders at PHE and the NHSCSP across all research stages, from inception of the projects to dissemination and (now) implementation. For over 3-years, I sat on the
NHSCSP National HPV Primary Screening Pilot Committee where I co-represented the psychological evaluation alongside my primary supervisor (Dr Jo Waller). At these national committee meetings, we presented emerging research findings and provided feedback on patient-centred and psychological aspects of HPV primary screening pilot. As a result of this continued involvement, I was then invited to sit on a smaller NHSCSP working group to develop patient communication materials and draft the invitation and result letters women received. Through all of these engagements, I formed important collaborations with PHE professionals, NHS service managers, PPI representatives, academics, senior clinicians, and third-sector representatives. Hence, my NIHR fellowship included a stakeholder engagement panel who provided valuable feedback, especially at the early design stages of the PhD.

It was on the NHSCSP patient communications working group that I recommended the need to include additional information for women receiving HPV-positive with normal cytology results. In large, due to the continued collaborative model of working with PHE and NHSCSP, they were receptive to our proposed changes and feedback. Along with the support of my PhD supervisors (Dr Jo Waller and Dr Laura Marlow), together, we directly drafted the FAQs which PHE then piloted through PPI groups. Separately, I also provided recommendations to PHE on clinician training content for psychological training modules at HPV primary screening.

Figures 6.2 and 6.3 display the final HPV-positive with normal cytology result letter and FAQs sent to women. Note, several other materials and letters were drafted as part of the NHSCSP working group (including all possible test result letters, screening invitation and reminder letters, information pamphlets); however, the ones most relevant to this PhD are provided as example outputs. Appendix 1.2 also displays the updated HPV primary screening information pamphlet which accompanies cervical screening invitation letters.
Dear <<PATIENT NAME>>,

Thank you for coming to cervical screening.

Your results show that you have HPV (human papillomavirus). This is called an ‘HPV positive’ result. HPV is a common virus and most people will have it at some point in their life without knowing. Usually it goes away on its own. However sometimes it can be long-lasting, and this may cause abnormal cells in your cervix. The cells can, over time, turn into cancer if left untreated. More information about HPV is on the back of this letter.

We also looked for abnormal cervical cells in your sample but we did not find any. This means you are currently at low risk of cervical cancer.

Because you have HPV we would like you to come back for screening on or around ********. This is so we can check that the HPV has been cleared by your immune system (like getting rid of a cold), and that abnormal cells haven’t developed. We will send you a reminder letter nearer the time.

Screening cannot prevent every cervical cancer. Cancer can develop in between screening tests. If you have any symptoms such as unusual bleeding between periods, after sex or after the menopause, or unusual vaginal discharge, please speak with your GP as soon as possible.

If you have any questions about your test result or would like more information about cervical screening or HPV testing, please contact your GP or the person who did your last test or visit www.NHS.UK.

Figure 5.2 - New test result letter for women who test HPV-positive with normal cytology at NHSCSP HPV primary screening in England.
More information about your result: HPV found, no abnormal cervical cells.

Your result means you have human papillomavirus (HPV), but it is not causing any problems. Regular cervical screening helps us monitor HPV and check that your immune system clears it.

Repeat screening in 12 months
Research has shown that waiting 12 months until your next screen is very safe. It is important that you attend this appointment, so we can check that your immune system has cleared the HPV. This happens in most cases.

How HPV can cause cell changes
In most cases, our immune systems can clear HPV, a bit like getting rid of a cold. Sometimes, if the virus doesn’t go away, it can start to cause abnormal cells. We will check for HPV in about 12 months’ time and if it is still there we will also look for cell changes. Abnormal cells can be treated very effectively.

If this is your second HPV positive result
It often takes a couple of years for our immune systems to get rid of HPV. Even if this is your second positive result, it is still likely that your immune system will get rid of HPV without causing any problems.

If you have been followed up after a colposcopy 12 months ago
If this is your first follow-up test 12 months after having a colposcopy, we will check for HPV again in 12 months’ time.

How people get HPV
HPV is very common. It is spread through close skin-to-skin contact during any type of sexual activity with a man or woman. HPV can stay in the body for many years. It can stay at very low or undetectable levels and not cause any problems. This means it is hard to know exactly when you got HPV or who you got it from.

HPV and relationships
Most men and women will have HPV at some point in their lives. In most cases it does not cause problems, and people don’t know they have it. There is no need for you to tell anyone that you have HPV if you don’t want to. Using a condom or dental dam during sexual activity can reduce the risk of passing on HPV to a partner but will not give full protection.

Getting rid of HPV
It is not possible to treat HPV. Our immune systems can usually get rid of it, but this doesn’t happen in every case. We don’t yet know why this is. We know that smoking can make it more difficult for your body to clear the virus. You can visit www.nhs.uk/smokefree for support and advice on stopping smoking.

HPV vaccination
The vaccination helps protect against the 2 high-risk types of HPV that cause around 70% of cervical cancers. But there are other high-risk types of HPV that can also cause abnormal cells in the cervix. This means it is still possible to develop abnormal cervical cells even if you have had the vaccination.

More information
You can talk to your GP, or find information about HPV and cervical screening at:

- [https://www.nhs.uk/conditions/cervical-screening](https://www.nhs.uk/conditions/cervical-screening)
- [https://www.jostrust.org.uk/faq/hpv](https://www.jostrust.org.uk/faq/hpv)

Figure 5.3 – Frequently Asked Questions found on the flip-side of HPV-positive with normal cytology result letters.
STRENGTHS AND LIMITATIONS

Overall, the studies presented in this thesis have advanced the HPV and cervical screening literature, addressing policy-relevant questions using rigorous and complementary methodologies. As highlighted previously, all primary research was conducted using large clinical samples and recruitment was linked to routine clinical management at NHS cervical cancer screening. This meant that all samples were relatively well-characterised and important sociodemographic and clinical characteristics were able to be statistically adjusted for where relevant.

Widely tested and validated measures were used as the main psychological outcomes. Some outcome measures were chosen to be directly comparable to previous psychological evaluations of cervical screening (e.g. S-STAI-6 (169)) and others were grounded in established CSM theory (e.g. B-IPQ and the symptoms subscale from IPQ-R (265, 266)). Although demographic and clinical characteristics were accounted for in analyses, some of these outcomes were self-reported and may be particularly subject to bias (e.g. self-reported anxiety disorder and clinical depression). Caution is particularly warranted with regard to the single-item non-validated measures used for concern, worry, and reassurance in Study 2. Again, these measures were chosen to be directly comparable to a previous NHSCSP evaluation (85, 88), but have not been given much overall weighting in the discussion due to the inherent potential limitations regarding construct validity (345).

Further, certain outcomes which are known to contribute to anxiety and psychological distress in the wider literature were not included, which may have been useful to include in the HPV context (e.g. intolerance of uncertainty scale (324), health anxiety inventory (346), cancer worry scale (237)). As identified in Study 1, there are also other emotions, cognitions, and behaviours following an HPV-positive result which may have been relevant but were not measured in my subsequent quantitative studies (e.g. cancer fear, shame, stigma, sexual activity). The reason for non-inclusion was pragmatic given that ethical applications had to be submitted prior to the results of the systematic review; hence these outcomes were not identified until the subsequent studies were underway.

In Studies 3 and 4, a strength was that time (days) from result exposure to survey completion were estimated and incorporated into the analyses, which is particularly
important when assessing temporal affective states (like state anxiety). No other psychological cervical screening studies (as identified in Study 1) have incorporated a specific measure of estimated time from exposure.

As highlighted throughout, the adoption and application of well-established and relevant psychological theory was a core strength of this PhD, advancing an otherwise atheoretical HPV-related cervical screening domain. The CSM and CBT were identified from the outset and embedded in the research designs, measures and topic guides, as well as result formulations and interpretations. In line with the theoretical aspects of this PhD, again, this body of research would have been strengthened by including other relevant emotional and behavioural outcomes within Study 2 and 3.

Like many studies, the primary quantitative research (studies 2 and 3) had low response rates and consisted of predominantly White and relatively well-educated samples that did not always reflect the racial/ethnic diversity and education levels of the UK population as a whole. Hence, generalisability may be low which limits some of the implications for policy and practice; sociodemographic factors could play a central role in the distribution and weighting of psychological burden or high-risk groups. Linked to this, however, concerted efforts were made in this PhD to recruit diverse samples through collaborating with multiple NHS sites with wide geographical coverage in Study 2. Also, one of the two NHS recruitment sites in Studies 3 and 4 was chosen due to the known ethnically diverse population in its catchment area (i.e. NHS North West London). Purposive sampling was also used to represent a range of sociodemographic groups in Study 4. In Study 2, Office for Data Release permissions were sought from PHE to access population demographics data from the HPV primary screening clinical pilot, which was then used to generate and apply statistical weights to the data in attempt to improve the representativeness of findings.

As highlighted throughout, the adoption of observational designs for all studies prohibited inferences of causality. However, the use of an overarching mixed methods design strengthened the breadth and scope of this PhD. Firstly, Study 1 used a rigorous result-based convergent synthesis mixed method design, which few systematic reviews (across all fields) have adopted or successfully employed (183). Secondly, a sequential explanatory mixed method design was used for Studies 3 and 4, where the quantitative results (Study 3) informed the purposive sampling method of the qualitative study (Study 4) (182). The qualitative research which compared themes for women with low and high
anxiety helped to build on, interpret, and explain some of the statistical associations found in the previous quantitative phases. Overall, the mixed methods approach facilitated a deep understanding of women’s psychological response to HPV-positive results. It helped to identify discrepancies (e.g. behavioural and physiological themes in the qualitative literature, not measured in quantitative studies), points of similarity (e.g. anxiety, concern about results, worry about cancer), and directions for future work (e.g. nuances in illness representations and anxiety (347)).

From a practical perspective, cervical screening research is notoriously challenging to conduct in the clinical context, which is part of the reason that much of the prior research has been pragmatically driven and sometimes used hypothetical scenario designs. The main barrier is that routine clinical contact with women attending screening usually happens prior to test result processing in NHS laboratories. In England, results are usually known and distributed around 3-weeks after a woman has been screened, meaning that opportunities for research recruitment and consent are extremely limited. Recruitment of women with a specific test result (e.g. HPV-positive with normal cytology) must be conducted outside of the routine clinical pathway. For this reason, clinical research at cervical screening requires several regulatory approvals beyond standard NHS ethics. This includes Section 251 approval from the CAG, which is extremely difficult to obtain and, if granted, permits a temporary lift in law to allow researchers to process sensitive information without patient consent (348). Studies 2-4 were all granted Section 251 approval (as well as Office for Data Release and ethical permissions), meaning that I was able to successfully make the case that the research was in the greater public good, and that the ethical benefits outweighed the consequences of not being able to obtain informed consent. Overall, although not an explicit strength of this research, these approvals reflect substantial efforts beyond those usually undertaken as part of a PhD (or most clinical research studies) and also reinforce the objective importance and policy implications of this work.

Another overarching strength is that most of the studies were co-developed with feedback integrated from a multidisciplinary stakeholder group and patient and public representatives. Adopting a collaborative process undoubtedly strengthened the design and impact of this PhD. Policymaker engagement meant that the research was useful for the NHSCSP and implementation of HPV primary screening. Patient and public representative involvement helped ensure that research foci and study materials were
CONCLUSION

In summary, the body of research presented in this thesis indicates that testing positive for HPV at cervical cancer screening is associated with adverse psychological impacts; which extends to the newly implemented NHSCSP HPV primary testing in England. These impacts appear to differentially affect subgroups of the population in terms of intensity, duration, and psychological sequelae. A majority of women likely experience minimal and/or short-term anxiety and distress. However, some display clinically significant levels of anxiety and describe negative emotional, cognitive, behavioural, and physiological responses. For women who have tested HPV-positive with normal cytology (the new result at HPV primary screening), maladaptive illness representations about HPV may partially explain reasons for clinically significant anxiety. Highly anxious women may be most fearful of developing cervical cancer, and also hold concerns about potential relationship infidelity and infertility. Future research should primarily focus on: (i) testing the validity of the relationships and pathways identified in this thesis; (ii) establishing the causal relationship between HPV positivity and psychological outcomes; and (iii) further characterising groups who are at highest risk of clinically significant adverse response. Cervical screening programmes should switch from wholly basing their patient communication materials on population research, and instead build an evidence-base for the development and testing of specific messages aimed at alleviating the concerns of the most highly anxious women.
REFERENCES


34. Oxford Vaccine Group. Vaccine Knowledge Project: HPV Vaccine (Human Papillomavirus Vaccine) 2019 [Available from: https://vk.ovg.ox.ac.uk/vk/hpv-vaccine#:~:text=Key%20facts%20about%20the%20HPV%20Vaccine,-This%20vaccine%20gives&text=There%20are%20three%20HPV%20vaccines,the%20virus%3A%2016%20and%2018].


172. O'Connor M, Costello L, Murphy J, Prendiville W, Martin CM, O'Leary JJ, et al. 'I don't care whether it's HPV or ABC, I just want to know if I have cancer.' Factors influencing women's emotional responses to undergoing human papillomavirus testing


259


267
287. Huberman M and Miles M. The Qualitative Researcher's Companion. 2002


316. O’Carroll RE. Self-regulation interventions – what do we know and where should we go? Health Psychol Rev. 2020;14(1):159-64.


340. Pike H. HPV self testing to be piloted in two areas. BMJ. 2019;364:l1357.


APPENDICES

Appendix 1.1 - HPV primary screening information sent alongside screening invite letters in the NHSCSP pilot sites (2 pages).

NHS Cervical Screening Programme

HPV primary screening

This leaflet tells you about HPV primary screening. This is a test carried out on the sample of cells we take during cervical screening.

• HPV stands for ‘human papillomavirus’.
• Primary screening means that it is the first test carried out on the sample of cells from your cervical screening.

HPV primary screening makes no difference to how your screening sample is taken.

For more information about going for screening, please read our leaflet NHS cervical screening.

Why have I been sent this leaflet?
You live in an area where HPV primary screening is being used in the NHS Cervical Screening Programme. This isn’t happening everywhere in England yet.

What is HPV?
The human papillomavirus (HPV) is very common. Most women get it at some point in their lives. There are many types of HPV, and most of them clear up by themselves without causing any problems. However, some types can cause cells in the cervix to change and become abnormal. These abnormal changes can, if left untreated, go on to turn into cervical cancer.

HPV is easily passed on during intimate sexual contact between partners; between men and women and between partners of the same sex. The virus has no symptoms. This means that you or a partner may have had HPV for many months or years without knowing it.

What is HPV primary screening?
Once your cervical screening sample is sent to the laboratory, the first test carried out on it will be to look for HPV. If HPV is found, your sample will also be looked at for abnormal cells. Looking for abnormal cells is called ‘cytology’. Cytology is still the test used for most cervical screening at the moment. If you don’t have HPV, then it is extremely unlikely that you will have any abnormal cervical cells.

HPV primary screening should benefit women because:
• more abnormal cervical cells will be picked up
• women without HPV can be reassured that they are at extremely low risk of developing cervical cancer.

Are all women being offered HPV primary screening?
Not yet. We are starting HPV primary screening in a few areas from 2013. This is to help us plan how this change to the screening programme can be put in place across the whole of England.

In places where HPV primary screening isn’t being used yet, women will either
• not have an HPV test or
• have an HPV test only after their sample has been checked for abnormal cells (cytology).
What screening results might I get?
There are three main types of results from HPV primary screening.

No HPV found (HPV negative)
If no HPV is found, then no further tests will be carried out. If you don’t have HPV, then it is highly unlikely that you will have any abnormal cervical cells. Even if you did, it would be extremely unlikely that they would cause a problem. You will simply be called back for screening again in three or five years’ time (depending on your age).

HPV found (HPV positive) but no abnormal cervical cells found
If HPV is found, the sample will also be tested for abnormal cervical cells. If none are found, your result will say you have HPV, but no abnormal cells. You will be asked to come back for screening again in 12 months’ time. This is so we can check that the HPV has been cleared by your immune system. If it hasn’t cleared, you may be at greater risk of developing abnormal cervical cells.

HPV found (HPV positive) and abnormal cervical cells found
There are several grades of abnormal cells. Some are more serious than others. You can read about this in our leaflet What your abnormal result means. If you have HPV and any grade of abnormal cervical cells, then you will be referred for colposcopy. Colposcopy is a closer examination of the cervix. It is carried out in much the same way as cervical screening. For more information, you can read our leaflet The colposcopy examination.

It is also possible to have an ‘inadequate’ result. This is when the laboratory cannot get an HPV test result from your sample, or cannot see if abnormal cells are present or not. If you have an inadequate result, you may be asked to have cervical screening again in three months’ time. The delay is so that there are enough cells again to get a sample from.

Can I get treatment for HPV?
No, there isn’t a treatment to get rid of the virus. For most women, their immune system will get rid of HPV – like getting rid of a common cold. But we can treat abnormal cervical cells, especially if they are found early on. Most types of cervical cancer take a long time to develop. Treating abnormal cells early on means that cervical cancer can be prevented.

Where can I get more information?
If you would like more information about HPV primary screening, or anything else in this leaflet, you can
- talk to the nurse at your GP practice;
- visit our website at www.cancerscreening.nhs.uk/cervical.

Copies of the leaflets mentioned can also be downloaded from our website.

A large print version of this leaflet is available at www.cancerscreening.nhs.uk/cervical

March 2013
Appendix 1.2 - The NHSCSP ‘Helping You Decide’ leaflet sent alongside screening invitation letters (10 pages).

NHS cervical screening
Helping you decide

Public Health England (PHE) created this leaflet on behalf of the NHS

It is your choice whether to have a cervical screening test or not. This leaflet aims to help you decide. Cervical screening used to be called a ‘smear test’.

Why we offer cervical screening
NHS cervical screening helps prevent cervical cancer. It saves thousands of lives from cervical cancer each year in the UK.¹² In England cervical screening currently prevents 70% of cervical cancer deaths. If everyone attended screening regularly, 83% could be prevented.³

Who we invite
Cervical screening is for women and people with a cervix. We offer screening every 3 years from age 25 to 49 and every 5 years from age 50 to 64. This is because most cervical cancers develop between these ages. First invitations arrive a few months before people turn 25. You can book your appointment as soon as you get your invitation. We invite some people more often due to a previous screening result (see page 9).

You should consider having screening regardless of your sexual orientation, sexual history, or whether you have had the HPV vaccination.

If you are a transgender (trans) man registered with your GP as female, we will send you invitations for cervical screening. If you are registered as male you will not receive invitations, but your GP or practice nurse can arrange an appointment for you if you have a cervix. If you are a trans woman you do not need cervical screening.
Cervical cancer

Cervical cancer happens when cells in the cervix grow in an uncontrolled way and build up to form a lump (also called a tumour). As the tumour grows, cells can eventually spread to other parts of the body and become life-threatening.

Your cervix is the lowest part of your uterus (or womb), and it is found at the top of your vagina.

Diagram showing the female reproductive system. The cervix is at the top of the vagina.

HPV and cervical cancer

Nearly all cervical cancers are caused by a virus called human papillomavirus (HPV).

HPV is very common. Most people will get the virus at some point in their life. It is spread through close skin to skin contact during any type of sexual activity with a man or woman. HPV can stay in the body for many years. It can stay at very low or undetectable levels and not cause any problems. This means an HPV infection may have come from a partner a long time ago.

There are many different types of HPV, but only some high-risk types can lead to cancer. The types of HPV that cause cervical cancer do not cause any symptoms. In most cases, your immune system can get rid of the virus without you ever knowing you had it. But sometimes, HPV can cause cells in your cervix to become abnormal.

Your body can usually get rid of the abnormal cells and your cervix returns to normal. But sometimes this does not happen, and the abnormal cells can go on to develop into cancer.

What affects your chances of getting cervical cancer

Having cervical screening lowers your chances of getting cervical cancer. Screening finds abnormal cells so they can be removed before they become cancer.

HPV is found on the skin around the whole genital area and can be spread through any type of sexual activity. This means that condoms or dental dams can help prevent infection, but they do
not provide total protection from HPV.

Smoking increases the risk of cervical cancer because it makes it harder for your body to get rid of HPV infections. Information about stopping smoking is available at www.nhs.uk/smokefree

The HPV vaccination protects against the types of high-risk HPV that cause most cervical cancers. If you have had the HPV vaccination you will still need to consider having cervical screening when you are invited. This is to check for other high-risk HPV types that can lead to cervical cancer.

Having a family history of cervical cancer does not affect your chances of developing cervical cancer.

How cervical screening works

Cervical screening is not a test for cancer. It looks for abnormal cells in the cervix. Abnormal cells can develop into cancer if left untreated.

The test involves using a soft brush to take a small sample of cells from the surface of your cervix. The sample is put into a small plastic container and sent to a laboratory. It is tested for the types of HPV that can cause cervical cancer. If you have a negative result for the most common types of HPV that cause cervical cancer, your risk of cervical cancer is very low and there is no need to check for abnormal cells even if you have had these in the past.

If you have a positive result for HPV we will check the sample for abnormal cells. Abnormal cells are not cancer, but they could develop into cancer if left untreated.

As a next step we may offer you another examination (called a colposcopy) to look at your cervix more closely. If we find abnormal cells during colposcopy we may suggest you have the cells removed. This is how screening can prevent cervical cancer.

No screening test is 100% effective. In cervical screening this is because:

- an HPV infection or abnormal cells can sometimes be missed (a ‘false negative’ result)
- abnormal cells can develop and turn into cancer in between screening tests
- there is a small chance that a result says abnormal cells are found when the cervix is normal (a ‘false positive’ result)

If screening does not find abnormal cells this does not guarantee that you do not have them, or that they will never develop in the future.

Having cervical screening

Before your appointment

Cervical screening is usually carried out by a female nurse or doctor. If you want to make sure a woman carries out your test, you can ask for this when you make your appointment.

Your appointment should be on a day when you are not having a period. If you don’t have periods, you can be screened at any time.

Please do not use any vaginal medications, lubricants or creams in the 2 days before you have your test because they can affect the results.
Please talk to your nurse or doctor if you:

- are pregnant
- have had a hysterectomy
- think it would be difficult for you to have the test

You can speak to your nurse or doctor if you are nervous about screening. They can talk through any questions or concerns you have. If you decide to go ahead with screening, they can make arrangements to help you feel more comfortable.

At your appointment
The actual test only takes 1 to 2 minutes. The whole appointment usually takes about 10 minutes.

The nurse or doctor will ask you to undress from your waist down (or just remove your underwear if you are wearing a loose skirt) and lie on a bed with your knees bent and apart. You will have a paper sheet or towel to cover your stomach and hips.

They will put a device called a speculum into your vagina and open it gently. This allows them to see your cervix. The speculum is usually made of plastic and a new one is used for each screening test. The nurse or doctor then uses a small soft brush to take a sample of cells from the surface of your cervix. You might feel some discomfort, but this should go away quickly. If it feels painful, tell the nurse or doctor and they will try to make it more comfortable for you.

You are in control of your screening appointment, and you can ask to stop at any time.

Cervical screening results

The nurse or doctor will tell you when you can expect your results letter. There are 4 possible results.

1. HPV negative
   An HPV negative result means we will not do any further tests. This result means it is highly unlikely that you will have any abnormal cervical cells. Even if you did, it would be extremely unlikely that they would cause a problem. We will simply call you back for screening again in 3 or 5 years’ time (depending on your age).
2. HPV positive: no abnormal cells
If your sample is HPV positive we also test it for abnormal cervical cells. If none are found, your result will say you have HPV, but no abnormal cells. We will ask you to come for screening again sooner than usual (your result letter will explain when). This is so we can check if your immune system has got rid of the HPV (this happens in most cases).

3. HPV positive: abnormal cells found
There are several ‘grades’ of abnormal cells as some are more serious than others. Your result letter will explain what your results mean. If you have HPV and any grade of abnormal cervical cells we will refer you for colposcopy (see page 11). We will send you our information leaflet ‘NHS cervical screening – having a colposcopy’.

4. Inadequate result
Occasionally a sample may be called ‘inadequate’. This may be due to a technical problem, for example if the laboratory cannot get an HPV test result from your sample or cannot see if abnormal cells are present or not. If you have an inadequate test, we will ask you to have cervical screening again in 3 months’ time. We wait so that there are enough cells again to get a sample from.
What happens to samples after screening
Depending on your screening result your screening sample may be kept by the laboratory for at least 10 years. Your result will be kept on a national secure computer system so that the NHS can compare your latest result with ones you have had before.

Find out how Public Health England and the NHS use and protect your screening information at: www.gov.uk/phe/screening-data

Colposcopy
Colposcopy is usually carried out in a hospital clinic. A specialist will take a close look at your cervix using a magnifying lens with a light (a ‘colposcope’). They may take a small tissue sample (a biopsy) to check any areas of your cervix which look unusual. If the abnormal cells are serious, you may need treatment to remove them. This helps prevent cervical cancer.

You can read more about colposcopy in our leaflet at: www.gov.uk/government/publications/cervical-screening-colposcopy

Possible benefits and risks of cervical screening
It is your choice whether to have cervical screening. To help you decide, we’ve included information on the possible benefits and risks.

Possible benefits
Cervical screening helps prevent cervical cancer. Cervical screening saves thousands of lives from cervical cancer every year in the UK.1,2

Possible risks
The main risks of cervical screening come from removing abnormal cells during a colposcopy and not from the screening test itself. Removing abnormal cells can sometimes cause bleeding or an infection, and it can also affect future pregnancies. Women who get pregnant after having abnormal cells removed are not at increased risk of having their baby early if they have standard treatment. If more cervical tissue needs to be removed, women are slightly more likely to have their baby 1 to 2 months early. This may affect around 16% of women (16 in 100) who have this more extensive treatment and then have a baby.4

Not everyone who has abnormal cells removed would have gone on to develop cervical cancer. We offer treatment to everyone with serious abnormal cells because it is not possible to tell who will and who will not develop cervical cancer.
Symptoms of cervical cancer
Cancer can start to develop between your regular screening tests. It is important to look out for anything that is unusual for you, especially:

- bleeding between your periods, during or after sex, or after the menopause
- changes to vaginal discharge

**Screening is not a test for investigating symptoms.**

If you have any of these changes, do not wait for your next cervical screening appointment. See your GP as soon as possible. Your GP can examine you and refer you to a gynaecology clinic if necessary.

Usually these symptoms will not mean you have cancer. But if you are found to have cancer, getting it diagnosed and treated early can mean you are more likely to survive.

More information and support
If you have any questions about cervical screening, you can talk to your GP, practice nurse or visit a local contraceptive/sexual health clinic.

There is more information about cervical screening at: www.nhs.uk/cervical

For more information about colposcopy, see our leaflet at: www.gov.uk/government/publications/cervical-screening-colposcopy

To opt out of screening, see: www.gov.uk/phe/screening-opt-out
References


An HTML version of this leaflet is available. You can view and download it in large print, and use a screen reader for an audio version. Visit: www.gov.uk/phe/cervical-screening-leaflet
We can provide a braille version. Email: phe.screeninghelpdesk@nhs.net

Image credit(s)
cover image: Shutterstock/Rawpixel.com
Page 8: Jo’s Cervical Cancer Trust

You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. Where we have identified any third party copyright information you will need to obtain permission from the copyright holders concerned.

PH&E publications gateway number: GW-339

First published: June 2019
This version: February 2020
Review due: June 2022

Leaflet reference: CSP14 PN334800 © Crown copyright 2019

Public Health England supports the UN Sustainable Development Goals
Emotional response to testing positive for human papillomavirus at cervical cancer screening: a mixed method systematic review with meta-analysis

Emily McBride, Ovidiu Tatar, Zeev Rosberger, Lauren Rockliffe, Laura M. Marlow, Roma Moss-Morris, Navdeep Kaur, Kristina Wade and Jo Waller

ABSTRACT

Tens of millions of women every year test positive for human papillomavirus (HPV) at routine cervical screening. We performed a mixed-methods systematic review using a results-based convergent design to provide the first comprehensive overview of emotional response to testing positive for HPV (HPV+). We mapped our findings using the cognitive behavioural framework. Six electronic databases were searched from inception to 09-Nov-2019 and 33 papers were included. Random-effects meta-analyses revealed that HPV+ women with abnormal or normal cytology displayed higher short-term anxiety than those with normal results (MD on State-Trait Anxiety Inventory = 7.6, 95% CI: 4.59–10.60 and MD = 6.33, CI: 3.25–11.35, respectively); there were no long-term differences. Psychological distress (general/sexual/test-specific) was higher in HPV+ women with abnormal cytology in the short-term and long-term (SMD = 0.63, CI: 0.22–1.03 and SMD = 0.42, CI: 0.03–0.80, respectively). Testing HPV+ was also related to disgust/shame, surprise and fear about cancer. Broadly, adverse response related to eight cognitive constructs (low control, confusion, cancer-related concerns, relationship concerns, sexual concerns, uncertainty, stigma, and low trust) and six behavioural constructs (relationship problems, social impact, non-disclosure of results, idiosyncratic prevention, indirect clinical interaction, changes to sexual practice). Almost exclusive use of observational and qualitative designs limited inferences of causality and conclusions regarding clinical significance.

CONTACT Emily McBride (e.mcbride@ucl.ac.uk) https://uk.linkedin.com/in/emily-mcbride-108152564 @EmilyMcBride

ARTICLE HISTORY

Received 20 August 2019
Accepted 24 April 2020

KEYWORDS

Human papillomavirus (HPV); cervical cancer screening; emotion; psychological; mixed method review; meta-analysis

Over 370,000 new cases of cervical cancer are diagnosed every year worldwide, virtually all caused by persistent infection with high-risk human papillomavirus (HPV), a common sexually transmitted infection (STI) (Bruni et al., 2019). Integration of HPV testing into cervical screening is now recommended by major health organisations due to its superior sensitivity for the detection of high-grade precancerous lesions.
lesions compared with cytology-based testing alone (where cervical cells are microscopically examined for abnormalities (Australian Government, 2017; US Preventive Services Task Force, 2018; von Karsa et al, 2015)). Using HPV as the primary (first) test in cervical screening is considered to be the gold standard in many high-income countries and means that all women who attend screening receive an HPV-positive or negative result (Cuzick et al, 2006; Kitchener et al, 2009, 2014; Tebojol et al, 2019). The Netherlands and Australia were first to fully implement HPV primary screening in 2017 (Australian Government, 2017; Aitken et al, 2019), and several high-income countries are in the planning, piloting, or early implementation stages (e.g., Sweden, Italy, UK, Norway, New Zealand) (National Screening Unit New Zealand Government, 2017; Rebojol et al, 2018; Wentzensen et al, 2017). Other middle- and high-income countries, which have not yet switched to HPV primary screening, use HPV testing to triage borderline or low-grade abnormal cytology (Arbyn et al, 2006). Globally tens-of-millions of women every year find out they are HPV-positive at their routine cervical screen.

Over the last few decades, the psychological impact of testing positive for HPV has attracted substantial research focus with many studies assessing emotional response, e.g., anxiety, concern about result, or worry about cancer. The rationale for research in this domain has usually been orientated towards attempts to mitigate unnecessary adverse psychological consequences (i.e., improve mental health outcomes) and to maximise screening re-attendance or help-seeking (i.e., improve behavioural outcomes). Given that cervical screening is usually a population-level intervention, assuming that HPV-diagnosis leads to even small percentages of women experiencing adverse effects, this translates to very large numbers experiencing negative psychological and/or behavioural sequelae.

Hence efforts to monitor emotional response have been prioritised and commissioned through some national health bodies (Andreason et al, 2019; Maissi et al, 2004; McBride et al, 2016). Despite research in this area however, to date, heterogeneity in local cervical screening protocols (e.g., screening tests used, order of tests) and study designs have meant that some major studies have produced mixed findings. For example, a large cross-sectional study found short-term anxiety and distress in women testing positive for HPV with abnormal cytology (Maissi et al, 2004, 2005). Qualitative research has also produced findings of anxiety, stigma, stress and concern about sexual relationships following positive HPV results (McCaffery et al, 2006; Waller, McCaffery, et al, 2007). However, a large randomised controlled trial which considered differences in anxiety and distress between women who were told their HPV-positive result vs. not told their result as part of routine screening practice found no overall differences (Kitchener et al, 2008). A qualitative study also reported indifference as a theme following HPV-positive results (O’Connor et al, 2014).

In addition to mixed findings, some psychological studies have adopted methodological designs using hypothetical scenarios (Brown et al, 2007; Kwan et al, 2010; Lee et al, 2007; Waller et al, 2009; Waller, McCaffery, et al, 2007). Since these studies ask participants to imagine their emotional response to testing positive for HPV, they lack ecological validity. Other studies have combined women with oncogenic and non-oncogenic HPV types, e.g., including women with genital warts (Graziotin & Serafin, 2009), or including women receiving treatment for precancerous cervical changes (O’Connor et al, 2013, 2016). Again, this has meant that emotional response specific to testing positive for HPV at routine cervical screening has been difficult to isolate.

Further, attempts to explain emotional response to HPV have been largely atheoretical to date. One study considered the role of illness representations and emotion in women with abnormal cervical screening results (without explicit HPV diagnosis), and found that emotion was explained by independent effects of a combination of demographic, cognitive and emotional representations (Hagger & Orbell, 2006). Leventhal’s Common Sense Model (Leventhal et al, 2016) and Cognitive Behavioural Theory (Westbrook et al, 2011) have also been used by few studies to guide HPV-related interview or survey questions, reportedly proving useful frameworks (Maggino et al, 2007; Marlow et al, 2009). Speculatively drawing from theories and models of emotional adjustment, it is possible that appraisal and representations related to HPV diagnosis (e.g., sexually transmitted cause, lack of cure, perceived seriousness or control) (Folkman et al, 1988; Leventhal et al, 2016), concerns about cervical screening or treatment (Phillips et al, 2014), cultural/social norms and access to social support.
(Bandura, 1991), and coping or attachment style (Mikulincer & Shaver, 2008; Pietromonaco et al., 2013) may be important. Cognitive Behavioural Theory which underpins cognitive behavioural therapy (CBT), in particular, may act as a promising theoretical framework for provisionally mapping emotional responses and their related constructs. The CBT model encompasses interacting dynamics between emotions, cognitions and behaviours, and has been applied widely across health domains to identify overarching areas of importance for specific conditions (David et al., 2018). Whilst researchers working on psychological aspects of HPV are yet to establish a cogent theoretical framework, the CBT model may help organise relevant psychological responses and isolate areas for further concentrated theoretical developments. This is particularly relevant given that adverse emotional response to testing positive for HPV is likely linked to several other (potentially interacting) cognitive and behavioural outcomes (e.g., sexual relationships, health literacy, understanding of result). Research, however, is needed to establish which theoretical constructs are most relevant.

As it stands, there is a body of research on emotional response to HPV, but a lack of conclusive evidence which is useful for cervical screening programmes or informing theoretical advancement. Despite imminent roll-out of HPV primary screening in several countries and significant international interest, there has been no review or synthesis of the literature on emotional response. This mixed methods systematic review aimed to provide a comprehensive overview of the quantitative and qualitative literature, guided by the research questions: how do women emotionally respond to testing positive for HPV at cervical screening; and what influences emotional response to testing positive for HPV at cervical screening? Since emotions interact with, and are dependent upon, other biopsychosocial systems, the cognitive behavioural model (Westbrook et al., 2011) was also adopted to provide an overarching theoretical framework, which mapped the systematic review findings for emotional response into related themes of cognitions and behaviours. This helped formulate a preliminary working model of emotional response to HPV, in an otherwise predominantly atheoretical domain.

Method

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) (See Supplementary File 1). The protocol was registered on PROSPERO on 15.08.2018 (reg: CRD42018105134).

Search strategy

Medline, Embase, PsycINFO, CINAHL, Global Health and Web of Science were searched to retrieve articles between 01.01.1980 and 09.11.2019. The year coverage is representative of the earliest available database record until the date the last search was performed. The search concepts (HPV, cervical cancer, screening, psychological) were agreed a priori and informed by breaking down the research questions. The search strategy was developed for Medline, then validated and adapted for the other databases by an experienced librarian. Additional papers were identified by screening reference lists of included papers and searching OpenGrey (www.opengrey.eu). See Supplementary File 2 for the full list of search terms.

Design

We used a results-based convergent synthesis design, where the qualitative and quantitative evidence was analysed and presented separately then integrated by juxtaposing the findings in a matrix table (Hong et al., 2017; Playe & Hong, 2014). For the purposes of this review, the integration synthesis was defined as refining, comparing and contrasting emotion-focused themes across all studies. Analysis of quantitative data estimated the relevance and representativeness of emotional responses by providing estimates of effect sizes and associations between testing HPV-positive
Figure 1. Overview of the results-based convergent synthesis design.

and emotional outcomes; and analysis of qualitative data provided in-depth explanations for emotional response. See Figure 1 for an overview of this design.

Eligibility

The titles, abstracts and full-text papers generated from the searches met the following inclusion criteria:

1. Adult population (18+) diagnosed with HPV in the context of cervical cancer screening.
2. At least one emotional outcome explicitly measured, explored, or emerged.
3. Quantitative, qualitative, or mixed-methods design.
4. Article written in English, French, or German.

Studies were excluded if they:

1. Employed a hypothetical scenario design.
2. Included participants who had cervical cancer or were receiving treatment for cervical lesions.
3. Primarily focused on HPV knowledge without linking to an emotional outcome.
4. Where data on HPV-positive results could not be extracted (e.g., grouped analysis combining test result groups).
Definition of emotion

Currently, there is no scientific consensus on an agreed definition of emotion. Popular theories, for example Plutchik's psycho-evolutionary theory of emotion (Plutchik, 2001), tend to be relatively consistent in how they describe primary emotions such as sadness, fear, happiness, disgust, surprise, anticipation, trust and anger. However, complex secondary and tertiary emotions, and their fusion with cognitions and physiological or behavioural cues, remain strongly debated across and within disciplines. Therefore, for the purposes of this review, we defined categories of emotion, and related cognitions and behaviours, based on a combination of the American Psychological Association (APA) published definitions (www.dictionary.apa.org/emotion), validated outcomes reported in papers, and the review team's interpretation in the coding and analysis stages.

Selection process

Extracted studies were included/excluded as part of a two-step screening process based on title/abstract and full text. All titles and abstracts were screened by two reviewers (EM, OT or KW). Abstracts that passed the initial screen progressed to full-text review. Each full-text paper was independently assessed by two reviewers (EM, LR, OT) and discrepancies were resolved through independent full-text assessment from a third reviewer (JWM), followed by discussion until consensus was reached. Agreement between reviewers prior to consensus was good (Kappa = 0.701). In some cases, authors of identified papers were contacted to request additional information where eligibility was not clear.

Data extraction

Data extraction was performed independently by two reviewers using customised Excel templates (EM, OT). Each reviewer's data extractions were compared and integrated to achieve the most comprehensive version. The information extracted across papers included: title, year published, study aims, sample size (total and by results group), population, study setting, participants (age, ethnicity, marital status and education), design, HPV and cytology results, outcome measures and analysis (where relevant), and main findings.

Data synthesis and meta-analysis

The data synthesis was conducted in three stages by two reviewers independently (EM, OT) with disagreements resolved through discussion or inclusion of a third reviewer until consensus was achieved (JWM or ZR) (Thomas et al., 2004).

Firstly, for quantitative studies, we assessed study designs, outcome measures and available data for inclusion in meta-analyses. We aimed to compare emotional responses in HPV-positive groups with a control group (e.g., HPV negative and/or normal cytology). Out of seventeen quantitative studies identified, six studies did not qualify for meta-analysis because their observational design did not include a comparison (control) group. A further three studies did not report data in a format suitable for inclusion in meta-analysis and corresponding authors were contacted in attempt to retrieve data; one author no longer had access to the data and two authors did not respond. Non-validated measures (e.g., single-item questions) were also excluded from meta-analyses. From the available data, we were able to perform three meta-analyses for the outcome ‘state-anxiety’, and two meta-analyses representing psychological distress (by analysing outcome measures of general distress, sexual distress and test-specific distress together). We split the meta-analyses by time point (result notification ≤ 2 months [short-term] vs. > 2 months [long-term]) and result group (HPV-positive with abnormal or normal cytology, vs. control). Statistical analyses were performed using RevMan Manager, version 5.2 (RevMan 5, 2012). Random effects models were chosen to account for heterogeneity in populations
and design. Unstandardised mean differences with 95% confidence intervals were reported for anxiety as the included studies used the same outcome measure (STAI (Marteau & Bekker, 1992; Spielberger, 1983)). Standardised mean differences with 95% confidence intervals were reported for psychological distress as outcome measures differed between studies. Tests of homogeneity were conducted using the $I^2$ statistic (Borenstein et al., 2009). Low heterogeneity was depicted by $I^2$ values of <25%, moderate heterogeneity as 50% and high heterogeneity as >75% (Higgins et al., 2003). Tau-squared ($\tau^2$) was reported to indicate estimates of between-study variance. We were unable to conduct meta-analyses for other emotional outcomes due to lack of data. See Supplementary File 3 for the raw data extracted for inclusion in meta-analyses.

Secondly, we synthesised all quantitative findings (including measures which could not be meta-analysed) by coding each measured outcome into themes of emotion, with related cognitive and behavioural themes also coded where relevant. Similarly for qualitative studies, the data were copied verbatim and thematic analysis was performed using descriptive and analytical coding to identify emotion themes, again with related cognitive and behavioural themes coded where relevant (Thomas & Harden, 2008).

Thirdly, to integrate the findings of the two syntheses (integrated synthesis stage), we refined the themes of emotion across the quantitative and qualitative studies. A conceptual matrix was then constructed by mapping the emotion themes by study, to allow for comparisons and contrasts. Narrative overviews of the quantitative and qualitative findings for each emotion-focused theme are presented, with meta-analysis findings integrated.

Cognitive behavioural framework – mapping interacting systems

Following the data synthesis stage, the cognitive behavioural model was adopted to provide an overarching and preliminary theoretical framework to map the findings into constructs of emotions, with related cognitions and behaviours (Westbrook et al., 2011). This helped address our second aim of understanding what influences emotional response to HPV. The cognitive behavioural model, which underpins cognitive-behavioural therapy, was chosen because it has a strong evidence-base for explaining emotional response across psychology and health domains (Dobson, 2013; Hofmann et al., 2013). We used the model in its simplest form as a triad, to illustrate how emotions (feelings), cognitions (thoughts, beliefs, attitudes) and behaviours (actions) may interact to influence one another. In practice, this meant that alongside the primary thematic analysis phase, the qualitative verbatim data and quantitative outcome measures were also coded to represent constructs of cognitions and/or behaviours. These thematic constructs where then illustratively mapped onto the triad model of the cognitive behavioural framework. Two reviewers independently coded and analysed all data (EM, OT), with disagreements resolved through discussion or inclusion of a third reviewer until consensus was achieved (JW or ZH).

Quality assessment (risk of bias)

The Mixed Methods Appraisal Tool v2018 (MMAT) is a critical appraisal tool that has been specially developed for performing quality assessments in mixed method systematic reviews, and was used to assess the methodological quality of the included studies and potential for bias (Hong et al., 2018). The MMAT has independent sets of quality criteria to guide judgements for qualitative studies, randomised controlled studies, non-randomised studies, observational descriptive studies and mixed-methods studies. The quality score for each reviewed study was based on criteria specific to the study design, which included five methodological domains and was calculated as an overall percentage. Mixed-methods studies were assessed using the mixed-methods criteria as well as the separate quantitative and qualitative criteria; their quality score could not exceed the weakest component. We intended for the MMAT to be used for illustrative and descriptive purposes and did not weight findings based on quality score alone. Rather, each study was assessed
independently on its merits, limitations and overall design in the cervical screening context by two reviewers (EM, LR, OT), with discrepancies discussed and resolved with a third reviewer (JW).

**Rigour**

Rigour was maintained by using a comprehensive search strategy along with documentation of eligibility decisions, which ensured descriptive validity (accuracy of data) (Sandelowski et al., 2006). Interpretive validity was achieved through use of at least two independent reviewers (EM, OT, LR) in the data extraction phase to create a comprehensive database and perform of quality assessments (Thomas & Harden, 2008). Following each stage of the data synthesis, two reviewers (EM, OT) plus a third reviewer (JW, ZR) discussed the thematic findings and resolved disagreements to help maintain theoretical validity (reliability of data interpretation) (Sandelowski et al., 2006). Pragmatic validity (efficacy and transferability of findings) was improved by inclusion of study characteristic tables providing the context around the studies, allowing readers to judge the usefulness of findings (Thomas & Harden, 2008).

**Results**

**Search results**

The database searches yielded 15,792 papers, with 9,343 titles and abstracts screened after removal of duplicates. Ninety-three papers were fully screened and 33 papers, representing 32 studies, met

![Flowchart](image)

**Figure 2.** PRISMA Flowchart: overview of searches and selection process. ⁴Phase 1 exclusion reasons for titles and abstracts: (1) not population of interest; (2) not outcomes of interest (e.g., HPV attitudes or knowledge without emotional outcome); (3) not empirical study; (4) no abstract; (5) HPV not in the context of cancer screening; (6) no clinical diagnosis of HPV (e.g., hypothetical scenario design); (7) only HPV vaccine related. ⁵Phase 2 exclusion criteria described in the eligibility section used for full text articles.
the selection criteria. See Figure 2 for a Prisma Diagram providing an overview of the searches and selection process.

**Study characteristics**

Seventeen papers were quantitative studies (Nay et al., 2019; Andreassen et al., 2019; Ferenidou et al., 2012; Garces-Palacio et al., 2019; Hsu et al., 2018; Kitchener et al., 2008; Kwan et al., 2011; Maggino et al., 2007; Massi et al., 2004, 2005; McBride et al., 2020; McCaffrey et al., 2004; Nagele et al., 2019; Ng et al., 2018; Rodriguez et al., 2019; Wang et al., 2010; Wang et al., 2011), 15 were qualitative (Barrena-Clavijo et al., 2015; Barreno et al., 2016; Bertram & Magnusson, 2008; Head et al., 2012; Kosenko et al., 2012; Lin et al., 2011; Linde et al., 2013; McCaffrey & Irwig, 2005; McCaffrey et al., 2006; McCurdy et al., 2011; O'Connor et al., 2014; Perin et al., 2006; Tiro et al., 2019; Waller, McCaffrey, et al., 2007; Wyndham-West et al., 2018) and one was mixed-methods (Daley et al., 2010). A total of 12,789 women aged between 18 and 65 participated in twenty studies (n=12,244 quantitative; n=545 qualitative), of whom 4,305 were reported as having tested positive for HPV (n=3,874 quantitative; n=431 qualitative). Seven studies were conducted in the UK, seven in the USA, six in China, two in Colombia and the remaining eleven in Australia, Austria, Brazil, Canada, Greece, Italy, Ireland, Mexico, Norway, Tanzania and Turkey. Twenty-one studies reported level of participant education: six used samples predominately educated to tertiary-level or above, and four primary-level or below. Fourteen studies reported a predominantly white ethnicity sample, and others predominantly African and Asian. Nearly all studies recruited women through clinical settings (e.g., hospitals, primary care), except two which used public advertisements and social media. Most studies ascertained diagnosis of HPV using clinical records; however, some relied on participant self-report. Time between participants receiving their HPV result and recruitment was not reported in the majority of studies (especially qualitative); but in those which did, the time from diagnosis ranged from shortly after receiving result (notification-2 months) to 2 years after result, with two outliers reporting 4.8 and 5 years. There were also variations in the combinations of HPV-positive and cytology result groups between studies: most used HPV-positive with abnormal cytology (any grade or mixed) and some used HPV with normal cytology, HPV with atypical squamous cells of undetermined significance, or HPV alone (no cytology test).

Observational (cross-sectional, prospective longitudinal, or cohort) designs were used in most quantitative studies (thirteen out of seventeen). Four quantitative studies used a randomised controlled design (Garces-Palacio et al., 2019; Kitchener et al., 2008; Maggino et al., 2007; Ng et al., 2018), but only one directly tested and reported differences in emotion between result groups (Kitchener et al., 2008). The same RCT study also included additional analyses on the observational findings from women in the study arm where participants were informed about their HPV results. All quantitative studies included at least one outcome with a core emotional component and most used widely-validated, validated scales; though some used single-item or non-validated scales and the mixed-methods study measured emotion descriptively. The most common outcomes measured were state anxiety, sexual distress, test-specific distress, general distress, depression, fear and shame/disgust. Fourteen of the qualitative studies conducted interviews and one conducted focus groups (Barrena-Clavijo et al., 2015); all qualitative studies described at least one emotional theme, mainly related to anxiety, test-specific distress, sexual distress, surprise and confusion, fear, shame and disgust, sadness, relief and indifference.

Summaries presenting descriptive overview of the studies and quality appraisal scores are presented in Tables 1 and 2.

**Quality assessment**

Overall, MMAT quality scores ranged from 40% to 100%. Qualitative studies scored highest for quality (median=100%, range 40–100%), followed by quantitative studies (median=60%, range 40–100%), and the mixed methods study (40%). The main reasons for quality deductions in the quantitative studies were non-complete reporting of data and not using appropriate measures; and in qualitative
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Total n</th>
<th>HPV+ n</th>
<th>Cytology</th>
<th>Population and setting</th>
<th>Study design</th>
<th>Time point</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alay et al. (2019)</td>
<td>Turkey</td>
<td>80</td>
<td>19 (hrHPV); 23 (hrHPV)</td>
<td>Normal; Abnormal</td>
<td>≥30 years old, referred to a gynecology outpatient clinic; ongoing with a HPV infection by the community-based cervical cancer screening program.</td>
<td>Prospective longitudinal</td>
<td>Baseline (before result) and 2-months later.</td>
<td>60%</td>
</tr>
<tr>
<td>Andreasen et al. (2019)</td>
<td>Norway</td>
<td>487</td>
<td>175; 84; 521 cytology arm</td>
<td>Normal; Abnormal (any grade); Abnormal (ASCUS and low grade)</td>
<td>34–69 years living in one of the four implementation counties taking part in the NCCSF project which trialed two methods of HPV-based screening (primary HPV vs. primary cytology testing).</td>
<td>Cross-sectional (embedded within a trial)</td>
<td>Ranging between 4 and 24 months after result.</td>
<td>100%</td>
</tr>
<tr>
<td>Daley et al. (2010)</td>
<td>USA</td>
<td>154</td>
<td>154</td>
<td>Abnormal (any grade)</td>
<td>18–45 years, recruited through a student health service and five parenthood planning clinics.</td>
<td>Mixed-methods: cross-sectional</td>
<td>Not reported.</td>
<td>40%</td>
</tr>
<tr>
<td>Ferencidou et al. (2012)</td>
<td>Greece</td>
<td>51</td>
<td>51</td>
<td>Not reported.</td>
<td>21–68 years, recruited through a gynecological outpatient clinic in ‘Areteion’ Hospital, Athens during 2008–2009.</td>
<td>Cross-sectional</td>
<td>Not reported.</td>
<td>60%</td>
</tr>
<tr>
<td>Garcia-Palacios et al. (2019)</td>
<td>Colombia</td>
<td>675</td>
<td>50</td>
<td>ASCUS</td>
<td>20–69 years old, with a first time Atypical Squamous Cells of Undetermined Significance (ASCUS) cytology result. This study was nested within the larger trial ‘Evaluating Strategies for Optimal Clinical Management of Women with Atypical Squamous Cells of Undetermined Significance’ (ASCUS-COL), conducted between 2011 and 2016 in the city of Medellín.</td>
<td>Nested within observational arm of a larger RCT.</td>
<td>Baseline (before result), shortly after result and 12-months later.</td>
<td>40%</td>
</tr>
<tr>
<td>Hsu et al. (2018)</td>
<td>Taiwan, China</td>
<td>70</td>
<td>21; 45</td>
<td>Normal; Abnormal</td>
<td>20–65 years old attending a gynecological clinic in southern Taiwan for their first follow-up visit after diagnosis.</td>
<td>Prospective longitudinal</td>
<td>One month, 6-months and 12-months after result.</td>
<td>80%</td>
</tr>
<tr>
<td>Kitchener et al. (2008)</td>
<td>UK</td>
<td>604</td>
<td>105; 71; 417</td>
<td>Normal; Abnormal (mild/ borderline); Abnormal (mild/ borderline)</td>
<td>20–64 years, participated in ARTISTIC: a RCT to determine the effectiveness of HPV testing in primary cytology screening.</td>
<td>1. RCT; 2. Cross-sectional (revealed arm).</td>
<td>Approx. 2 weeks after result.</td>
<td>100%</td>
</tr>
<tr>
<td>Kwan et al. (2011)</td>
<td>Hong Kong, China</td>
<td>299</td>
<td>157</td>
<td>ASCUS</td>
<td>Mean age across groups of 36.8, recruited via routine cervical screening at one of five community health clinics of the Family Planning Association of Hong Kong.</td>
<td>Prospective cross-sectional</td>
<td>Baseline (result notification) and 6 months after result.</td>
<td>100%</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Total n</th>
<th>HPV+ n</th>
<th>Cytology</th>
<th>Population and setting</th>
<th>Study design</th>
<th>Time point</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maggino et al.</td>
<td>Italy</td>
<td>72</td>
<td>36</td>
<td>Not reported</td>
<td>20–45 years, during periodical check-up at obstetrics and gynaecology clinic.</td>
<td>RCT</td>
<td>Not reported</td>
<td>40%</td>
</tr>
<tr>
<td>Maisi et al.</td>
<td>UK</td>
<td>1376</td>
<td>536</td>
<td>Abnormal (mild/borderline)</td>
<td>Mean age across groups of 37.6, recruited through the English pilot study of liquid-based cytology and HPV testing (clinics).</td>
<td>Cross-sectional</td>
<td>Within 4 weeks of result.</td>
<td>100%</td>
</tr>
<tr>
<td>Maisi et al.</td>
<td>UK</td>
<td>1011</td>
<td>369</td>
<td>Abnormal (mild/borderline)</td>
<td>Mean age across groups of 37.9, initially recruited through the English pilot study of liquid-based cytology and HPV testing (clinics).</td>
<td>Cross-sectional</td>
<td>6-months after result</td>
<td>80%</td>
</tr>
<tr>
<td>McBride et al.</td>
<td>UK</td>
<td>1127</td>
<td>258;</td>
<td>Normal; Abnormal</td>
<td>24–65 years, who had attended screening at one of five sites piloting HPV primary screening in England, including a control group with normal cytology who were not tested for HPV.</td>
<td>Cross-sectional</td>
<td>Mailed within 1 month after result.</td>
<td>100%</td>
</tr>
<tr>
<td>McBride et al.</td>
<td>UK</td>
<td>428</td>
<td>23</td>
<td>Abnormal or Unsatisfactory</td>
<td>20–61 years, attending a National Health Service well-woman clinic in central London for routine conventional cervical screening.</td>
<td>Cross-sectional</td>
<td>Within one week of results.</td>
<td>60%</td>
</tr>
<tr>
<td>Nagele et al.</td>
<td>Austria</td>
<td>209</td>
<td>82</td>
<td>Normal or Unsatisfactory</td>
<td>Mean age of 47.5, recruited from a university-based colposcopy clinic after referral for evaluation for suspect precancerous genital lesions.</td>
<td>Prospective cohort</td>
<td>Baseline (not defined), 6-months and 12-months.</td>
<td>60%</td>
</tr>
<tr>
<td>Ng et al.</td>
<td>Hong Kong, China</td>
<td>121</td>
<td>121</td>
<td>Normal</td>
<td>Mean age of 47.5, recruited from clinics in another RCT on primary screening in Hong Kong (COCY study).</td>
<td>RCT</td>
<td>Not reported.</td>
<td>60%</td>
</tr>
<tr>
<td>Rodríguez et al.</td>
<td>Mexico</td>
<td>201</td>
<td>201</td>
<td>Not reported</td>
<td>≥18 years with an HPV diagnosis for at least 12 months, recruited via mass media (radio, television and social networks).</td>
<td>Cross-sectional</td>
<td>At least 1 year after result (Mean = 1.85 years)</td>
<td>60%</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>Taiwan, China</td>
<td>249</td>
<td>44</td>
<td>Abnormal (any grade)</td>
<td>18–35 years, recruited through three hospitals in Taiwan.</td>
<td>Cross-sectional</td>
<td>Within 3-months of result.</td>
<td>60%</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>China</td>
<td>2605</td>
<td>179</td>
<td>Abnormal (any grade)</td>
<td>18–65 years, recruited through multicentre hospitals.</td>
<td>Cross-sectional</td>
<td>Within 3-months of result.</td>
<td>80%</td>
</tr>
</tbody>
</table>

* hHPV = high-risk HPV (type 16/18) extracted from available data. ASCUS = atypical squamous cells of undetermined significance.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Country</th>
<th>Total n</th>
<th>HPV+ n</th>
<th>Cytology</th>
<th>Population and setting</th>
<th>Study design</th>
<th>Time point</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrera-Clavijo et al.</td>
<td>Colombia</td>
<td>93</td>
<td>55</td>
<td>Not reported</td>
<td>30–55 years, participating in the Colombian HPV testing screening pilot.</td>
<td>Focus groups</td>
<td>Not reported</td>
<td>80%</td>
</tr>
<tr>
<td>Barretto et al.</td>
<td>Brazil</td>
<td>14</td>
<td>14</td>
<td>No cytology test</td>
<td>20–42 years, attending a Specialised Medical Care Service (SAME).</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>60%</td>
</tr>
<tr>
<td>Bertram and Magnusson</td>
<td>USA</td>
<td>10</td>
<td>Not stated</td>
<td>Abnormal (mixed)</td>
<td>18–35 years, purposive sample of demographically diverse women attending one Women's Health outpatient clinic that typically serves a multiethnic, low-income population.</td>
<td>Semi-structured interviews</td>
<td>Within 5 years from test result</td>
<td>100%</td>
</tr>
<tr>
<td>Daley et al.</td>
<td>USA</td>
<td>52</td>
<td>52</td>
<td>Abnormal (any grade)</td>
<td>18–45 years, recruited through a student health service and five parenthood planning clinics.</td>
<td>Mixed-methods semi-structured interviews</td>
<td>Not reported</td>
<td>40%</td>
</tr>
<tr>
<td>Head et al.</td>
<td>USA</td>
<td>30</td>
<td>17; 5</td>
<td>Normal cytology; Abnormal cytology</td>
<td>Mean age of 27.8 years, attending for two clinical visits approximately 6 weeks apart.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>Kosenko et al.</td>
<td>USA</td>
<td>25</td>
<td>25</td>
<td>Not reported</td>
<td>19–56 years, recruited through advertisements posted across cities in southeastern USA and on social media.</td>
<td>Semi-structured interviews</td>
<td>Average of 4.8 years after HPV diagnosis</td>
<td>100%</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>Taiwan, China</td>
<td>20</td>
<td>20</td>
<td>Not reported</td>
<td>20–60 years, recruited using purposeful sampling through a gynaecology outpatient clinic in a university-based hospital.</td>
<td>Semi-structured interview</td>
<td>Not reported</td>
<td>40%</td>
</tr>
<tr>
<td>Linde et al.</td>
<td>Tanzania</td>
<td>15</td>
<td>15</td>
<td>Not reported</td>
<td>27–55 years, who had tested HPV-positive during a patient-initiated screening and been appointed for a follow-up screening 14 months later.</td>
<td>Semi-structured interview</td>
<td>At least 14 months after result.</td>
<td>100%</td>
</tr>
<tr>
<td>McCaffrey and Irwig</td>
<td>Australia</td>
<td>19</td>
<td>19</td>
<td>Abnormal (mixed)</td>
<td>53% &lt;35 years (47% ≥35 years), recruited through general practice, family planning clinics and specialist gynaecologists.</td>
<td>Unstructured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>McCaffrey et al.</td>
<td>UK</td>
<td>74</td>
<td>57</td>
<td>Abnormal and normal cytology</td>
<td>20–64 years, recruited through clinical trials of HPV testing and colposcopy clinics in Manchester and London.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>McCurdy et al.</td>
<td>USA</td>
<td>18</td>
<td>18</td>
<td>Abnormal (mixed)</td>
<td>21–45 years, who attended one of three clinics open to the general public in a medically underserved area in Cameron County, Texas.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>O'Connel et al.</td>
<td>Ireland</td>
<td>27</td>
<td>6</td>
<td>Abnormal (mixed)</td>
<td>26–61 years, recruited via colposcopy clinics in Ireland.</td>
<td>Semi-structured interviews</td>
<td>Within 6 months from HPV test</td>
<td>100%</td>
</tr>
<tr>
<td>Perrin et al.</td>
<td>USA</td>
<td>52</td>
<td>52</td>
<td>Abnormal (mixed)</td>
<td>18–44 years, recruited via three clinical sites in west central Florida – two Planned Parenthood clinics and the Student Health Service clinic at the University of South Florida (Tampa campus).</td>
<td>Semi-structured interviews</td>
<td>Within 1 week of HPV result</td>
<td>100%</td>
</tr>
<tr>
<td>Tiro et al.</td>
<td>USA</td>
<td>46</td>
<td>15 (HR HPV); 31 (other HPV type)</td>
<td>Mixed</td>
<td>Mean age 55.5 years, recruited a subset of women who were randomized as part of a pragmatic trial to receive an</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
<tr>
<td>Authors</td>
<td>Country</td>
<td>Total n</td>
<td>HPV+ n</td>
<td>Cytology</td>
<td>Population and setting</td>
<td>Study design</td>
<td>Time point</td>
<td>Quality score</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>------------------</td>
<td>-------------------------------------------------------------</td>
<td>-----------------------</td>
<td>-------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Waller, McCaffrey, et al. (2007)</td>
<td>UK</td>
<td>30</td>
<td>30 (at baseline); 21 (at 12-months)</td>
<td>Normal cytology; No cytology test</td>
<td>Unsolicited mailed high-risk HPV self-sampling kit, and returned the kit and tested positive.</td>
<td>Semi-structured interviews</td>
<td>Not reported after second HPV test</td>
<td>100%</td>
</tr>
<tr>
<td>Wyndham-West et al. (2018)</td>
<td>Canada</td>
<td>20</td>
<td>Not reported</td>
<td>Not reported.</td>
<td>Above 20 years, recruited through the ARTISTIC trial (UK clinical screening trial) 12-months after testing HPV-positive with normal cytology.</td>
<td>Semi-structured interviews</td>
<td>Not reported</td>
<td>100%</td>
</tr>
</tbody>
</table>

* hrHPV = high-risk HPV (type 16/18).
studies, not sufficiently substantiating result interpretation with data. See Supplementary File 4 for a breakdown of the quality scores by study and design.

**Emotional response**

We identified eight main themes of emotion which were measured or had emerged in women testing positive for HPV: anxiety; psychological distress (three types: sexual, test-specific and general); fear; surprise; shame and disgust; sadness; positive affect; and apathy. Each of these emotions are discussed separately with an overview of the synthesised evidence. See Table 3 for a brief definition these emotions. The main findings from the primary mixed methods study (Daley et al., 2010) were integrated with the relevant quantitative and qualitative components throughout.

Tables 4 and 5 provide an overview of the main results for the quantitative and qualitative studies, respectively. Supplementary File 5 provides the integration matrix of the themes measured or emerged across all studies.

**Anxiety**

**Quantitative (anxiety)**

Ten quantitative studies measured anxiety at different time points (Alay et al., 2019; Garces-Palacio et al., 2019; Kitchener et al., 2008; Kwan et al., 2011; Maggino et al., 2007; Maisse et al., 2004, 2005; McBride et al., 2020; McCaffery et al., 2004; Ng et al., 2018) mostly using the state subscale from the state-trait anxiety inventory (Martell & Bekker, 1992; Spielberger, 1983).

We were able to perform meta-analyses including seven out of eleven studies, comparing HPV-positive with abnormal cytology groups vs. control groups (normal or negative results) for both short-term anxiety (result notification ≤2 months) and long-term anxiety (>2 months). Results revealed higher short-term anxiety for women who were HPV-positive with abnormal cytology compared to the control groups across six studies (mean difference [MD] in STAI of 7.6, 95% CI: 4.59-10.60, p < .001, I² = 11.11%, P² = 85%); however no differences were observed for long-term anxiety across four studies (MD = 0.03, 95% CI: -1.45-1.51, p = 0.96, I² = 0, P² = 0%). A small meta-analysis of three studies also compared HPV-positive with normal cytology groups vs. controls, which revealed higher short-term anxiety for HPV-positive with normal cytology (MD = 6.33, 95% CI:

<table>
<thead>
<tr>
<th>Table 3. Brief definition of each of the emotions identified as themes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brief definition</strong></td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Distress</td>
</tr>
<tr>
<td>Fear</td>
</tr>
<tr>
<td>Disgust and shame</td>
</tr>
<tr>
<td>Surprise</td>
</tr>
<tr>
<td>Sadness</td>
</tr>
<tr>
<td>Positive affect</td>
</tr>
<tr>
<td>Apathy</td>
</tr>
<tr>
<td>Authors</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Akyk et al. (2019)</td>
</tr>
<tr>
<td>Andreason et al. (2019)</td>
</tr>
<tr>
<td>Daly et al. (2010)</td>
</tr>
<tr>
<td>Ferris et al. (2012)</td>
</tr>
<tr>
<td>Garces-Fabregas et al. (2019)</td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
<tr>
<td>Rodríguez et al. (2019)</td>
</tr>
<tr>
<td>Hu et al. (2018)</td>
</tr>
<tr>
<td>Kitchenor et al. (2008)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Psychological aim</th>
<th>Relevant outcome(s)</th>
<th>Measures(s)</th>
<th>Main relevant findings</th>
<th>Direction of effect for emotion in HPV+</th>
<th>Predictions of adverse emotion in HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kwan et al. (2011)</td>
<td>To assess the psychological burden of testing positive for high-risk human papillomavirus (HPV) on Chinese women with atypical squamous cells of undetermined significance (ASCUS).</td>
<td>Anxiety (state); Cervical cancer worry; Psychological burden of HPV (test-specific distress).</td>
<td>S-STAHI-6 (Marteau &amp; Bekker, 1992); Adapted Breast Cancer Worry Scale (May et al., 2005); HPV-impact Profile (HPV-IMP) (Mest et al., 2009)</td>
<td>Psychological burden, higher in HPV-positive groups. At 6 months post-result, women with higher HPV-IMP score were more distressed.</td>
<td>1. Regardless of whether women knew their HPV result, higher anxiety, fear about cervical cancer and test-specific distress were higher in HPV+.</td>
<td>N/A</td>
</tr>
<tr>
<td>Magin et al. (2007)</td>
<td>To evaluate the impact of the communication of an HPV diagnosis on the cognitive-behavioral aspect, emotional experiences, psychologic physical well-being and psychosexual sphere.</td>
<td>Anxiety (state and trait); Psychophysiologic reactions; Fear; Depressive thoughts; Intuitive thoughts and compulsive behaviors; Quality of life; Sexual functioning.</td>
<td>Cognitive Behavioral Assessment (CEA-26) (Bertolotti et al., 1999); SAT-P (Majer et al., 1999); BDI-W (Mazer et al., 2000)</td>
<td>At 6 months post-result, there were no significant differences in anxiety, cervical cancer worry, and sexual functioning between HPV+ and HPV-. Most frequent emotional reactions to HPV were fear (25%), anxiety (17%), and sadness (11%).</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Märtens et al. (2004)</td>
<td>To describe the psychological impact on women of being tested for HPV when they have a non-atypical smear test.</td>
<td>Anxiety (state); General psychological distress; Concern about result.</td>
<td>S-STAHI-6 (Marteau &amp; Bekker, 1992); GHQ-12 (Goldberg &amp; Williams, 1988)</td>
<td>Higher state anxiety, distress and concern in HPV+ group compared to other test result groups.</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Higher anxiety, general distress and test-specific distress. Younger age (β=0.11), higher perceived risk of cancer (β=0.17) and reporting not understanding results (β=0.17).
Märlin et al. (2005) To describe the psychological impact on women of being tested for HPV when smear test results are borderline or mildly dyskaryotic at 6 months follow-up.

Anxiety (state); General psychological distress; Concern about result; Sexual health worries.

Non-validated 2-item questionnaire (concern).

S-STAIA (Martens & Bekker, 1992)
GHQ-12 (Goldberg & Williams, 1988)
Non-validated 2-item questionnaire (concern).

PEAPS-Q (Bennett et al., 1995)

No differences in state anxiety and general distress at 6 months.
Concern about result and sexual health worries higher in HPV- group compared to other test result groups at 6 months.

Mclride et al. (2020) To examine short-term anxiety and distress in women receiving different results following routine HPV primary testing at cervical screening.

Anxiety (state); General Psychological distress; Concern about result; Reassurance by result; Worry about cancer.

Non-validated questions assessing concern, reassurance and worry.

S-STAIA (Martens & Bekker, 1992)
GHQ-12 (Goldberg & Williams, 1988)
Non-validated questions assessing concern, reassurance and worry.

Anxiety was significantly higher in women testing HPV-positive with either normal cytology or abnormal cytology, compared with the control group (normal cytology). Distress was slightly higher in women who tested HPV-positive with abnormal cytology, compared with the control group. There were also increased odds of very high anxiety (STAI score >69) in women who tested HPV-positive with normal or abnormal cytology compared to the control group. This pattern of results was only observed among women receiving their first HPV-positive result, not among women found to havepersistent HPV at 12-month follow-up. Odds of concern and worry were higher and reassurance lower, in HPV-positive groups compared to HPV-negative and normal cytology groups.

Higher anxiety shortly after HPV-positive with normal cytology (first time) or abnormal cytology.
Higher distress higher only for HPV-positive and abnormal cytology.
Higher concern and worry and lower reassurance.

McCaffrey et al. (2004) To examine the psychological impact of testing positive for high-risk HPV among women attending primary cervical screening.

Anxiety (state); Screening/test-specific distress; feelings towards sexual partner.

Non-validated 3-item questionnaire (feelings towards sexual partner).

S-STAIA (Martens & Bekker, 1992)
CSQ (Fiddick et al., 1992)
Non-validated 3-item questionnaire (feelings towards sexual partner).

No differences in anxiety and test-specific distress for HPV+ with normal cytology, compared with HPV- with normal cytology.
No differences in anxiety and test-specific distress for HPV+ with abnormal or unsatisfactory cytology, compared to HPV-.

Higher anxiety, test-specific distress and sexual distress.

(Continued)
<table>
<thead>
<tr>
<th>Authors</th>
<th>Psychological aim</th>
<th>Relevant outcome(s)</th>
<th>Measure(s)</th>
<th>Main relevant findings</th>
<th>Direction of effect for emotion in HPV+</th>
<th>Predictors of adverse emotion in HPV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagele et al.</td>
<td>To examine the impact of different treatment strategies – surgical treatment or watchful waiting – on sexual activity, psychosocial distress and fear of progression in women with HPV-associated premalignant genital lesions. Note: one arm were extracted for this review.</td>
<td>Fear of Progression; Sexual distress.</td>
<td>SF-36 (Henschel et al., 2002); SF-36 sexual &amp; reproductive consequences subscale (Shin et al., 2004).</td>
<td>with same cytology result. HPV+ had worse feelings towards sexual partner, regardless of cytology result. During an observational period of 12 months (baseline, 6, 12 months) there were no significant differences in fear of progression or sexual distress.</td>
<td>No effect over 12-months.</td>
<td>N/A</td>
</tr>
<tr>
<td>Ngu et al. (2018)</td>
<td>To compare the effect of two educational interventions on the psychosocial wellbeing. Note: descriptive pre-intervention data and data from the leaflet (control arm) were extracted for this review.</td>
<td>Anxiety and Depression; Cervical cancer worry; Screening-related anxiety; HPV-related shame.</td>
<td>HAQ (Zigmond &amp; Snaith, 1983); CSQ (Warde et al., 1995); Adapted Breast Cancer Worry Scale (Custers et al., 2014); Adapted STD-related shame questionnaire (Gunningham et al., 2002).</td>
<td>Before randomization to leaflet vs. counselling, 38% of women had clinically relevant anxiety and depression scores, respectively. Anxiety and cervical cancer worry were slightly lowered after receiving information in the form of a leaflet, but there were no differences in depression scores. Anxiety and cervical cancer worry decreased over time. There were no differences in HPV-related shame over time.</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang et al. (2010)</td>
<td>To describe the psychological impact of HPV.</td>
<td>Psychosocial burden of HPV (test-specific distress).</td>
<td>HPV-Impact Profile (HPV) (Mast et al., 2009)</td>
<td>Higher HPV-impact score in HPV+ with abnormal cytology compared to normal cytology. Higher HPV-impact score in HPV+ with abnormal cytology compared to normal cytology: HP domains ‘sexual impact’, ‘self-image’ and ‘control/life impact’ had the highest scores. HPV+ with abnormal cytology showed sustained burden at 30 days, compared to HPV- with abnormal cytology which decreased.</td>
<td>Higher test-specific and sexual distress.</td>
<td>N/A</td>
</tr>
<tr>
<td>Wang et al. (2011)</td>
<td>To assess the psychological burden of Chinese women with different HPV-related diseases.</td>
<td>Psychosocial burden of HPV (test-specific distress).</td>
<td>HPV-Impact Profile (HPV) (Mast et al., 2009)</td>
<td></td>
<td>Higher test-specific and sexual distress.</td>
<td>Psychosocial burden higher for women living in urban areas compared to rural.</td>
</tr>
<tr>
<td>Authors</td>
<td>Aim</td>
<td>Main themes relating to emotional outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrera-Clavijo et al. (2015)</td>
<td>To evaluate the effect of communication and education strategies designed for women who participated in the comparative HPV testing and cervical cancer screening study, as an alternative technique to cervical cytology.</td>
<td>Anxiety, fear of cancer and fatalism in HPV-positive women. Also, blame towards partner. Face-to-face discussion with a health care professional reduced anxiety for many women.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barreto et al. (2016)</td>
<td>To understand the feelings of women infected with HPV.</td>
<td>Fear, sadness and shame in HPV+ women.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertram and Magnusen (2008)</td>
<td>To describe the experience of women with abnormal Pap smears with a particular focus on their informational needs.</td>
<td>Initial anxiety at disclosure. Stigma associated with a sexually transmitted disease (STD) and a dearth of information available for male partners were problematic and influenced decisions about disclosure of human papillomavirus (HPV) infection to current or future partners.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daley et al. (2010)</td>
<td>To assess the emotional impact and behavioural consequences following HPV diagnosis among women who had received abnormal Pap test results.</td>
<td>Fear, self-blame, stigma, powerlessness, anger.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head et al. (2017)</td>
<td>To evaluate women’s understanding of test results (Pap and HPV)</td>
<td>Confusion and anxiety in HPV+ women.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koczenko et al. (2012)</td>
<td>To determine the sources of uncertainty experienced by women living with HPV</td>
<td>Seven sources of uncertainty: meaning of diagnosis; potential for disease progression; source of the infection; disclosure; sex and reproduction; and the HPV vaccine.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al. (2011)</td>
<td>To determine the psychological response of HPV infected women and their responses in terms of cognition, emotions and behaviour.</td>
<td>Primarily fear, worry and suspicion. Also, disgust, shock, denial, guilt and self-blame.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linde et al. (2019)</td>
<td>To understand causes of attendance and non-attendance to a follow-up cervical cancer screening among HPV-positive women.</td>
<td>Fear of cancer, confusion and relief that HPV was not cancer.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery and Inglis (2005)</td>
<td>To explore women’s understanding of HPV, their information needs and experience of HPV infection using a method grounded in women’s experience</td>
<td>Anxiety and negative psychological response moderated by uncertainty about HPV, clinical communication and mode of delivery of result. Anxiety most associated with receiving the test result by letter and searching the internet for further information.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCaffery et al. (2006)</td>
<td>To examine the social and psychological impact of HPV testing in the context of cervical cancer screening.</td>
<td>Anxiety, stress, concern about sexual relationships, and worry about disclosure. Psychological burden related to relationship status and history, social and cultural norms, and understanding of key features of HPV.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McCurdy et al. (2011)</td>
<td>To examine Hispanic women’s responses to learning they were HPV+, their decisions to disclose their HPV+ status, and their own and others’ reactions to their disclosure.</td>
<td>All expressed surprise and fear; some expressed issues with disclosure. Higher concern expressed in single, unmarried women under 28 years.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Connor et al. (2014)</td>
<td>To explore emotional responses and predictors of negative reactions among women undergoing HPV tests in routine clinical practice.</td>
<td>Adverse emotional response (shame, embarrassment, stigma, regret, self-blame, anxiety, worry) linked to HPV infection rather than testing. Negative emotional response primarily influenced by concerns about abnormal cytology or diagnosis of CIN. Also, to a lesser extent, by HPV knowledge, awareness of HPV being sexually transmitted, awareness of HPV prevalence and HPV information needs.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perin et al. (2006)</td>
<td>To explore women’s reactions to HPV diagnosis.</td>
<td>Emotions related primarily to stigma, fear, self-blame, powerlessness and anger.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiro et al. (2019)</td>
<td>To explore patient perspectives after a positive HPV self-sampling result.</td>
<td>Main relevant emotional themes: intense affect after receiving positive results (e.g., fear of cancer and shock) and confusion about purpose and meaning of HPV testing. Also, relief after speaking to a healthcare professional and apathy (indifference).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker, McCaffery et al. (2007)</td>
<td>To examine the way in which anxiety and concern transitioned over the course of the 12 months between two HPV tests to explore the impact of a</td>
<td>Adverse emotional impact (anxiety, shock, confusion, distress) reported initially for first test result. However, this did not generally last in the</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Continued.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Aim</th>
<th>Main themes relating to emotional outcomes</th>
</tr>
</thead>
</table>

1.31–11.35, p = .01, $r^2 = 17.55$, $I^2 = 91\%$. It is worth noting that although the direction of effects were consistent across studies, high levels of statistical heterogeneity were identified in significant meta-analyses ($I^2 > 75\%$), therefore caution is warranted in the interpretation. See Figure 3a–c for the meta-analysis findings and papers included.

Four studies which measured anxiety could not be meta-analysed due to study design (e.g., no suitable control group; Nguyen et al., 2018) or lack of published data in the necessary format for extraction (Alay et al., 2019; Andreasen et al., 2019; Maggino et al., 2007). Consistent with the meta-analysis findings, two of these studies reported higher short-term anxiety in HPV-positive groups compared to controls (Alay et al., 2019; Maggino et al., 2007) but not long-term anxiety (Andreasen et al., 2019) and one study without a suitable control group found that anxiety decreased over time (Nguyen et al., 2018).

Interestingly, a RCT which considered differences in anxiety between HPV-positive women who were told (revealed) vs. not told (concealed) their HPV status as part of an embedded trial in routine practice, found no differences between the groups (Kitchener et al., 2008). Predictors of anxiety in HPV-positive women were also explored in one study (Mäss et al., 2004); younger age, higher perceived risk of cervical cancer and not understanding the meaning of test results predicted higher anxiety within 4 weeks of results; but no predictive relationships were found for perceived importance of HPV and perceived severity of cervical cancer.

![Figure 3.](image)

(a) Forest plot comparing short-term anxiety (result notification ≤ 2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups). (b) Forest plot comparing short-term anxiety (result notification ≤ 2 months) between those testing positive for HPV with normal cytology and control groups (HPV-negative and/or normal cytology groups). (c) Forest plot comparing long-term anxiety (> 2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups).
Qualitative (anxiety)
Ten qualitative studies reported anxiety as a theme following HPV-positive results (Barrera-Clavijo et al., 2015; Bertram & Magnusson, 2008; Daley et al., 2010; Head et al., 2017; Kosenko et al., 2012; McCaffrey & Irwig, 2005; McCaffrey et al., 2006; O'Connor et al., 2014; Waller, McCaffrey, et al., 2007; Wyndham-West et al., 2018). Women who were anxious often had poor understanding of their results and/or HPV, expressed uncertainty about HPV, had often received their results by letter, and reported searching for further information on the internet (Head et al., 2017; Kosenko et al., 2012; McCaffrey & Irwig, 2005; McCaffrey et al., 2006; Waller, McCaffrey, et al., 2007). Two studies found that women who had discussed their results face-to-face with a healthcare professional were less anxious (Barrera-Clavijo et al., 2015; McCaffrey & Irwig, 2005). One study (Waller, McCaffrey, et al., 2007) interviewed women after two HPV test results (12 months apart) and found that anxiety was a dominant theme shortly after a first or second HPV-positive result, but that it did not generally persist in the time between the two tests. A second HPV-positive test compared to a first one, however, was described as being more anxiety-inducing for some women.

Distress
Three forms of psychological distress were identified across studies: test-specific distress, sexual distress, and general distress. Test-specific distress related to the psychological burden of HPV and screening test results. Sexual distress related mostly to impacts on sexual relationships, a partner, or concerns about transmission of HPV. General distress related to adverse impacts on everyday functioning (e.g., lack of sleep and concentration).

Quantitative (distress)
Sixteen quantitative studies included a measure of psychological distress: ten included test-specific distress (Ferenidou et al., 2012; Garces-Palacio et al., 2019; Kwan et al., 2011; MaisiSi, 2004, 2005; McBride et al., 2020; McCaffrey et al., 2004; Ngui et al., 2018; Wang et al., 2010, 2011), eleven sexual distress (Alay et al., 2019; Ferenidou et al., 2012; Hsu et al., 2018; Kitchener et al., 2008; Kwan et al., 2011; Maggino et al., 2007; MaisiSi, 2005; McCaffrey et al., 2004; Nagele et al., 2019; Wang et al., 2010, 2011) and six general distress (Andreassen et al., 2019; Hsu et al., 2018; Kitchener et al., 2008; MaisiSi, 2004, 2005; McBride et al., 2020). Test-specific distress was consistently higher (worse) for women testing HPV-positive with any cytology result compared to normal results up to 6-months post-result (MasiSi, 2005), but not at 12-months post-result (Garces-Palacio et al., 2019). There were mixed quantitative findings for sexual distress and general distress. Sexual distress was found to be higher (worse) for women testing HPV-positive in five studies; however one low quality study showed no effect (Maggino et al., 2007), and another high quality found mixed findings depending on how they analysed their data (Kitchener et al., 2008). Another small study found lower sexual desire but no differences in overall sexual function between HPV-positive groups and the control (Alay et al., 2019); and a descriptive study reported that 33.3% and 43.1% of women endorsed reduced sexual interest and reduced frequency of sexual intercourse, respectively (Ferenidou et al., 2012). In terms of longer-term impact, sexual distress was found to persist at 6-months in two studies (Kwan et al., 2011; MasiSi, 2005); one study examined the trajectory of adjustment to sexual distress over a 12-month period and found that adjustment occurred from one-to-six-months after HPV diagnosis (Hsu et al., 2018). Consistently, another study found no differences over a 12-month period (Nagele et al., 2019). General psychological distress (Goldenberg & Williams, 1988) was found to be slightly higher (worse) in women testing HPV-positive with abnormal cytology 4-weeks after their result in two studies (MasiSi, 2004; McBride et al., 2020). However, no differences were found 6-months later in a follow-up study (MasiSi, 2005) or up to 12 or 24 months later in two other studies (Andreassen et al., 2019; Nagele et al., 2019). The Kitchener et al. (2008) trial again had mixed findings for general distress. Among women who were told their HPV result, being HPV-positive (vs. HPV negative) was associated with slightly higher general
distress 2 weeks after the result. However, when women who had been told they were HPV-positive were compared with HPV-positive women who had not been told their HPV test result, no differences were found. Husu et al. (2018) found that adjustment to general distress occurred between 1- and 6-months after HPV diagnosis.

We performed meta-analyses to combine the available data for test-specific distress, sexual distress, and general distress to represent an overall measure of psychological distress in both the short-term (result notification ≤ 2 months) and long-term (>2 months). One study (Mallis et al., 2005) measured two forms of long-term distress (general and sexual); therefore, two meta-analyses were performed including each of these variables independently, to avoid bias through double-counting in the total sample.

Results revealed higher short-term distress for HPV-positive with abnormal cytology compared to the control across six studies (Standardised Mean Difference [SMD] = 0.68, 95% CI: 0.32–1.03, p < .001, τ²=0.18, I²=94%). Similarly, higher long-term distress was also observed for HPV-positive with abnormal cytology compared to the control across six studies, irrespective of whether we included the general or sexual distress outcome in the Malli et al. (2005) study (SMD = 0.42, 95% CI: 0.05–0.80, p = .03, τ²=0.19, I²=92%) and SMD = 0.49, 95% CI: 0.19–0.80, p = .001, τ²=0.12, I²=88%, respectively). Long-term effects appeared to be limited to test-specific and sexual distress outcomes, given that the two studies which measured general distress showed no differences (Mallis et al., 2005; McBride et al., 2020). Overall, although direction of effects were relatively consistent across studies, high levels of statistical heterogeneity were identified in all the meta-analyses (I²>75%), therefore caution is advised in the interpretations. See Figure 4 (a)–(c) for the meta-analysis findings for psychological distress.

![Figure 4](image_url)

(a) Forest plot comparing short-term distress (result notification ≤ 2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups). (b) Forest plot comparing long-term distress (>2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups), using the Malli et al. (2005) general distress measure. (c) Forest plot comparing long-term distress (>2 months) between those testing positive for HPV with abnormal cytology and control groups (HPV-negative and/or normal cytology groups), using the Malli et al. (2005) sexual distress measure.
Qualitative (distress)
Themes indicative of test-specific distress emerged in thirteen qualitative studies (Barrera-Clavijo et al., 2015; Barreto et al., 2016; Bertram & Magnusson, 2008; Head et al., 2017; Kosenko et al., 2012; Lin et al., 2011; McCaffery & Inwig, 2005; McCaffery et al., 2006; McCurdy et al., 2011; O’Connor et al., 2014; Perin et al., 2006; Waller, McCaffery, et al., 2007; Wyndham-West et al., 2018). Clear adverse impacts were reported, with many women describing concerns about HPV infection and/or the meaning of their test results. A small number of women reported that test-specific distress influenced their behaviours through triggering what they believed to be preventive action (often idiosyncratic, e.g., avoiding sharing soap/towels, exercising, or eating fruit) (Barreto et al., 2016; Wyndham-West et al., 2018). One study reported that test-specific distress primarily arose from concerns about abnormal cytology rather than HPV infection; however, it only included six women who were HPV-positive (O’Connor et al., 2014). The other studies reported that HPV infection had notably adverse impacts independent of abnormal cytology. Sexual distress was also a theme in nine qualitative studies (Barrera-Clavijo et al., 2015; Barreto et al., 2016; Bertram & Magnusson, 2008; Kosenko et al., 2012; Lin et al., 2011; McCaffery et al., 2006; McCurdy et al., 2011; Perin et al., 2006; Waller, McCaffery, et al., 2007), with HPV-positive women describing a range of concerns about their sexual relationships, transmission of HPV and/or impact on their partner. Some women reported anger towards their partner and arguments due to suspected infidelity, or changing their sexual behaviours (e.g., avoiding sex) as a consequence of HPV.

Fear
Quantitative (fear)
Two studies descriptively reported that fear was an adverse reaction to HPV diagnosis, with 82.4% and 25% of women endorsing it descriptively (Ferenidou et al., 2012; Maggino et al., 2007). Similarly, the quantitative component of the mixed-methods study reported >75% endorsed fear; however, the authors categorised their definition of fear as endorsements of ‘anxious’ and ‘worried’ (Daley et al., 2010). Another study found that cervical cancer worry was higher in HPV-positive women shortly after result notification, but differences disappeared at 6-months (Kwan et al., 2011); and one study reported that worry about developing cervical cancer decreased over time (Ngu et al., 2018). During an observational period of 12 months (baseline, 6, 12 months) there were no significant differences in fear of disease progression (Nagère et al., 2019).

Qualitative (fear)
Fear emerged as a dominant theme in ten qualitative studies (Barrera-Clavijo et al., 2015; Barreto et al., 2016; Bertram & Magnusson, 2008; Lin et al., 2011; Linde et al., 2019; McCurdy et al., 2011; O’Connor et al., 2014; Perin et al., 2006; Tiro et al., 2019; Waller, McCaffery, et al., 2007). Women mainly described fears related to the development of cervical cancer, their future health and potential infertility. Other women were afraid about the impact of their result or cancer on their family, partner and/or friends.

Disgust and shame
Quantitative (disgust and shame)
Six quantitative studies included measures of HPV-related shame or disgust (Daley et al., 2010; Ferenidou et al., 2012; Rodríguez et al., 2019; Ng et al., 2018; Wang et al., 2010, 2011); two used the ‘self-image’ domain within a distress measure (Mast et al., 2009); one adapted an STD-related shame scale (Cunningham et al., 2002) and two used non-validated measures. Shame and disgust were higher in women testing positive for HPV with abnormal cytology when compared to normal cytology (Wang et al., 2010, 2011), or HPV-negative with abnormal cytology (Wang et al., 2011) within 3-months of the result. Statements relating to shame and disgust were descriptively endorsed by the majority
 (>50%) in a qualitative study (Daley et al., 2010); and ‘guilt’, ‘shame’ and ‘stigmatisation’ were endorsed by 41.1%, 21.5% and 15.7% respectively in another study (Ferentinos et al., 2012). HPV-related shame did not change over time (up to 6-months post result) (Ng, et al., 2018), and one correlational study found that higher stigma was significantly associated with utilising fewer coping strategies and reporting less protective behaviour related to cervical cancer (Rodriguez et al., 2019).

Qualitative (disgust and shame)
Shame and/or disgust also emerged as themes in eleven qualitative studies (Barreto-Clavijo et al., 2015; Barreto et al., 2016; Bertram & Magnussen, 2008; Lin et al., 2011; McCaffrey & Irwig, 1995; McCaffrey et al., 1995; McCurdy et al., 2011; O’Connor et al., 2014; Perrin et al., 2006; Waller, McCaffrey, et al., 2007; Wyndham-West et al., 2018). These emotions mostly centred on concerns about disclosure of results to partner/family/friends, judgement from others and the belief that negative connotations (such as sexual promiscuity) were associated with HPV, sometimes leading to reports of stigma (McCaffrey et al., 2006; O’Connor et al., 2014; Wyndham-West et al., 2018). Some women described feeling ashamed and reported variations of feeling ‘unclean’ or ‘dirty’. Although shame and disgust appeared to be reported across different ethnic groups, these themes seemed more dominant in studies focusing on women from non-white ethnic backgrounds.

Surprise (and confusion)
Quantitative and qualitative (surprise)
Despite surprise and/or confusion emerging as themes in ten qualitative studies (Barreto et al., 2016; Head et al., 2017; Kosenko et al., 2017; Lin et al., 2011; Linde et al., 2019; McCaffrey & Irwig, 2005; Perrin et al., 2006; Tiro et al., 2019; Waller, McCaffrey, et al., 2007; Wyndham-West et al., 2018), these responses were not measured using validated scales in any of the quantitative studies. One descriptive study reported that 70.1% of HPV-positive women endorsed that they felt ‘shocked’ (Daley et al., 2010). In qualitative studies, women often expressed surprise as the first emotion experienced after receiving their HPV-positive result. Many reported subsequent confusion about the meaning of HPV and how they had acquired it. Often surprise and confusion appeared to be linked with knowledge that HPV is sexually transmitted, raising questions about its source and concerns about potential infidelity (linking to sexual distress).

Sadness
Quantitative (sadness)
One quantitative study descriptively reported that 14.9% of women who tested HPV-positive had clinically relevant depression scores; however, there was no control group to indicate population norms (Ng, et al., 2018). Another low quality study found that depressive/insensitive thoughts were slightly higher in women who tested HPV-positive compared to HPV-negative (time point not reported) (Maggino et al., 2007). A descriptive study reported that 51.7% of HPV-positive women endorsed that they felt ‘depressed’ (Daley et al., 2010).

Qualitative (sadness)
Only two out of eleven qualitative studies reported sadness or feelings of depression, and in both they were minor themes (Barreto et al., 2016; Waller, McCaffrey, et al., 2007).

Positive affect (relief, acceptance)
Quantitative and qualitative (positive affect)
In the quantitative studies, positive emotional responses, as indicated by improved outcomes following an HPV-positive result, were rarely observed. The only exception was one study where sexual
satisfaction was higher in HPV-positive women (Kitchener et al., 2008). ‘Relief’ was also endorsed by 27.4%, ‘encouraged’ endorsed by 35.9%, and ‘in control’ endorsed by 68% of HPV-positive women in a descriptive study (Daley et al., 2010). Ten qualitative studies reported positive emotions such as relief, increased trust and acceptance, though they were minor themes (Barrera-Clavijo et al., 2015; Head et al., 2017; Kosenko et al., 2012; Lin et al., 2011; Linde et al., 2019; McCaffery & Inwig, 2005; Perrin et al., 2006; Tiro et al., 2019; Waller, McCaffery, et al., 2007; Wyndham-West et al., 2018). Women who reported positive emotional responses to their HPV results described receiving their test results in person by a healthcare professional, consulting with a healthcare professional after results, having a supportive partner and/or mobilising social support. Relief that the result was HPV and not cancer was a less common theme.

Apathy

Quantitative (apathy)

One study descriptively measured apathy and found that 38% of women reported no reactive emotion to their HPV diagnosis (Maggino et al., 2007). Although the other quantitative studies did not directly measure indifference or apathy, the lack of observed differences in emotional outcomes between women receiving HPV-positive vs. negative results may be suggestive of apathetic or ambivalent responses, reported across quantitative papers under each individual emotion.

Qualitative (apathy)

Two qualitative studies reported indifference (O’Connor et al., 2014; Tiro et al., 2019), however this was either a minor theme or related more to the HPV testing procedures than response to testing HPV-positive.

Cognitive behavioural framework – interacting systems

The emotional response findings for quantitative and qualitative studies were additionally coded to identify related cognitions and behaviours, as a starting point to determine how these three factors interact. Within the eight broad emotion-focused themes, twelve cognitive constructs and ten behavioural constructs were identified (many of which are described in the results under each emotion).

Cognitions related to emotional response

Broadly, adverse emotional response to testing positive for HPV was linked to eight negative cognitions: low perceived control, confusion, stigma, relationship concerns, sexual concerns, cancer-related concerns, lack of trust in others and uncertainty about meaning of result or future health.

Conversely, neutral or positive emotional responses were linked with high perceived control, trust in others and acceptance.

Behaviours related to emotional response

Related to behaviours, six areas were linked to adverse emotional response: negative impact on relationships, negative social impact, non-disclosure of results, idiosyncratic prevention, indirect clinical interaction (e.g., results by letter) and changes in sexual behaviour. In brief, negative impact on relationships and negative social impact referred to themes such as reports of arguments with a partner or avoiding contact with others. Non-disclosure of results represented women who expressed that they deliberately concealed their result from others. Idiosyncratic prevention referred to reports of attempts to prevent the spread of HPV through engaging in activities that are not evidence-based, such as washing toilet seats. Indirect clinical interaction referred to receiving results by methods with no personal contact such as a mailed letter and/or not seeking advice from a healthcare professional. Changes in sexual behaviour described lower sexual activity, avoiding sex and/or using a condom.
Conversely, four behavioural themes were linked with positive or neutral emotional response: direct clinical interactions; social support; behaviour of others; and future screening attendance. In brief, women who reported speaking to a healthcare professional after their HPV-positive result (direct clinical interactions) or their partner/family/friends (social support) expressed feeling more reassured, less anxious, relieved and/or more accepting. Helpful behaviours of others related to partners/friends/family sourcing information on HPV or encouraging help-seeking behaviours. Attendance at a screening appointment after receiving an HPV-positive result (future screening attendance) was described by some women as providing reassurance.

According to the cognitive behavioural model, these three constructs of emotions, cognitions and behaviours are likely to directly influence and/or interact with one another. This formulates a working model of what may influence emotional response to testing positive for HPV. See Figure 5 for an overview of emotions, cognitions and behaviours mapped on to the cognitive behavioural framework.

Discussion

This systematic review provides a comprehensive overview of emotional response to HPV diagnosis at cervical cancer screening, as well as a provisional model for understanding how emotions may interact with cognitions and behaviours using the cognitive behavioural framework. Testing positive for HPV at cervical screening appears to be most strongly associated with short-term anxiety, short and long-term psychological distress, and related to feelings of disgust and shame, surprise and fear about cancer. There was little evidence of sadness or depression and a minority of women reported apathy or relief that they had been diagnosed with HPV rather than cancer.

Anxiety was one of the most common adverse responses reported shortly after women had received their HPV-positive result across all studies. Our meta-analyses revealed higher short-term state anxiety in women testing positive for HPV with abnormal cytology or normal cytology when compared with normal screening results (mean difference on STAI (Spielberger, 1983) of 7.6 and 6.33, respectively); though high statistical heterogeneity was observed, potentially due to differences in screening contexts and magnitudes of effect sizes ($I^2 >75\%$). These findings are consistent with

![Figure 5. Emotional response to testing positive for HPV from all studies (quantitative, qualitative, mixed-methods) mapped on to a cognitive behavioural framework](image-url)
another systematic review which found elevated anxiety in women with abnormal cytology who were attending for colposcopy (a more advanced stage in the screening process) (O'Connor et al., 2016). Interestingly, when comparing our results to this review, anxiety scores observed in colposcopy patients appeared to be descriptively similar to women testing positive for HPV with abnormal cytology (mean STAI score range: 34.0 - 49.0 pre-colposcopy vs. 39.6 - 46.0 after test result). These similarities suggest that anxiety associated with an HPV-positive screening result may be comparable to the anxiety experienced at follow-up investigative procedures (colposcopy); or may persist from the time of result to colposcopy.

Reassuringly, however, the results from our meta-analysis revealed that anxiety did not appear to persist in the long-term (> 2 months after notification), when comparing HPV-positive with abnormal cytology vs. normal/negative result groups. Also, overall, the mean anxiety scores observed across studies did not generally exceed thresholds for clinical significance. The anxiety scores associated with a HPV-positive result tended to be higher than expected in the general population but lower than the cut-off for clinically important anxiety. Although, it is worth noting that all quantitative studies accessed anxiety across the whole study sample without conducting subgroup analyses. From a clinical perspective, it is highly unlikely that acute adverse emotional response to HPV would be expected or detectable at the population level. It is more likely that certain groups of women would be at higher risk of clinically important anxiety (e.g., low socioeconomic status, ethnic minority groups, low health literacy) who should additionally be studied or analysed separately. Anxiety was a dominant theme in the qualitative literature which, due to the likelihood of self-selection bias in qualitative studies, supports the notion that certain groups of women may be prone to very high anxiety.

HPV positivity was also related to psychological distress in both the short-term and long-term. Our meta-analyses (which combined sexual, test-specific and general distress) revealed higher distress in women testing HPV-positive with abnormal cytology when compared with normal/negative results, at both result notification to 2-months and 2-months onwards. Long-term distress (> 2-months), however, seemed to be specific to sexual and test-specific distress, as the studies which measured general distress at this time point found no differences.

Experiencing distress related to sexual relationships, infidelity and potential transmission of the virus (sexual distress) is consistent with the broader literature on emotional response to other STIs and HPV in non-screening contexts (e.g., genital warts, other cancers) (Dodd et al., 2016; Graziotin & Serafini, 2009). In this review, sexual distress appeared mostly, but not exclusively, limited to women in relationships and/or with current sexual partners in the qualitative literature, which may help explain some heterogeneity in findings. For some women, it was also reported as associated with relationship problems (e.g., arguing over suspected infidelity) and changes in sexual practice (e.g., avoiding sex).

Distress related to the meaning of screening test results (test-specific distress) was very common in the qualitative literature and was often described as the successor to surprise and confusion. It was mostly linked to low HPV awareness, not understanding result meaning, confusion about the aetiology of HPV and concerns about future health. As HPV cannot be cured and there are no clear (practical) prevention methods available (except vaccination prior to exposure), some women reported feeling that they were not in control of their health. Low perceived control appeared related to higher test-specific distress. A small number of women also reported engaging in idiosyncratic prevention methods to help treat or contain HPV, such as washing toilet seats or increasing physical activity. As a psychological formulation, these forms of prevention could be interpreted as behavioural attempts to gain control and reduce distress (Westbrook et al., 2011). High levels of distress about result also appeared to be closely related to fears about developing cancer which, together, intensified overall adverse emotional response.

Shame and disgust emerged as themes in the qualitative studies and a small number of women also reported feeling that there was stigma attached to HPV, which is consistent with broader STI research (Bickford et al., 2007; Jeynes et al., 2009; Nock, 2000). In line with sexual distress and test-
specific distress, shame and disgust seemed to be associated with maladaptive behaviours. Some women reported reluctance to disclose their HPV result to others and/or to seek social support from their partner, family, or peers because of feeling ashamed. To further assess the relevance of shame and disgust in the cervical screening context, future quantitative research should incorporate validated measures which include relevant behavioural impacts.

Relatively few studies measured sadness, depression, or generalised distress. In those studies which did, there was little evidence of adverse (clinically important) effects associated with any HPV-positive result. A small number of qualitative studies reported positive or neutral emotional responses, such as relief that a test result was HPV and not cancer or indifference. However, these were not common and/or dominant responses.

Across all studies (quantitative and qualitative), adverse emotional response was mainly related to not understanding the meaning of the result, being in a relationship or having a current sexual partner, non-white ethnicity, receiving test result by letter, not discussing the result with a healthcare professional, little social support and lower levels of education. Adverse emotional response was observed across all studies but appeared most prominent in the qualitative literature. Although fear and surprise/confusion were common themes in the qualitative studies, they were rarely measured in the quantitative studies, highlighting a gap in qualitative research which warrants further exploration. Overall, our findings suggest that receiving an HPV-positive result at cervical screening can cause significant disturbance for some women, however, likely the minority of the population and/or certain groups.

Methodological considerations

Importantly, this systematic review raises some relevant methodological considerations. Nearly all studies adopted cross-sectional, descriptive and/or qualitative designs, prohibiting inferences of causality between testing positive for HPV and emotional response. The persistence of HPV infection (and the development of abnormal cells) are closely intertwined with immunological response; and there is a body of literature which suggests that psychological or social stressors can impair immune response (Fang et al., 2008; Marsland et al., 2017; Steptoe et al., 2007). Therefore, it cannot be ruled out that HPV activation and/or persistence are functions (or sub-functions) of psychological stress (i.e., adverse emotion). Interestingly, the one large RCT study in this review which compared anxiety and general distress between women testing HPV-positive who were told (revealed) vs. not told (concealed) about their HPV status (Kitchener et al., 2009), found similarly elevated anxiety scores (no differences). This suggests that elevated levels of anxiety and distress may be present prior to learning HPV-positive screening results, which supports the notion that psychological stress could play a role in HPV activation/persistence. Other research suggesting that anxiety associated with HPV is usually temporary and normalises at 6-month follow-up may provide evidence against this mechanism; although it is worth noting that 41% of HPV cases clear within 6 months (Bulkmans et al., 2007), meaning effects may be confounded. Further research is needed to test the validity of such psychobiological mechanisms and/or other potential causative pathways.

Very few studies also analysed and/or interpreted their data in terms of clinical significance, meaning it was not possible to distinguish between normal and clinically relevant emotional responses for most outcomes. Negative response to adverse information is usually a temporary process constituting a normal part of human consciousness. Therefore, studies in this review which drew implicative conclusions based on between-group differences without further interpretation provided little insight distinguishable from healthy response. To progress this field of psychological research, future studies should be designed and appropriately powered to test for clinical significance rather than between-group differences alone.

Most participants were educated to secondary level or above (where it was reported) and there were relatively few studies from low-and-middle-income countries. The highest quality studies
consisted of well-educated (tertiary level) white patients living in high-income countries which used organised screening programmes. Consequently, the main findings of this review are weighted towards relatively homogenous samples and may not be directly translatable to other settings or lower-income countries. The qualitative studies which were conducted in low-and-middle-income countries (Brazil, Colombia, Taiwan, Tanzania) reported stronger adverse emotional impacts (Barrera-Clavijo et al., 2015; Barreto et al., 2016; Lin et al., 2011; Linde et al., 2019). Therefore, the findings reported in this review may be conservative compared to other health systems or cultural contexts.

Finally, HPV-positive results in the reviewed studies were usually accompanied by abnormal cytology. This meant that we were unable to determine the relative impact of HPV vs. abnormal cytology for many of the emotions described. However, there were some emotions which seemed inherently related to HPV, such as sexual distress and test-specific distress. Receiving both HPV and cytology results is, nevertheless, reflective of routine screening practice, meaning that the findings of this review should provide valuable and pragmatic insights into the patient experience at screening.

**Limitations**

Our timely systematic review benefits from the adoption of a relatively novel and rigorous mixed methods review design. Like most reviews, we have a number of limitations worth considering when interpreting the results. Firstly, although we used a comprehensive search strategy to identify papers across six major databases, our grey literature search was limited to OpenGrey and we did not contact authors or Listservs to identify additional literature. Also, given that there is no clear agreed or distinct theoretical definition for many emotions, emotion categorisations were often based on judgements and interpretations by the review team, especially where data was measured using non-validated scales or qualitative data. The meta-analyses were also performed using small numbers of studies (range: 3 – 6) which can be unreliable and subject to bias, and prohibited moderator analyses. Therefore, relevant mechanisms could not be explored and caution is warranted in meta-analysis interpretations. Lastly, whilst we used the cognitive behavioural framework to map our findings, there are several other potentially more relevant theoretical models which could be used to structure emotional reactions to HPV, e.g., Williams’ Affect and Health Behavioural Framework (Williams & Evans, 2014) or Leventhal’s Common Sense Model of Self-Regulation (Leventhal et al., 2016). Using alternative theoretical frameworks may have led to different formulations but we are confident that our overall conclusions are valid.

**Implications for policy and practice**

As HPV primary screening is being implemented around the world, our findings provide rich insight for policymakers and clinicians into women’s experience of receiving HPV-positive results. In attempts to mitigate adverse response, common themes highlighted in this review (e.g., related to confusion around cancer risk or sexual transmission) could be targeted through tailored information in screening result letters or accompanying leaflets. Clinicians working in primary care and cervical screening in areas where HPV-testing is being implemented could also use this information to preempt or address women’s questions and concerns, especially in low-and-middle-income countries where adverse emotional response may be greater. Public health or third sector organisations running campaigns on cervical cancer screening could frame their communications to target some of the key areas, e.g., to tackle stigma associated with sexually transmitted aspects. Clinical signposting and pathways could also be embedded within cancer screening programmes to provide support for some of the sub-groups highlighted, who may be at higher risk of clinically important adverse responses (e.g., women from ethnic minority backgrounds, or those with low health literacy or without access to social support).
Conclusion
Short-term anxiety, distress about test results, distress about sexual relationships, feelings of disgust and shame, surprise, and fear about cancer appear to be the most common emotional responses to testing positive for HPV. Almost exclusive use of observational and qualitative designs, however, limits conclusions regarding clinical significance and prohibits some important inferences. We hope this comprehensive review, paired with our provisional framework of relevant emotion, cognitive and behavioural factors, will act as a springboard for the development of a cogent theoretical literature on this topic.

Author contributions
EM, ZR, OT and JW conceived the study. OT, KW and ZR conducted the searches. EM, OT, LR and JW selected eligible studies. RMM, LM and NK provided intellectual input on the review design. EM, OT, LR and JW assisted with data extraction and quality assessments. EM, OT and JW conducted the syntheses and analyses. EM drafted the paper. All authors contributed to the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
This review was funded by the National Institute for Health Research (NIHR) as part of a fellowship awarded to Emily McBride (DRF-2017-10-105); the views expressed in this paper are not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Jo Walker and Laura Madlow were funded by Cancer Research UK (C7492/A17219).

ORCID
Emily McBride  http://orcid.org/0000-0001-9926-429X
Ovidia Tatar  http://orcid.org/0000-0003-1886-6390
Zoev Raschege  http://orcid.org/0000-0003-4248-1909
Laura M. Marlow  http://orcid.org/0000-0003-1709-2397
Rona Mas-Morris  http://orcid.org/0000-0002-2927-3446
Jo Walker  http://orcid.org/0000-0003-4025-9132

References


Thomas, J., Harden, A., Oakley, A., Oliver, S., Sutcliffe, K., Rees, R., Brunton, G., & Kavanagh, J. (2009). Integrating qualitative research with trials in systematic reviews. *British Medical Journal*, 338(7446), 1010-1012. https://doi.org/10.1136/bmj.338.7446.1010


Appendix 2.2 - Search Strategy for Systematic Review (3 pages)

**HPV concept**
1. Papillomaviridae/ or Human papillomavirus 16/ or Papillomavirus Infections/
2. human.mp.
5. 3 and 4
7. hpv.mp.
8. Wart*.mp.
9. 4 and 8
10. 5 or 6 or 7 or 9
11. 2 and 10
12. 1 or 11

**Cervical cancer concept**
13. Carcinoma, Squamous Cell/
14. carcinoma/ or carcinoma in situ/
15. Neoplasms/
16. 13 or 14 or 15
17. cancer.mp.
18. "neopla*".mp.
19. "dysplas*".mp.
20. "carcin*".mp.
21. 17 or 18 or 19 or 20
22. 16 or 21
23. uterus/ or cervix uteri/
25. "cervic*".mp.
26. cervix.mp.
27. endocervix.mp.
29. genit*.mp.
30. 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 22 and 30
32. CIN.mp.
33. Cervical Intraepithelial Neoplasia/
34. exp Uterine Cervical Dysplasia/
35. uterine neoplasms/ or uterine cervical neoplasms/
36. uterine cervical diseases/ or uterine cervical dysplasia/
37. 32 or 33 or 34 or 35 or 36
38. 31 or 37

**Screening concept**
39. Vaginal Smears/
40. Papanicolaou Test/
41. Colposcopy/
42. DNA Probes, HPV/
43. 39 or 40 or 41 or 42
44. smear.mp.
45. "stain*".mp.
46. "Pap*".mp.
47. DNA.mp.
48. "cytolog*".mp.
49. "colposco*".mp.
50. 44 or 45 or 46 or 47 or 48 or 49
51. 43 or 50
52. Mass Screening/
53. "Early Detection of Cancer"/
54. 52 or 53
55. screening.mp.
56. "prevent*".mp.
57. 55 or 56
58. mass.mp.
59. primary.mp.
60. 58 or 59
61. 57 and 60
62. 51 or 54 or 61

**Psychological concept**
63. Social Stigma/
64. "Quality of Life"/
65. Anxiety/
66. 63 or 64 or 65
68. Distress*.mp.
69. Stigma*.mp.
70. Quality of life.mp.
71. Anxiety*.mp.
72. 67 or 68 or 69 or 70 or 71
73. Sexual Behavior/
74. interpersonal relations/ or family conflict/ or trust/
75. 73 or 74
76. Sexual*.mp.
77. Relation*.mp.
78. 76 and 77
79. Confusion/
80. guilt/ or shame/
81. Harm Reduction/
82. Emotions/
83. Body Image/
84. social support/ or psychosocial support systems/
85. Behavior/
86. Attitude/
87. 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86
88. Confusion.mp.
89. Trust*.mp.
90. Fidelit*.mp.
91. Blame.mp.
92. Protectio*.mp.
93. Harm*.mp.
94. Psychologic*.mp.
95. Regret*.mp.
96. body image.mp.
97. Embarrassment*.mp.
98. behavio*.mp.
99. attitud*.mp.
100. 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99
101. 66 or 72 or 75 or 78 or 87 or 100

**Combination of concepts**
102. 12 and 38 and 62 and 101

**Additional limits**
103. limit 102 to (yr="1980 -Current" and (english or french or german) and (journal article or "review" or systematic reviews))
Appendix 2.3 – Table containing raw data used for the meta-analyses (4 pages).

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (HPV positive groups)</th>
<th>Group 2 (Control) (HPV negative/normal cytology groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Garces-Palacio et al. (2019)</strong></td>
<td>1. Anxiety (STAI) from survey 2 (2-weeks) for HPV+ result: M=21.4, SD=14.81, N=50.</td>
<td>1. Anxiety (STAI) from survey 2 (2-weeks) for HPV- result: M=10.8, SD=11.26, N=97.</td>
</tr>
<tr>
<td></td>
<td>2. Anxiety (STAI) from survey 3 (1-year) for HPV+ result: M=16.5, SD=16.62, N=12.</td>
<td>2. Anxiety (STAI) from survey 3 (1-year) for HPV- result: M=12.7, SD=10.64, N=25.</td>
</tr>
<tr>
<td></td>
<td>3. Test-specific distress (HIP overall score) from survey 2 (2-weeks) for HPV+ result: M=35.9, SD=19.91, N=50.</td>
<td>3. Test-specific distress (HIP overall score) from survey 2 (2-weeks) for HPV- result: M=23.2, SD=15.1, N=97.</td>
</tr>
<tr>
<td></td>
<td>4. Test-specific distress (HIP overall score) from survey 3 (1-year) for HPV+ result: M=22.0, SD=12.3, N=12.</td>
<td>4. Test-specific distress (HIP overall score) from survey 3 (1-year) for HPV- result: M=19.5, SD=13.02, N=25.</td>
</tr>
<tr>
<td><strong>Kwan et al. (2011)</strong></td>
<td>1. Anxiety (S-STAI-6) at baseline: SEM=52.28, SE=1.24, N=157.</td>
<td>1. Anxiety (S-STAI-6) at baseline: SEM=43.73, SE=1.18, N=142.</td>
</tr>
<tr>
<td></td>
<td>2. Anxiety (S-STAI-6) at 6-months: SEM=37.39, SE=0.98, N=157.</td>
<td>2. Anxiety (S-STAI-6) at 6-months: SEM=37.27, SE=0.93, N=142.</td>
</tr>
<tr>
<td></td>
<td>3. Test-specific distress (HIP overall score) at baseline: SEM=36.56, SE=1.44, N=157.</td>
<td>3. Test-specific distress (HIP overall score) at baseline: SEM=26.52, SE=1.37, N=142.</td>
</tr>
<tr>
<td></td>
<td>4. Test-specific distress (HIP overall score) at 6-months: SEM=30.25, SE=1.45, N=157.</td>
<td>4. Test-specific distress (HIP overall score) at 6-months: SEM=24.36 SE=1.36, N=142.</td>
</tr>
</tbody>
</table>

*Note: data taken from the observational HPV test arm.*
<table>
<thead>
<tr>
<th>Study</th>
<th>Used in the meta-analyses for short-term and long-term anxiety and distress.</th>
<th>1. Anxiety (S-STAI-6) for HPV+ with abnormal cytology: $M=42.1$, $SD=14.9$, $N=148$.</th>
<th>1. Anxiety (S-STAI-6) for normal cytology: $M=34.9$, $SD=12.5$, $N=185$.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maissi et al. (2004)</td>
<td>Used in the meta-analyses for short-term anxiety and distress.</td>
<td>1. Anxiety (S-STAI-6) for HPV+ with abnormal cytology: SEM=39.6, SE=0.6, N=536.</td>
<td>1. Anxiety (S-STAI-6) for normal cytology: SEM=36.4, SE=0.7, N=366.</td>
</tr>
<tr>
<td></td>
<td><em>HPV positive with abnormal cytology vs. normal cytology.</em></td>
<td>2. General distress (GHQ-12) for HPV+ with abnormal cytology: SEM=2.8, SE=0.2, N=536.</td>
<td>2. General distress (GHQ-12) for normal cytology: SEM=2.0, SE=0.1, N=366.</td>
</tr>
<tr>
<td></td>
<td><em>For sexual distress only: HPV positive with abnormal cytology vs. HPV negative with abnormal cytology.</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maissi et al. (2005)</td>
<td>Used in the meta-analyses for long-term anxiety and distress.</td>
<td>5. Anxiety (S-STAI-6) at 6-months for HPV+ with abnormal cytology: SEM=36.7, SE=0.7, N=369.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>For anxiety and general distress: HPV positive with abnormal cytology vs. normal cytology.</em></td>
<td>6. General distress (GHQ-12) at 6-months for HPV+ with abnormal cytology: SEM=2.3, SE=0.2, N=369.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Sexual distress (PEAPS-Q) at 6-months for HPV+ with abnormal cytology: SEM=1.8, SE=0.1, N=369.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For sexual distress only: HPV positive with abnormal cytology vs. HPV negative with abnormal cytology.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McBride et al. (2020)</td>
<td>Used in the meta-analyses for short-term and long-term anxiety and distress.</td>
<td>1. Anxiety (S-STAI-6) at baseline for HPV+ with abnormal cytology: SEM=36.8, SE=0.8, N=288.</td>
<td>5. Anxiety (S-STAI-6) at 6-months for normal cytology: SEM=36.8, SE=0.8, N=288.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6. General distress (GHQ-12) at 6-months for normal cytology: SEM=2.0, SE=0.2, N=288.</td>
<td>6. General distress (GHQ-12) at 6-months for normal cytology: SEM=2.0, SE=0.2, N=288.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7. Sexual distress (PEAPS-Q) at 6-months for normal cytology: SEM=1.0, SE=0.1, N=288.</td>
<td>7. Sexual distress (PEAPS-Q) at 6-months for normal cytology: SEM=1.0, SE=0.1, N=288.</td>
</tr>
<tr>
<td>Study</td>
<td>Anxiety (STAI) for HPV+ with abnormal cytology: M=46.0, 95% CI=40.6 – 51.4, N=23.</td>
<td>Anxiety (STAI) for HPV+ with normal cytology: M=43.5, 95% CI=39.7 – 47.3, N=46.</td>
<td>Test-specific distress (CSQ) for HPV+ with abnormal cytology: M=17, 95% CI=16-18, N=23.</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>HPV positive with normal cytology vs. normal cytology; and HPV positive with abnormal cytology vs. normal cytology.</strong></td>
<td>2. Anxiety (STAI) for HPV+ with normal cytology: M=38.3, SD=14.3, N=224.</td>
<td>3. Anxiety (STAI) for HPV+ with normal cytology: M=38.3, SD=14.3, N=224.</td>
<td>4. General distress (GHQ-12) at baseline for HPV+ with abnormal cytology vs. normal cytology: M=3.3, SD=3.8, N=167.</td>
</tr>
<tr>
<td><strong>McCaffery et al. (2004)</strong></td>
<td>1. Anxiety (S-STAI-6) at baseline for HPV+ with normal cytology: M=38.3, SD=14.3, N=224.</td>
<td>2. Anxiety (S-STAI-6) at 12-months represented by HPV-persistent group: M=36.8, SD=13.1, N=157.</td>
<td>3. General distress (GHQ-12) at baseline for HPV+ with abnormal cytology vs. normal cytology: M=3.3, SD=3.8, N=167.</td>
</tr>
<tr>
<td><strong>Kitchener et al. (2008)</strong></td>
<td><strong>HPV positive with abnormal cytology vs. HPV negative with normal cytology.</strong></td>
<td>1. Anxiety (STAI-STATE) for HPV+ with abnormal cytology: M=39.77, SD=12.05, N=204.</td>
<td>2. Anxiety (STAI-STATE) for HPV+ with normal cytology: M=38.87, SD=13.33, N=410.</td>
</tr>
<tr>
<td>Study</td>
<td>Compare Groups</td>
<td>General Distress (GHQ-12) for HPV+ with abnormal cytology: M=4.57, SD=5.44, N=201.</td>
<td>Test-specific distress (HIP overall score) for HPV+ with abnormal cytology: M=48.8, N=44, MD compared to normal cytology group=20.5, 95% CI=12.2-28.9.</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Wang, Jeng et al. (2010)</strong></td>
<td>HPV positive with normal cytology vs. HPV negative with normal cytology.</td>
<td>3.</td>
<td>1.</td>
</tr>
<tr>
<td></td>
<td>Note: data taken from the observational ‘revealed’ arm (test result revealed to women).</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wang, Shi et al. (2010)</strong></td>
<td>HPV positive with abnormal cytology vs. normal cytology.</td>
<td></td>
<td>1. Test-specific distress (HIP overall score) for HPV+ with abnormal cytology: M=45.8, 95% CI=43.8–47.8, N=179.</td>
</tr>
<tr>
<td></td>
<td>Used in the meta-analysis for long-term distress.</td>
<td></td>
<td>1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.</td>
</tr>
</tbody>
</table>

*M = mean; SEM = adjusted mean; SE = standard error; SD = standard deviation; 95% CI = 95% confidence interval; N = sample size.

Note: For inclusion in meta-analyses, we used the Cochrane Collaboration meta-analysis conversion calculator (available through RevMan v5) to calculate means and standard deviations based on other reported statistics (e.g. standard error or confidence intervals as reported in this table), where the raw data was not available in this form.
Appendix 3.1 - Published paper for Study 2 in International Journal of Cancer (9 pages).

Anxiety and distress following receipt of results from routine HPV primary testing in cervical screening: The psychological impact of primary screening (PIPS) study

Emily McBride 1, Laura A.V. Marlow 1, Alice S. Forster 1, Deborah Ridout 1, Henry Kitchener 2, Julietta Patrick 4 and Jo Waller 2

1Research Department of Behavioural Science and Health, Institute of Epidemiology and Health Care, University College London, London, United Kingdom
2Population, Policy and Practice Programme, UCL Great Ormond Street Institute of Child Health, London, United Kingdom
3Women’s Cancer Centre, Institute of Cancer Sciences, University of Manchester, Manchester, United Kingdom
4Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

We used a cross-sectional survey to examine short-term anxiety and distress in women receiving different results following routine human papillomavirus (HPV) primary testing at cervical screening. Participants were women aged 26–65 (n = 1,127) who had attended screening at one of five sites piloting HPV primary screening in England, including a control group with normal cytology who were not tested for HPV. Women completed a postal questionnaire 2–8 weeks after their screening result. Unadjusted mean anxiety scores ranged from 32.9 (standard deviation (SD) = 12.2) in HPV-negative women to 42.1 (SD = 14.9) in women who were HPV-positive with abnormal cytology. In adjusted analyses, anxiety was significantly higher in women testing HPV-positive with either normal cytology (mean difference [MD] = 3.5; CI: 0.6–6.4) or abnormal cytology (MD = 7.2, CI: 3.7–10.6) than the control group. Distress was slightly higher in women who tested HPV-positive with abnormal cytology (MD = 0.9, CI: 0.02–1.8), than the control group. We also found increased odds of very high anxiety in women who tested HPV-positive with normal or abnormal cytology compared to the control group. This pattern of results was only observed among women receiving their first HPV-positive result, not among women found to have persistent HPV at 12-month follow-up. Testing HPV-positive with normal cytology for the first time, is associated with elevated anxiety despite carrying very low immediate cervical cancer risk. However, receiving the same test result at 12-month early recall does not appear to be associated with higher anxiety, suggesting anxiety may normalise with repeated exposure and/or over time.

Introduction

Over 3 million women take part in the National Health Service Cervical Screening Programme (NHSCSP) in England every year. In the UK and elsewhere, cervical screening is changing to incorporate primary human papillomavirus (HPV) testing.

Key words: psychological impact, cancer screening, human papillomavirus, women, psychological wellbeing

Abbreviations: ANCOVA: analysis of variance; GHQ: General Health Questionnaire; HPV: human papillomavirus; HRA: health research authority; IMD: index of multiple deprivation; MD: mean difference; NHS: National Health Service; NHSCSP: National Health Service Cervical Screening Programme; OR: odds ratio; SD: standard deviation; 6-STA: short-form state-trait anxiety inventory

Additional Supporting Information may be found in the online version of this article.

Conflict of Interest: None declared.

Grant sponsor: Cancer Research UK; Grant number: C8896/A17429, C7490/A17319; Grant sponsor: National Institute for Health Research; Grant number: DRF-2017-10-105; Grant sponsor: Public Health England

DOI: 10.1002/j.2058-5864.2019.02580

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

History: Received 15 May 2019; Accepted 26 Jun 2019; Online 28 Jun 2019
Correspondence to: Jo Waller, Research Department of Behavioural Science and Health, Institute of Epidemiology and Health Care, University College London, Gower Street, London, WC1E 6BT, United Kingdom. Tel: +44-20-7679-5958; E-mail: jwaller@ucl.ac.uk

in six sentinel NHS sites. This provided the opportunity to evaluate the psychological impact of HPV primary screening prior to full implementation.

Psychological considerations are central to the successful implementation of HPV primary screening. Under the primary screening protocol, all women who attend will be told whether they test positive or negative for high-risk HPV. Testing positive for HPV can lead to elevated anxiety, fear and concern related to the possible development of cervical cancer. When HPV testing is used to triage women with borderline or mildly abnormal cytology, anxiety and distress have been found to be higher in women testing positive for HPV than those who test negative or do not have an HPV test, although the difference seems relatively short-lived. HPV can also carry a negative label due to its sexually transmitted nature, sometimes resulting in shame, stigma and concerns about fidelity and relationships. As well as testing for greater numbers of women for HPV, the primary screening protocol also creates a new group of women who have normal cytology, but test positive for high-risk HPV. These women are at very low immediate risk of cervical cancer but are recalled at 12 months for repeat HPV testing. The prevalence of this result was 8.5% in the English HPV primary screening pilot which would mean around 270,000 women receiving it in England every year. Women’s psychological response to this result in routine cervical screening is unknown.

We aimed to compare anxiety and distress between women receiving the different possible test results in HPV primary screening. The partial conversion of the pilot screening laboratories to HPV screening allowed us to compare these women with those receiving a normal result as part of the current cytology-based programme. To the best of our knowledge, this is the first major study to quantitatively measure the short-term psychological impact of HPV primary testing within a routine programme.

Materials and Methods
Design
A cross-sectional between-groups design was employed to assess women’s psychological responses shortly after receiving their cervical screening test results (baseline), as well as 6 months, and 12 months later. This article reports baseline findings.

Participants
Participants were women aged 24–65 years who had been screened in one of five NHS sites in England using HPV primary testing as part of the NHS Clinical Programme: North West London, Sheffield, North and Norwich, Liverpool and Central Manchester. The NHS pilot sites had catchment areas with broad geographical coverage across England. Baseline recruitment to our study commenced on 18/11/2016 and ceased on 14/03/2017 with approximately 2–5 months of active recruitment per site. Health Research Authority (HRA) approval was granted on 26/09/2016 (Research Ethics Committee reference: 16/LO/0902 and Confidentiality Advisory Group reference: 16/CAG/0047).

Women were eligible if they had received one of six possible combinations of HPV and/or cytology test results within the last 2 weeks, as indicated by their NHS clinical records. The sampling strategy aimed to recruit roughly equal numbers of women from each test result group. Five of the groups were recruited from women included in the HPV primary screening pilot. We also included a control group who had received a normal cytology result at standard cytology-based screening within the same geographical areas and processed by the same laboratories. Table 1 provides an overview of the six result groups. A full description of the recruitment procedure can be found in our protocol.

Procedures and clinical management
Prior to participant identification, women were notified about the study via a web link which was printed in HPV primary screening information leaflets and sent alongside their screening result.

<table>
<thead>
<tr>
<th>HPV result</th>
<th>Cytology result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (control)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Group 2</td>
<td>Negative</td>
</tr>
<tr>
<td>Group 3</td>
<td>Positive</td>
</tr>
<tr>
<td>Group 4</td>
<td>Positive</td>
</tr>
<tr>
<td>Group 5</td>
<td>Persistent positive</td>
</tr>
<tr>
<td>Group 6</td>
<td>Negative at 12 months</td>
</tr>
</tbody>
</table>

Table 1 has been adapted from our protocol paper.

Women in Groups 5 and 6 had all tested HPV positive with normal cytology at their first HPV primary screen and were recruited to the study after their 12-month follow-up test.
invitation letters. The link directed women to our university
departmental website which provided study information as well
as details of how to opt-out of being approached to take part.
No women opted out.
Eligible women were identified by staff in NHS cytology
and virology departments at each of the five participating
sites. Staff allocated each potential participant a unique iden-
tity number, which they recorded and linked to patient name,
address, age, screening history, NHS site and test result; these
outcomes will collectively be referred to as "NHS data."
Potential participants were mailed invitation packs to their
home, which contained an invitation letter, participant infor-
mation sheet, consent form, questionnaire booklet and prepaid
return envelope. To maximise the response rate, a reminder
pack containing the same documents was mailed 3 weeks later.
Women opted to take part by returning their completed
consent form and questionnaire to the university. All docu-
ments were preprinted with unique identity numbers which
allowed questionnaire data to be linked with NHS data. At the
end of recruitment, UCL received NHS data on all of the
women approached (n = 5,494) in non-identifiable format
(name and address removed, and replaced with Index of Mul-
tiple Deprivation score and quintile) to allow for demographic
comparisons between responders and non-responders.

Outcome measures
Primary outcomes were state anxiety and general distress
(measured using the state-trait anxiety inventory [STAI-T-A]53
and General Health Questionnaire [GHQ-12],54 respectively).
Secondary outcomes reported include very high anxiety
(score > 49.80 on STAI-T-A), case-level distress (score > 3/12
on GHQ-12), self-reported response to test results (concern
and reassurance) and worry about developing cervical cancer.
See Table 2 for a more detailed overview of the primary and
secondary outcome measures.

Demographic characteristics based on self-report were the
highest level of education, ethnicity, marital status and HPV
vaccine status. NHS data included information on age, cervical
screening history (number of previous screens), NHS site and
Index of Multiple Deprivation score and quintiles (IMD), a
marker of area-level deprivation, based on residential post-
code.13 Further details on descriptive outcomes can be found
in our protocol paper.16

Sample size and response rate
The study was powered to detect a small-to-medium between-
group difference (f = 0.14) in anxiety (as measured by the
STAI-T-A) at the 12-month time-point.16 Based on previous
studies,16,18 we expected anxiety scores across groups to be in
the range of 36–46, with a standard deviation (SD) of 12. With
an n of 0.05, we calculated that a minimum sample size of
673 in total with roughly 182 per group would give us 80%
power to detect between-group differences in anxiety. We there-
fore initially planned to approach 3,415 participants anticipating
a baseline response rate of 35%, with 75% of baseline
responders returning a 6-month follow-up questionnaire and
72% of 6-month responders returning a 12-month follow ques-
tionnaire. However, as the study progressed, our response rate
was lower than expected at approximately 22%. In line with our
protocol16 we increased the number of women approached to
adjust for this (to n = 5,494). We estimated that approaching
approximately 5,500 women would yield a total sample size of
1,210 at baseline, 908 at 6-months and 681 at 12-months. Our
baseline sample was 1,148 at baseline.

Data analysis
Ten per cent of data were checked independently for errors by
a member of the research team who was not involved in the
initial data entry. Error rates were substantially below the
prescribed cut-off for no further action to be taken (<1% error
for all outcomes). Demographic characteristics were
compared between the six groups using one-way ANOVA
and Chi-squared tests as appropriate.

We compared the demographic characteristics of responders
and non-responders (including age, test results, number of pre-
vious screens, NHS site and IMD quintile) which revealed small
variations. See Supporting Information Table S1 for an over-
view of nonresponder demographic characteristics. To adjust
for the fact that our approached sample may not have been
fully representative of the screening population in the pilot
sites, we generated and applied population weights based on
age group (24–34, 35–44, 45–54, 55–63) and IMD quintile
within each test result group. With permission from the Office
for Data Release, we used data from 953,387 women who
attended HPV primary screening (and primary cytology for the
cardinal group) within the NHS CSP in the five sites included in
our study in 2014–2018 to calculate the weights.

For each of the primary outcomes (anxiety and distress),
we compared the mean scores between the six groups using
univariate regression analysis. Further to this, multiple regres-
sion analysis was performed to adjust for confounding factors:
age, IMD score, ethnicity, marital status, education, number
of previous cervical screens and NHS site. Results are pre-
sest ed as mean difference (MD) compared to the control
group, along with 95% confidence intervals. We also present
descriptive mean values and standard deviations for each of
the six groups. For the secondary outcomes (very high anxiety,
case-level distress, worry about cancer, concern and reassur-
ance about results), we fitted both univariate and multiple
logistic regression models adjusting for the same confounding
factors. Results are presented as odds ratios, indicating the
odds of the outcome for each of the groups relative to the
control group, with 95% confidence intervals. Due to skewed
responses to the concern and reassurance items in the control
group, we used the HPV positive with normal cytology group
as the reference category for analyses of these outcomes.

Data completions was >90% for the majority of outcomes
and factors, with the exception of anxiety (89%) and IMD
Table 2. A summary of the primary and secondary outcomes measures

<table>
<thead>
<tr>
<th>Description</th>
<th>Scoring and Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (S-STAI-4)</td>
<td>The short-form state-anxiety inventory (S-STAI-4) is a six-item, validated questionnaire measuring anxiety. Cronbach’s alpha was 0.86 across all groups (n = 993), indicating a high level of internal consistency. Scoring range from 20 to 80. Normal score expected in the general population at 34-36. Very high anxiety at 40.</td>
</tr>
<tr>
<td>General distress (GHSQ-12)</td>
<td>The General Health Questionnaire (GHSQ-12) is a 12-item validated questionnaire used to measure general distress. Cronbach’s alpha was 0.91 across all groups (n = 1,106), indicating a high level of internal consistency. Scoring range from 0 to 12. Case-level distress at 10.</td>
</tr>
<tr>
<td>Concern about test result</td>
<td>Concern relating to test result was measured by asking: “How concerned do you feel about your recent screening result?” This question was adapted from the previous MHSQCP psychological evaluation. Five-point Likert scale indicating: 1 = not at all concerned, 2 = slightly concerned, 3 = somewhat concerned, 4 = moderately concerned, 5 = very concerned. Scores of 1–3 were classified as lower concern; scores of 4–5 were classified as higher concern.</td>
</tr>
<tr>
<td>Reassurance from test result</td>
<td>Reassurance relating to test result was measured by asking: “How reassured do you feel about your recent screening result?” This question was adapted from the previous MHSQCP psychological evaluation. Five-point Likert scale indicating: 1 = not at all reassured, 2 = slightly reassured, 3 = somewhat reassured, 4 = moderately reassured, 5 = very reassured. Scores of 1–2 were classified as lower reassurance; scores of 3–5 were classified as higher reassurance.</td>
</tr>
<tr>
<td>Worry about cervical cancer</td>
<td>Worry about developing cervical cancer was measured by asking: “How worried are you about getting cervical cancer in the next 10 years?” This question was adapted from the previous MHSQCP psychological evaluation. Five-point Likert scale indicating: 1 = not at all worried, 2 = slightly worried, 3 = somewhat worried, 4 = moderately worried, 5 = very worried. Scores of 1–3 were classified as lower worry; scores of 4–5 were classified as higher worry.</td>
</tr>
</tbody>
</table>

Primary outcomes were anxiety and general distress. Secondary outcomes included concern, reassurance and worry. *Cutoff points for high/low concern, reassurance and worry were based on the most stable estimates and distribution of participant responses; sensitivity analyses were performed comparing the different possible cut-off points which revealed consistent findings.

(93%). We used multiple imputation assuming data were missing at random to account for missing data. The imputation model included primary outcomes and all socio-demographic factors, which we assumed included all predictors of missingness. The final models were derived by fitting a regression model including all confounders, and estimates were combined using Rubin’s rules. Demographic characteristics have been presented using non-weighted data. All primary and secondary results have been adjusted using the weights described above and using the imputed data. Supporting Information Table S2 presents the data availability. The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

Results

Five-thousand-four-hundred-ninety-four women were invited to take part and 1,148 returned a questionnaire (response rate of 21%). Thirteen participants were excluded from the study due to returning a questionnaire over 90 days after date of identification and eight due to ineligible age (<65). 1,127 participants were included in the analysis. See Figure 1 for an overview of recruitment.
Figure 1. Overview of recruitment and response.

Demographics
Table 3 shows unweighted demographic characteristics across the whole sample and by test result group. Overall, characteristics were similar across each of the test result groups, with some small differences relating to age, number of previous screens, marital status, IMD quintile and NHS site. These potential confounding variables were adjusted for in the analyses.

Primary outcomes
Anxiety (S-STAT-6). Regression analysis revealed statistically significant differences in anxiety between test result groups. Women who tested HPV positive with normal cytology or abnormal cytology had higher mean anxiety scores than women in the control group (no HPV test; MD = 2.5, 95% CI: 0.6-6.4, p = 0.02, and MD = 7.2, 95% CI: 3.7-10.6, p < 0.001, respectively). There were no differences in mean anxiety scores between the other groups and the control group.

General distress (GHQ-12). Regression analysis also revealed a higher mean general distress score for the HPV positive with abnormal cytology group compared to the control group (MD = 0.9, 95% CI: 0.02-1.8, p < 0.04). There were no differences in general distress between the other groups and the control group. Tables 4 and 5 provide an overview of the results for anxiety and distress.

Secondary outcomes
Very high anxiety and case-level general distress. Logistic regression was performed to compare the odds of having very high anxiety scores (S-STAT-6 score > 49/80) between the results groups. We found significantly increased odds of very high anxiety in the HPV positive with normal cytology group (OR: 1.9, 95% CI: 1.1-3.5) and HPV positive with abnormal cytology group (OR: 3.5, 95% CI: 1.9-6.6), compared to the control group (no HPV test). None of the other groups differed significantly from the control group.

Logistic regression was also performed to determine the effects of test result group on case-level general distress (GHQ-12 score > 3/12). None of the groups differed significantly from the control group.

Worry about developing cervical cancer. We used logistic regression to ascertain the effects of receiving different test results on the likelihood that women scored highly for worry about developing cervical cancer in the next 10 years (worrying score > 4) (moderately/very worried). After adjusting for potential confounding factors, all three HPV positive groups were found to be at significantly increased odds of high worry when compared to the control group (no HPV test), all with odds ratios over 4 (see Table 5).

Concern and reassurance related to results. Logistic regression was also performed to ascertain the effects of receiving different test results on the likelihood that women scored highly for concern (score > 3, moderately/very concerned) and highly for reassurance (score > 2; somewhat/moderately/very reassured). After adjusting for potential confounding factors, the odds of high concern in the HPV positive with abnormal cytology group was 1.8 (95% CI: 1.2-2.9) when compared to the HPV positive with normal cytology group. The odds of high concern were significantly lower for the three normal results groups (control, HPV negative and HPV cleared) when compared to the HPV positive with normal cytology group. All three normal results groups had significantly higher odds of high reassurance compared to the HPV positive with normal cytology group. Reassurance was similarly high across these three normal results groups. Tables 4 and 5 provide an overview of the results for all secondary outcome measures.

Discussion
Informing women that they test positive for high-risk HPV accompanied by any cytology result appears to be associated with some adverse psychological effects at the population level, at least in the short-term. Our findings are consistent with previous studies showing that testing positive for HPV with abnormal cytology is associated with raised anxiety and distress.23,24 However, unique to HPV primary screening and unique to the literature, we also found evidence of raised anxiety, concern about the screening result and worry about developing cervical cancer in women who tested positive for HPV with normal cytology. These women were more anxious than the control group (normal cytology, no HPV test) and displayed a mean anxiety score slightly above the upper threshold expected in the general population (mean score of 38.3 compared to the normal range of 34–36).22,23 They were also 1.9 times more likely to exhibit very high anxiety compared to the control group (indicated by a STA1 score > 49/80), scoring
similarly to individuals with clinically important symptoms or an anxiety disorder.20–27 Women who test positive for HPV with normal cytology carry a very low absolute risk of developing high-grade cervical abnormalities or cancer in the near future.28,29 Therefore, for many women, informing them of this test result may lead to unnecessary adverse psychological responses. At the population level, it is unlikely that the levels of anxiety observed in our study would cause significant disruptions to women’s daily functioning. This is supported by our small between-group differences for general distress paired with wider evidence indicating that screening-related anxiety is usually temporary.30,31,32 However, it is important to remember that 72% of women aged 25–64 living in the UK attend for screening when invited,3 of whom 8.3% are likely to be HPV positive with normal cytology.33 Given the very large numbers of women affected, it is imperative that we do not lose sight of subgroups of individuals who may be more at risk of acute adverse reaction (eg, very high anxiety). Clinically significant levels of anxiety may be more common in women who do not understand their result34,35; however, research is needed to establish the risk factors and trajectory of high anxiety following an HPV positive result to inform efforts to mitigate this adverse response.

Reassuringly, women with persistent HPV and normal cytology at 12 months did not have significantly higher anxiety than the control group, although descriptively they displayed slightly higher anxiety than would be expected in the general population (mean score of 36.8 compared to normal range of 34–36). This suggests that raised levels of anxiety and distress associated with an initial HPV positive result may

---

**Table 3. Demographic characteristics of the whole sample (n = 1,127) and by results group (no weights or adjustments applied)**

<table>
<thead>
<tr>
<th></th>
<th>Control (no HPV test)</th>
<th>HPV positive, normal</th>
<th>HPV positive, abnormal</th>
<th>HPV persistent at 12 months</th>
<th>HPV clear at 12 months</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>204 (18.3%)</td>
<td>248 (22.0%)</td>
<td>528 (23.9%)</td>
<td>170 (15.1%)</td>
<td>191 (17.0%)</td>
<td>1,127 (100%)</td>
</tr>
<tr>
<td>Age (n = 1,125)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years (SD)</td>
<td>43.8 (11.0)</td>
<td>43.9 (11.4)</td>
<td>39.9 (12.2)</td>
<td>37.0 (10.6)</td>
<td>40.6 (11.7)</td>
<td>41.2 (11.4)</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current partner</td>
<td>164 (80.9%)</td>
<td>214 (87.3%)</td>
<td>184 (77.4%)</td>
<td>111 (66.9%)</td>
<td>131 (71.9%)</td>
<td>855 (77.2%)</td>
</tr>
<tr>
<td>No partner</td>
<td>39 (19.2%)</td>
<td>24 (12.7%)</td>
<td>55 (22.6%)</td>
<td>55 (33.1%)</td>
<td>44 (25.1%)</td>
<td>235 (22.8%)</td>
</tr>
<tr>
<td>Ethnicity n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (British or other)</td>
<td>180 (89.6%)</td>
<td>217 (88.6%)</td>
<td>235 (93.9%)</td>
<td>151 (91.0%)</td>
<td>167 (94.9%)</td>
<td>695 (96.9%)</td>
</tr>
<tr>
<td>Other ethnicity</td>
<td>20 (10.0%)</td>
<td>27 (11.0%)</td>
<td>17 (6.7%)</td>
<td>15 (9.0%)</td>
<td>2 (1.1%)</td>
<td>101 (3.1%)</td>
</tr>
<tr>
<td>Prefer not to say</td>
<td>1 (0.5%)</td>
<td>1 (0.4%)</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>IMD Quintile, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (most deprived)</td>
<td>43 (21.1%)</td>
<td>66 (26.2%)</td>
<td>44 (18.1%)</td>
<td>24 (15.6%)</td>
<td>35 (20.5%)</td>
<td>176 (16.9%)</td>
</tr>
<tr>
<td>2</td>
<td>38 (20.0%)</td>
<td>46 (17.5%)</td>
<td>55 (22.7%)</td>
<td>33 (21.4%)</td>
<td>28 (16.9%)</td>
<td>211 (20.2%)</td>
</tr>
<tr>
<td>3</td>
<td>44 (23.2%)</td>
<td>69 (29.2%)</td>
<td>53 (21.5%)</td>
<td>40 (26.0%)</td>
<td>53 (31.9%)</td>
<td>276 (26.3%)</td>
</tr>
<tr>
<td>4</td>
<td>27 (14.2%)</td>
<td>46 (17.3%)</td>
<td>54 (22.3%)</td>
<td>30 (19.5%)</td>
<td>31 (18.7%)</td>
<td>193 (18.5%)</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>39 (20.5%)</td>
<td>53 (22.9%)</td>
<td>34 (14.0%)</td>
<td>27 (17.1%)</td>
<td>29 (17.1%)</td>
<td>183 (16.7%)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree or Higher</td>
<td>91 (45.0%)</td>
<td>106 (41.2%)</td>
<td>169 (69.6%)</td>
<td>72 (43.9%)</td>
<td>76 (43.7%)</td>
<td>306 (44.2%)</td>
</tr>
<tr>
<td>Qualification below degree</td>
<td>92 (45.5%)</td>
<td>126 (51.1%)</td>
<td>124 (49.5%)</td>
<td>82 (50.0%)</td>
<td>83 (46.2%)</td>
<td>357 (48.8%)</td>
</tr>
<tr>
<td>No formal qualifications</td>
<td>19 (9.4%)</td>
<td>17 (7.0%)</td>
<td>17 (6.8%)</td>
<td>19 (12.1%)</td>
<td>18 (10.8%)</td>
<td>75 (7.1%)</td>
</tr>
<tr>
<td>No. of previous screens (n = 1,027)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean screen (SD)</td>
<td>6.8 (4.7)</td>
<td>6.6 (4.4)</td>
<td>5.9 (3.3)</td>
<td>4.8 (4.7)</td>
<td>7.2 (5.5)</td>
<td>6.9 (5.0)</td>
</tr>
<tr>
<td>HPV vaccine status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 doses</td>
<td>10 (5.0%)</td>
<td>16 (4.1%)</td>
<td>22 (8.3%)</td>
<td>18 (10.6%)</td>
<td>18 (10.1%)</td>
<td>67 (6.1%)</td>
</tr>
<tr>
<td>NHS site, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>18 (8.7%)</td>
<td>17 (7.5%)</td>
<td>24 (14.1%)</td>
<td>24 (14.1%)</td>
<td>23 (13.9%)</td>
<td>183 (16.6%)</td>
</tr>
<tr>
<td>Liverpool</td>
<td>23 (11.2%)</td>
<td>46 (18.5%)</td>
<td>47 (18.2%)</td>
<td>29 (17.1%)</td>
<td>54 (30.7%)</td>
<td>212 (18.8%)</td>
</tr>
<tr>
<td>Sheffield</td>
<td>11 (5.5%)</td>
<td>15 (6.2%)</td>
<td>11 (5.4%)</td>
<td>9 (5.3%)</td>
<td>13 (7.5%)</td>
<td>121 (10.8%)</td>
</tr>
<tr>
<td>London North West</td>
<td>23 (11.2%)</td>
<td>39 (15.7%)</td>
<td>27 (10.5%)</td>
<td>31 (18.2%)</td>
<td>18 (10.1%)</td>
<td>93 (14.3%)</td>
</tr>
<tr>
<td>Norfolk and Norwich</td>
<td>26 (12.6%)</td>
<td>30 (12.3%)</td>
<td>37 (14.3%)</td>
<td>34 (20.9%)</td>
<td>37 (20.7%)</td>
<td>266 (24.5%)</td>
</tr>
<tr>
<td>Manchester</td>
<td>116 (56.3%)</td>
<td>86 (34.2%)</td>
<td>96 (37.2%)</td>
<td>52 (31.6%)</td>
<td>29 (16.2%)</td>
<td>385 (34.2%)</td>
</tr>
</tbody>
</table>

Total n can be found in the end column for the categorical variables.

1Marital status: current partner (married, civil partnership, living with partner, in a relationship) and no partner (single, divorced, widowed).

2No formal qualifications included those with no qualifications and those who were still studying.

Table 4: Descriptive characteristics for primary and secondary outcomes by results group (no weights or adjustments applied)

<table>
<thead>
<tr>
<th></th>
<th>HPV negative</th>
<th>HPV positive, normal</th>
<th>HPV positive, abnormal</th>
<th>HPV persistent at 12 months</th>
<th>HPV cleared at 12 months</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety (Mean (SD))</td>
<td>36.9 (2.5)</td>
<td>32.9 (12.2)</td>
<td>38.3 (14.3)</td>
<td>42.1 (14.9)</td>
<td>36.8 (13.1)</td>
<td>37.0 (12.1)</td>
</tr>
<tr>
<td>n (%)</td>
<td>185 (8.4%)</td>
<td>232 (23.1%)</td>
<td>224 (22.3%)</td>
<td>149 (14.7%)</td>
<td>157 (15.6%)</td>
<td>60 (6.0%)</td>
</tr>
<tr>
<td>Distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score ≥ 49 (Mean (SD))</td>
<td>2.3 (0.3)</td>
<td>1.9 (3.0)</td>
<td>2.7 (3.6)</td>
<td>3.3 (3.8)</td>
<td>2.5 (3.2)</td>
<td>2.5 (3.7)</td>
</tr>
<tr>
<td>n (%)</td>
<td>204 (8.3%)</td>
<td>244 (21.9%)</td>
<td>257 (23.1%)</td>
<td>167 (15.0%)</td>
<td>177 (15.9%)</td>
<td>65 (5.8%)</td>
</tr>
<tr>
<td>Very high anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score ≥ 5 (Mean (SD))</td>
<td>25 (0.5%)</td>
<td>31 (13.4%)</td>
<td>50 (22.3%)</td>
<td>52 (31.2%)</td>
<td>28 (17.8%)</td>
<td>11 (18.3%)</td>
</tr>
<tr>
<td>n (%)</td>
<td>160 (6.5%)</td>
<td>205 (8.4%)</td>
<td>174 (77.7%)</td>
<td>56 (64.9%)</td>
<td>159 (92.5%)</td>
<td>40 (81.7%)</td>
</tr>
<tr>
<td>Case-level distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score ≥ 3 (Mean (SD))</td>
<td>49 (4.6%)</td>
<td>53 (21.6%)</td>
<td>71 (27.5%)</td>
<td>53 (31.5%)</td>
<td>50 (28.3%)</td>
<td>16 (24.2%)</td>
</tr>
<tr>
<td>n (%)</td>
<td>155 (6.6%)</td>
<td>192 (78.4%)</td>
<td>187 (72.6%)</td>
<td>115 (60.0%)</td>
<td>127 (71.8%)</td>
<td>50 (75.8%)</td>
</tr>
<tr>
<td>Worry about cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher worry</td>
<td>30 (4.7%)</td>
<td>33 (11.4%)</td>
<td>114 (44.4%)</td>
<td>78 (46.2%)</td>
<td>78 (44.1%)</td>
<td>11 (16.7%)</td>
</tr>
<tr>
<td>Lower worry</td>
<td>174 (83.5%)</td>
<td>213 (86.6%)</td>
<td>143 (55.6%)</td>
<td>91 (53.8%)</td>
<td>99 (59.3%)</td>
<td>55 (83.7%)</td>
</tr>
<tr>
<td>Concern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher concern</td>
<td>7 (0.4%)</td>
<td>7 (2.9%)</td>
<td>84 (33.7%)</td>
<td>79 (46.5%)</td>
<td>56 (31.5%)</td>
<td>3 (4.9%)</td>
</tr>
<tr>
<td>Lower concern</td>
<td>198 (9.6%)</td>
<td>238 (97.1%)</td>
<td>173 (67.3%)</td>
<td>91 (53.6%)</td>
<td>122 (68.5%)</td>
<td>63 (95.5%)</td>
</tr>
<tr>
<td>Reassurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher reassurance</td>
<td>186 (9.0%)</td>
<td>220 (89.8%)</td>
<td>108 (42.0%)</td>
<td>76 (45.0%)</td>
<td>80 (45.2%)</td>
<td>54 (81.8%)</td>
</tr>
<tr>
<td>Lower reassurance</td>
<td>19 (0.9%)</td>
<td>25 (10.2%)</td>
<td>149 (58.0%)</td>
<td>93 (53.0%)</td>
<td>97 (54.8%)</td>
<td>12 (18.3%)</td>
</tr>
</tbody>
</table>

All binary variables are presented as number (%) by test result group. Abbreviation: SD, standard deviation.

normalise with repeated exposure to the result and/or over time, which is consistent with previous research.39,40 Our findings suggest that efforts to reduce anxiety should therefore primarily focus on women who test HPV positive with normal cytology for the first time. HPV primary screening has a high negative predictive value and therefore has the potential to reassure the majority of women who are at extremely low risk of cervical cancer. Our findings indicate that testing HPV negative at any point (including 12 months after an HPV positive result) is associated with high levels of reassurance. However, although an HPV negative result offers better protection from cervical cancer than normal cytology,41,42 women in our study felt similarly reassured after receiving an HPV negative result compared to normal cytology. Low knowledge of HPV and the benefits associated with an HPV negative result may partially account for this.39 Normal or “good” results may also demand little cognitive attention and therefore reduce the likelihood of differentiation.39

Strengths and limitations

To the best of our knowledge, this is the first major study to evaluate the short-term psychological impact of primary HPV testing within a routine national programme. Participant recruitment linked to routine clinical management through the NHGISCP HPV primary screening pilot ensured accurate data collection and broad geographical coverage across England. A control group with primary cytology allowed additional between-group comparisons, strengthening our cross-sectional design. Our sample size was smaller than we anticipated for the group who desired HPV at 12-months (n = 66); however, this group had similar scores to the other normal and HPV negative groups. Our response rate was 21% which raises uncertainty regarding the extent to which our sample is representative of the wider screening population.

We were, however, able to statistically weight our data to the wider screening population for age and BMD quintile as well as compare demographic characteristics between responders and non-responders. For consistency with the previous NHGSIP evaluations of HPV triage methods,35 some of our secondary outcomes were single-item, nonvalidated measures. Finally, like many cross-sectional survey studies, we had an underrepresentation of nonwhite participants, and self-selection bias may have resulted in an overrepresentation of the most anxious women.

Implications

Cervical screening programmes should aim to mitigate unnecessary anxiety, worry and concern in women testing positive for HPV with any cytology result. Use of clear, evidence-based communication in test result letters and information materials will help ensure that women understand their results and the implications for cancer risk. Provision of communication

Table 5. Results for primary and secondary outcomes by test result groups (weighted and adjusted)

<table>
<thead>
<tr>
<th></th>
<th>Control (no HPV test)</th>
<th>HPV negative</th>
<th>HPV positive, normal cytology</th>
<th>HPV positive, abnormal cytology</th>
<th>HPV persistent at 12 months</th>
<th>HPV cleared at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD (95% CI)</td>
<td>Ref</td>
<td>−1.1 (−3.9, 1.8)</td>
<td>3.5 (0.4, 6.4)</td>
<td>7.2 (3.7, 10.6)</td>
<td>2.1 (−1.1, 5.3)</td>
<td>1.0 (−3.3, 5.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.45</td>
<td>0.02</td>
<td>&lt;0.001</td>
<td>0.21</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD (95% CI)</td>
<td>Ref</td>
<td>−0.2 (−0.9, 0.4)</td>
<td>0.6 (−0.1, 1.3)</td>
<td>0.9 (0.4, 1.8)</td>
<td>0.1 (−0.7, 0.9)</td>
<td>0.2 (−1.1, 1.6)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.49</td>
<td>0.11</td>
<td>0.04</td>
<td>0.81</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Very high anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Ref</td>
<td>1.3 (0.7, 2.4)</td>
<td>1.9 (1.1, 3.5)</td>
<td>3.5 (1.9, 6.4)</td>
<td>1.4 (0.7, 2.8)</td>
<td>1.2 (0.5, 2.9)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.43</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>0.31</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Case-level distress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Ref</td>
<td>1.0 (0.6, 1.7)</td>
<td>1.4 (0.9, 2.3)</td>
<td>1.6 (0.8, 2.4)</td>
<td>1.3 (0.7, 2.1)</td>
<td>1.0 (0.4, 2.3)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.92</td>
<td>0.17</td>
<td>0.25</td>
<td>0.48</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Worry about cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Ref</td>
<td>1.1 (0.6, 2.1)</td>
<td>4.8 (2.8, 7.9)</td>
<td>4.9 (2.7, 8.8)</td>
<td>3.0 (2.8, 8.9)</td>
<td>0.90 (0.4, 2.1)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.67</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>High concern</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Ref</td>
<td>0.05 (0.02, 0.1)</td>
<td>0.07 (0.03, 0.2)</td>
<td>1.8 (1.2, 2.9)</td>
<td>1.1 (0.7, 1.8)</td>
<td>0.10 (0.02, 0.5)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.001</td>
<td>0.01</td>
<td>0.60</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>High reassurance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>Ref</td>
<td>12.0 (6.6, 21.7)</td>
<td>10.9 (6.3, 18.7)</td>
<td>13.0 (8.2, 21.3)</td>
<td>13.0 (8.2, 20.7)</td>
<td>5.7 (2.4, 13.1)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.001</td>
<td>0.001</td>
<td>0.24</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*p ≤ 0.05 interpreted as statistically significant (shown in bold). Adjusted for age, marital status, ethnicity, index of multiple deprivation (IMD), education, number of previous screens and NMS site. Weighted by age group and IMD quintile.

The reference group for concern and reassurance is HPV positive with normal cytology due to very low and very high proportions (respectively) of positive responses in the control group for these two outcomes.

Abbreviations: 95% CI, 95% confidence intervals; IMD, mean difference; Ref, reference group.

Skills training for sample taken to areas which are anticipated to increase women’s anxiety (e.g., fear of cancer, sexual implications, transmission) should help minimise adverse psychological responses. Reasons for the switch to HPV primary screening should also be clearly communicated to the public ahead of implementation, to reduce the risk of a public backlash like the one recently observed in Australia, where a majority of individuals believed that switching to HPV primary screening would miss some cervical cancers. So far, there does not seem to have been any opposition to HPV primary screening in the English pilot site, suggesting that current communication efforts are working effectively. The findings of our study should help to inform national screening implementation policies and evaluations in other countries where HPV primary screening is being implemented. Future research should explore what makes women most anxious and determine the strongest modifiable predictors of anxiety (and very high anxiety) in women testing HPV positive, to inform the development of interventions.

Conclusions
Testing positive for HPV with normal or abnormal cytology was associated with short-term adverse psychological effects in routine HPV primary screening, although it is unlikely that this will lead to significant disruption of daily functioning for most women. Our cross-sectional comparison of women receiving their first vs second HPV positive with normal cytology test result suggests that anxiety is likely to be short-lived and does not persist for women on 12-month early recall.

Acknowledgements
We would like to thank the NHS clinical laboratory managers and staff at the HPV primary screening pilot sites who helped us gain HRA approval and recruit participants (Kay Ellis, Christopher Swain, Nicola Fagan, Viki Fene, Mike Holbrook, Janet Parker, David Smith and Cami Taylor). We thank Ruth Stables and Karen Denton at Public Health England for facilitating the public-facing aspects of the study and helping with HRA approval. Thank you to Maritza Rebol and Christopher Matthews at King’s College London who provided us with population-level screening data to allow us to weight our sample, as well as providing helpful guidance at several points in the study. Thanks to Lauren Rodreque and Riey Bennett who helped with participant recruitment and data entry. Finally, thank you to the women who kindly gave up their time to participate. Our study was funded by Public Health England (PHE). PHE funded Emily McAuley from 03/03/2016 until 30/09/2017. EM was funded by the National Institute for Health Research (NIHR) from 01/10/2017 (1387- 2017-1805); the views expressed in this article are not necessarily those of the NIHR, the NIHR or the Department of Health and Social Care. PHE
also funded to DB, JW, LM and AF are funded by Cancer Research UK (C7492A17219 and C49986/A174295). HK and JP were not funded.

Author contributions

McBride E, Forster A. Project management: McBride E, Weller J. Experimental analyses: Ridout D, McBride E. McBride E. Drafted the manuscript: McBride E, Weller J. Final version of the manuscript: all authors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

References
34. Cremers F, Dall B, Borren C, et al. It has saved the author’s life; is why change it? Con- tent analysis of objections to cervical screening programmes changes in Australia. BMJ Epub 2018;369:k137.
Appendix 3.2 - Published protocol paper for Study 2 in BMJ Open (7 pages).
(hrHPV) DNA testing as the primary test in cervical screening is more sensitive for detecting cervical intraepithelial neoplasia (CIN2 or worse) and may be more cost-effective, although not all studies have found this to be the case.5,6 Also, given that the HPV vaccine was introduced into UK schools in 2008, HPV primary testing may be the most appropriate option for vaccinated cohorts entering the cervical screening programme.7,8 In the UK, shifting to a HPV primary testing algorithm would mean that samples taken from women attending cervical screening would first be tested for hrHPV, and cytology would only be carried out on the residual samples of women who were HPV negative. Women who were HPV negative would return to routine recall in 3 or 5 years, while those who were HPV positive would be managed according to their HPV and cytology results. In line with HPV triage methods, women testing positive for hrHPV with abnormal cytology would be referred immediately for colposcopy. However, a key difference of HPV primary testing, relative to the current algorithm, is that it would generate a new group of women with normal cytology and hrHPV-positive results, with these women being recalled for repeat HPV testing at 12 months.

HPV testing has a high negative predictive value, which means that there is the possibility to reassure women who are concerned or anxious about developing cervical cancer and, potentially, to increase the interval between screening tests. Since 2013, the NHSCSP has been using primary HPV testing across six sites in England, and the Department of Health has recently announced its intention to roll this out nationally.9 A full description of the primary HPV screening algorithm can be found on the Public Health England website.10

The evidence is mixed regarding whether HPV testing in the context of cervical screening is associated with adverse psychological effects. A cross-sectional evaluation of HPV triage in the NHSCSP found temporary adverse psychological effects, whereby increased anxiety, distress and concern were present shortly after women received HPV-positive results, but not at 6 months follow-up.11 12 This is in line with qualitative research, which suggested that communication of HPV-positive results may lead to feelings of anxiety, stigma, stress and concern about sexual relationships.13 However, a large randomised controlled trial which considered differences in anxiety and distress between women receiving cytology results alone and women also receiving HPV results indicated no overall differences between the groups. The study did find, however, that among women whose HPV results were revealed to them, anxiety and distress were higher in those who received HPV-positive results relative to HPV-negative results.14

Thus, although previous research has suggested a trend towards increased anxiety and distress associated with HPV-positive results, the psychological impact is not clear in the context of HPV primary testing, where communication of HPV results to all women entering the programme will be routine and there will be far greater numbers of women receiving hrHPV-positive results compared with HPV triage for low-grade and borderline cytology. Previous research has indicated poor knowledge and understanding of the link between HPV and cervical cancer, and between HPV and sexual activity, among women in the UK.14 15 Therefore, if the meaning of HPV results and cancer risk are not well understood, this has the potential to induce unnecessary anxiety. This is particularly relevant for women who are told that they are HPV positive with normal cytology results given that, under the new algorithm, they will be aware that they have hrHPV but there will be no further clinical investigation for 12 months. The likelihood of this subgroup developing cervical cancer in the interim period is extremely low. However, it is possible that women may still feel anxious and/or distressed. Anxiety and distress may be accentuated if women do not fully understand the meaning of these test results. In the light of the high prevalence of HPV, especially in younger women (under 30 years),16 it is expected that a large number of women will fall into this new 12-month recall category. In order for the NHSCSP to achieve the sensitivity gains of switching to HPV primary testing, it is important that women in this group attend their recall appointment at 12 months without experiencing significant anxiety in the interim.

Rationale for the study
With changes to the protocol for screening and follow-up, it is important that psychological factors are evaluated to help determine the information needs and support required for women engaging in HPV primary testing. Information materials for HPV primary testing have already been developed by NHSCSP.17 However, it is unclear whether these are sufficient to ensure that women have a good understanding of their screening results and their own cervical cancer risk.

In line with a previous psychological evaluation of HPV triage within the NHSCSP,17 18 our primary aim is to consider the impact of this new cervical screening algorithm on anxiety and distress. Epidemiological and cost-effectiveness analyses of HPV primary testing are already under way. This study protocol is for an evaluation of the psychological aspects of introducing primary HPV testing into the NHSCSP.

METHODS AND ANALYSIS

Design
A cross-sectional between-groups design will be employed to assess women at baseline (shortly after receiving their screening result), 6 months postscreening result and 12 months postscreening result.

Participants and eligibility
Participants will include women aged 25–64 years who have taken part in the NHSCSP in one of five sites
where HPV primary testing has been introduced: North London, Sheffield, Norfolk and Norwich, Liverpool and Manchester NHS Trusts.

Eligible women will include those who have received a test result within the recruitment period at each NHS site (~12 weeks recruitment at each).

We will recruit three groups of women following their first HPV test, including those who test negative for HPV, those who are HPV positive with normal cytology and those who are HPV positive with abnormal cytology (groups 1 to 3 in table 1). In addition, we will recruit two groups of women who had initially tested positive for HPV with normal cytology, and who have recently attended their 12-month follow-up appointment, including women who have persistent HPV, and those who tested HPV negative at the recent test (groups 4 and 5 in table 1). We will also recruit a control group of women who have been screened using cytology only and have received a normal result (the participating sites have not yet introduced HPV primary screening for all women). This means there will be a total of six possible combinations of HPV and cytology results for eligibility in this study (six recruitment groups). See table 1 for an overview.

Table 1: HPV and cytology results for the six groups included in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>HPV result</th>
<th>Cytology result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Negative</td>
<td>Not tested</td>
</tr>
<tr>
<td>2</td>
<td>Positive</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>Positive</td>
<td>Abnormal</td>
</tr>
<tr>
<td>4</td>
<td>Persistent positive at 12 months</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>Negative at 12 months</td>
<td>None</td>
</tr>
<tr>
<td>6 (control)</td>
<td>None</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Women in groups 1 and 5 will all have tested HPV positive with normal cytology at their first screen and will be recruited to the study after their 12-month follow-up test. HPV, human papillomavirus.

Potential participants will be mailed invitation packs to their home address. Invitation packs will include an invitation letter, participant information sheet, consent form and a baseline questionnaire booklet. If participants have not returned the questionnaire after 3 weeks, Docmail will send a reminder pack containing the same documents. Those who opt to take part can do so by returning a completed consent form and questionnaire booklet to UCL.

Participants will also be mailed postal questionnaire packs at 6 and 12 months follow-up. Again, they will be sent a reminder pack containing a reminder letter and another copy of the questionnaire 3 weeks later.

Data from NHS clinical records

Patient age, index of multiple deprivation score (derived from postcode), date of most recent cervical screen, date of last (previous) cervical screen, number of previous cervical screens and test results will be transferred as population data to UCL, from each NHS site for all potential participants approached, with the exception of patients who have opted out. These data will contain no identifiable information; data will be pseudonymised using unique identity numbers. These additional data sets will include survey non-responders to allow for examination of response biases in relation to demographic and screening factors.

Primary outcomes

State anxiety, measured by the State Trait Anxiety Inventory (STAI)-62, and general distress, measured by the General Health Questionnaire (GHQ-28) will be the primary outcome measures.

HPV and cytology screening results (groups 1 to 6 as outlined in table 1) will be the independent variable for primary analyses. See table 2 for an overview of primary outcome measures.

Secondary outcomes

Understanding of screening results, knowledge of HPV-related risk of developing cervical cancer, concern about screening result, psychosocial functioning and intention to engage in future screening will act as secondary outcome measures. Health-related quality of life will also be collected; however, it will be used by Public Health England as part of the health economic evaluation, and will not form part of this psychological evaluation. See table 3 for an overview of secondary outcome measures.

Descriptive measures

Age, ethnicity, marital status, index of multiple deprivation (a measure of deprivation linked to an individual's residential postcode), education level, NHS site, previous screening history and HPV vaccine status will be collected for descriptive information and as potential control factors. See table 4 for an overview.
Table 2. Primary outcome measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>State-trait anxiety</td>
<td>The state-trait anxiety inventory short-form (STAI-6) is a six-item validated questionnaire used to measure state-trait anxiety.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
<tr>
<td>General distress</td>
<td>The General Health Questionnaire (GHQ-12) is a 12-item validated questionnaire used to measure general distress.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
<tr>
<td>Test results (HPV and cytology)</td>
<td>HPV and cytology screening results will be communicated to UCL from participating laboratories at NHS sites. Participants will receive one of six possible standardized results (see eligibility criteria for breakdown of groups). Screening result will act as the independent variable for primary analyses.</td>
<td>Communicated to researchers at UCL from NHS clinical records.</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus; NHS: National Health Service; UCL: University College London.

Sample size

The study has been powered to detect a small-medium between-group difference (f=0.14) in anxiety (as measured by the STAI-6). On the basis of previous studies, we expect anxiety scores across groups to be in the range of 30–40, with an SD of 12. With an α of 0.05, a sample size of 673 will give us 80% power to detect a between-group difference in anxiety.

Assuming an initial response rate of 85%, with 75% of initial responders returning a second questionnaire at 6-month follow-up, and 75% of responders at 6 months completing a third questionnaire at 12 months, we plan to approach 5415 participants to achieve the target sample size. Response rate will be monitored as the study progresses so that the number of women approached at baseline can be adjusted if the response rate is higher or lower than expected (within our funding constraints).

Data analyses and statistics

Data will be coded and analysed using SPSS, R and Stata. An α level of p<0.05 will be used throughout.

Preliminary analyses (analysis of variance (ANOVA)s) and χ² will be conducted to explore descriptive statistics and to identify significant group differences, as potential control measures, for age, index of multiple deprivation, marital status, ethnicity and educational attainment. Primary analyses will comprise between-groups ANOVA to explore whether anxiety and general distress differ between screening result groups shortly after initial presentation of screening result (baseline).

Mixed ANOVA will be conducted to explore whether differences in anxiety and general distress are observed between screening result groups over time (baseline, 6 months and 12 months).

General linear modelling will be conducted to consider whether understanding of screening results, knowledge of HPV, perceived risk of developing cervical cancer, concern about screening result, psychosocial functioning and intention to engage in future screening differ between screening result groups for secondary analyses.

Health-related quality of life data will be analysed in the health economic cost-effectiveness evaluation (not as part of this psychological evaluation). Post hoc comparisons will be conducted where appropriate and effect sizes will be calculated.

DISCUSSION

This psychological evaluation of HPV primary testing within the NHSCSP will provide evidence about the psychological consequences of testing positive for HPV in this context and is expected to show that the negative consequences are minimal and short-lived, as has been found when HPV testing is used to triage women. The findings should help identify any unmet information needs of women taking part in the programme. If adverse psychological effects are observed, the results will help to inform the development of materials and/or procedures aimed at ensuring clarity in the meaning of test results and reducing psychological burden. Given that a ministerial announcement has now been made, stating that HPV primary screening is to be rolled out across England and incorporated into routine NHS practice, the study findings are likely to directly inform finalised NHSCSP test invitation letters, result letters and accompanying HPV information materials. They may also help inform the development of pragmatic interventions (e.g., training programmes, written information) for healthcare professionals working in cervical screening, to promote effective communication and address common concerns for women undergoing HPV primary screening.

We will be gathering certain population-level data from NHS databases on all women approached to take part in this study, including index of multiple deprivation score, age, test results and cervical screening history. From this information, along with questionnaire data collected from study participants, we will explore predictive relationships between outcomes. This may help identify certain groups of women likely to need additional support. For example, previous research has suggested that younger age and lower understanding...
<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Understanding of results</td>
<td>Understanding of screening results will be measured via a scale developed for this study, which consists of six questions considering perceived meaning of results and cervical screening information sources. Participants will be asked: 1. What do you think your screening result means for your current health?—I have/am likely to have/am unlikely to have/am very unlikely to have/definitely do not have cervical cancer, or I do not know. 2. Can you remember what your screening result was?—HPV and cytology results indicated separately via prompted response. 3. How confident are you that you understand the meaning of your screening result?—five-point Likert scale ranging from 'not at all confident' to 'very confident'. 4. When were invited for your recent screening test, how much of the information did you read?—six-point Likert scale ranging from 'none' to 'all of it', or 'cannot remember'. 5. Did you look for any extra information about the screening test or your result?—Yes/no/cannot remember. 6. Do you have any unanswered questions about cervical screening or HPV testing?—Presented with free text box. Understanding of results will only be measured at baseline.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
<tr>
<td>Knowledge of HPV</td>
<td>Knowledge of HPV will be measured using an adapted tool which asks participants to answer true or false to 10 statements about HPV. This tool has been adapted by only including those questions reflective of the information provided to women in the NHSCSP materials. Participants will also be asked whether they have heard of HPV before today and how they would rate their knowledge on a five-point Likert scale between 'very poor' and 'very good'. Knowledge will only be measured at baseline.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
<tr>
<td>Perceived risk of cervical cancer</td>
<td>Perceived risk of developing cervical cancer will be assessed by asking participants to answer: 'Compared with other women the same age as you, do you think your chances of developing cervical cancer in the next 10 years are...?'. Answers will range on a five-point Likert scale from 'much below average' to 'much above average'. This is an adapted scale from Maresi et al. As in Maresi et al, concern will be measured by asking (1) how concerned and (2) how worried you feel about your recent screening result? Participants will also be asked an additional question: 'how worried are you about getting cervical cancer in the next 10 years?'.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
<tr>
<td>Concern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to attend future screening</td>
<td>Participants will be asked one question: 'will you go for cervical screening next time you are invited?' Answers will be indicated on a five-point Likert scale ranging between 'yes, definitely' and 'definitely not'.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
<tr>
<td>Psychosexual functioning</td>
<td>The Psychosocial Effects of Abnormal Pap Smear Questionnaire short-form (PEAPS-Q-S) is a five-item validated questionnaire used to measure distress experienced by women undergoing follow-up investigation after an abnormal Pap smear result. Not all participants will have received abnormal test results; therefore, we slightly adapted this scale by inserting a 'not applicable' option after each question.</td>
<td>Self-reported by participants with HPV results in questionnaire.</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>The Health-Related Quality of Life Questionnaire short-form (EQ-5D) is a 5-item validated tool used to assess five dimensions related to quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This will be collected by UCL but analysed and reported as part of the PHE health-economic evaluation.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
</tbody>
</table>
Table 4 Descriptive outcome measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Ethnicity, educational attainment, employment and marital status will be assessed via questionnaire. Age of participant will be communicated to UCL from participating laboratories at plot sites. This will be measured at baseline.</td>
<td>Self-reported in questionnaire. Age at baseline, communicated to UCL from NHS clinical records.</td>
</tr>
<tr>
<td>Index of multiple deprivation</td>
<td>Index of Multiple Deprivation score (IMD) will be assigned to participants by laboratories and communicated to UCL. The IMD is a measure of area level deprivation which can be derived from a postcode. It takes into account: income deprivation; employment deprivation; educational, skills and training deprivation; health deprivation and disability; crime; barriers to housing services; and living environment deprivation.</td>
<td>Calculated by the NHS via clinical records and communicated to UCL in score form.</td>
</tr>
<tr>
<td>NHS Site</td>
<td>The NHS site where women are screened and receive test results will be recorded via communication from participating laboratories.</td>
<td>Communicated to UCL by NHS site.</td>
</tr>
<tr>
<td>Previous screening history</td>
<td>Previous screening history will be communicated to UCL from participating laboratories. This information will include date of last screening and number of previous screenings. Participants will be asked to indicate whether they have received the HPV vaccine and how many doses they had. This will be measured at baseline.</td>
<td>Communicated to UCL from NHS clinical records.</td>
</tr>
<tr>
<td>HPV vaccine status</td>
<td>Participants will be asked to indicate whether they have received the HPV vaccine and how many doses they had. This will be measured at baseline.</td>
<td>Self-reported by participant in questionnaire.</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; NHS, National Health Service; UCL, University College London.

DISSEMINATION

We plan to publish the results of this study in two peer-reviewed journal articles. In the first paper, we will report between-group differences at baseline for all outcomes. In the second paper, we will report outcomes which are relevant to analyses over time (6 and 12 month follow-up) and explore predictive relationships. Results will also be disseminated through presentations at national and international conferences and will be communicated to the NHSCSP and relevant third sector organisations, such as Jo’s Cervical Cancer Trust.

Funding: This project is funded by Public Health England, JWH and LM are funded by Cancer Research UK (C4992A1T2019) and AF is also funded by Cancer Research UK (C4992A1T2019).

Competing interests: None declared.

Ethics approval: Health Research Authority approval was obtained on 24 September 2016 and approval from London-Surrey NHS Research Ethics Committee (REC) on 30 August 2016. Section 251 approval was also obtained from the Confidentiality Advisory Group (CAG) for the purposes of participant approach on 24 August 2016.

Provenance and peer review: Not commissioned, externally peer reviewed.

Data sharing statement: Data will be available for data sharing from the corresponding author, after publication of our final paper.

Open Access: This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/

REFERENCES


Appendix 3.3 - HRA Approval Letter for Study 2 (2 pages).

Health Research Authority

26 September 2016
Dear Dr Waller

Study title: Psychological Impact of Primary Screening for HPV
IRAS project ID: 199464
RFC reference: 160/0/10562
Sponsor: UCLH

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England
The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. Please read Appendix B carefully, in particular the following sections:

- Participating NHS organisations in England – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities.

- Confirmation of capacity and capability – this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.

- Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria) – this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices
The HRA Approval letter contains the following appendices:
- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval
The document “After Ethical Review – guidance for sponsors and investigators”, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the After Ethical Review document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope
HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/ira-hra-nd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback
The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application
Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of any other Regulatory Approvals e.g. NICE and all</td>
<td>1</td>
<td>25 August 2016</td>
</tr>
<tr>
<td>correspondence [CAS first letter]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Covering letter on headed paper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)</td>
<td>1</td>
<td>22 February 2016</td>
</tr>
<tr>
<td>Letter to confirm UCLH NHS FT insurance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)</td>
<td>1</td>
<td>22 February 2016</td>
</tr>
<tr>
<td>Insurance certificate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRAS Application Form [IRAS_Form_20042016]</td>
<td>1</td>
<td>26 April 2016</td>
</tr>
<tr>
<td>Letter from funder [from FHI]</td>
<td>1</td>
<td>18 August 2016</td>
</tr>
<tr>
<td>Letters of invitation to participant [Reminder Letter]</td>
<td>1</td>
<td>24 August 2016</td>
</tr>
<tr>
<td>Letters of invitation to participant [Cover Letter]</td>
<td>2</td>
<td>23 September 2016</td>
</tr>
<tr>
<td>Non-validative questionnaire [Non-Validated Questionnaires]</td>
<td>1</td>
<td>25 April 2016</td>
</tr>
<tr>
<td>Non-validative questionnaire [Questionnaire booklet]</td>
<td>1</td>
<td>04 July 2016</td>
</tr>
<tr>
<td>Other [Statement of Activities]</td>
<td>2</td>
<td>23 September 2016</td>
</tr>
<tr>
<td>Other [Schedule of Events]</td>
<td>2</td>
<td>23 September 2016</td>
</tr>
<tr>
<td>Participant information sheet (PIS)</td>
<td>1</td>
<td>23 September 2016</td>
</tr>
<tr>
<td>Research protocol or project proposal [PIPS Protocol]</td>
<td>2</td>
<td>24 March 2016</td>
</tr>
<tr>
<td>Summary CV for Chief Investigator (CD) [ie Walker CV]</td>
<td></td>
<td>01 April 2016</td>
</tr>
<tr>
<td>Summary, synopsis or diagram (flowchart) of protocol in non</td>
<td>1</td>
<td>24 February 2016</td>
</tr>
<tr>
<td>technical language [Information on data flows between NHS Trust,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UCL and DoQsmail]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validated questionnaire [General Distress]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validated questionnaire [State-Trait Anxiety]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validated questionnaire [Health-related Quality of Life]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Validated questionnaire [Psychosocial Functioning]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3.4 – Questionnaire and consent form used for Study 2 (5 pages).
**TODAY’S DATE:** ___________________________

First, we’d like to know how you’re feeling at the moment.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Somewhat</th>
<th>Moderately</th>
<th>Very much so</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel calm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel tense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel upset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel relaxed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel content</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel worried</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Have you recently...

**Been able to concentrate on what you’re doing?**

- Better than usual
- Same as usual
- Less than usual
- Much less than usual

**Lost much sleep over worry?**

- Not at all
- No more than usual
- Rather more than usual
- Much more than usual

**Felt that you are playing a useful part in things?**

- More so than usual
- Same as usual
- Less useful than usual
- Much less useful

**Felt capable of making decisions about things?**

- More so than usual
- Same as usual
- Less than usual
- Much less capable

---

**Study ID:**

<table>
<thead>
<tr>
<th>Have you recently...</th>
<th>Not at all</th>
<th>No more than usual</th>
<th>Rather more than usual</th>
<th>Much more than usual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felt constantly under strain?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Felt you couldn’t overcome your difficulties?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Been able to enjoy your normal day-to-day activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Been able to face up to your problems?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Been feeling unhappy and depressed?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Been losing confidence in yourself?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Been thinking of yourself as a worthless person?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Been feeling reasonably happy, all things considered?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**344**
Under each heading, please tick the box that describes your health TODAY:

**Mobility – walking about**
- I have no problems in walking about
- I have slight problems in walking about
- I have moderate problems in walking about
- I have severe problems in walking about
- I am unable to walk about

**Self-care – looking after myself**
- I have no problems washing or dressing myself
- I have slight problems washing or dressing myself
- I have moderate problems washing or dressing myself
- I have severe problems washing or dressing myself
- I am unable to wash or dress myself

**Usual activities, e.g. work, leisure**
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

**Pain or discomfort**
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

**Anxiety or depression**
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

---

**Study ID:**

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100
100 means the best health you can imagine.
0 means the worst health you can imagine.
Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below:

YOUR HEALTH TODAY = 

---

The best health you can imagine

The worst health you can imagine

345
Thinking about the results of your recent cervical screening test...

How concerned do you feel about your recent screening result?

☐ Not at all concerned
☐ Slightly concerned
☐ Somewhat concerned
☐ Moderately concerned
☐ Very concerned

How reassured do you feel by your recent screening result?

☐ Not at all reassured
☐ Slightly reassured
☐ Somewhat reassured
☐ Moderately reassured
☐ Very reassured

How worried are you about getting cervical cancer in the next ten years?

☐ Not at all worried
☐ Slightly worried
☐ Somewhat worried
☐ Moderately worried
☐ Very worried

Thinking about the results of your recent cervical screening test...

Can you remember what your screening result was?
You may have had an HPV test (to see if HPV was present) or a cytology test (to see if cells looked normal) or both.

HPV result (please tick one)

☐ HPV was found
☐ HPV was not found
☐ No HPV test
☐ Not sure

Cytology (smear) test (please tick one)

☐ Normal cytology (no cell changes)
☐ Abnormal cytology (cell changes found)
☐ No cytology test
☐ Not sure

How confident are you that you understand the meaning of your screening result?

☐ Not at all confident
☐ Slightly confident
☐ Somewhat confident
☐ Moderately confident
☐ Very confident

What do you think your screening result means for your current health?

☐ I definitely do not have cervical cancer
☐ I am very unlikely to have cervical cancer
☐ I am unlikely to have cervical cancer
☐ I am likely to have cervical cancer
☐ I have cervical cancer
☐ I don't know
Compared with other women the same age as you, do you think your chances of developing cervical cancer in the next ten years are...

- Much below average
- A little below average
- Average for women of my age
- A little above average
- Much above average

When you were invited for your recent screening test, how much of the information did you read?

- None
- A little
- Some of it
- Most of it
- Almost all of it
- All of it
- Can’t remember

Did you look for any extra information about the screening test or your results?

- Yes
- No
- Can’t remember

If yes, where did you get the extra information?

- GP or practice nurse
- Internet (please say where)
- Family member or friend
- Other (please say where)
- Leaflet or book

Do you have any unanswered questions about cervical screening or HPV testing?

- Yes
- No
- Not sure

Before today, had you ever heard of HPV (human papillomavirus)?

- Never heard of HPV
- Very poor
- Poor
- Fair
- Good
- Very good

Please look at these statements and say whether you think each one is true or false. If you haven’t heard of HPV, you can leave this section blank.

<table>
<thead>
<tr>
<th>Statement</th>
<th>True</th>
<th>False</th>
<th>Don’t Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV is very rare</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV always has visible signs or symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV can cause cervical cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV can be passed on by genital skin-to-skin contact</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>There are many types of HPV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV can be passed on during sexual intercourse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men cannot get HPV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV usually doesn’t need any treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most sexually active people will get HPV at some point in their lives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A person could have HPV for many years without knowing it</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Since receiving your screening result...

- Have you been worried whether you should continue having sex?
  - Not at all
  - A little
  - A fair bit
  - Quite a lot
  - Very much
  - Not applicable

- Have you been worried others think you have had more sexual partners than you should?
  - Not at all
  - A little
  - A fair bit
  - Quite a lot
  - Very much
  - Not applicable

- Have you been worried about whether your test result would have a bad effect on your relationship with your partner?
  - Not at all
  - A little
  - A fair bit
  - Quite a lot
  - Very much
  - Not applicable

- Have you been worried whether having sex will make the problem worse?
  - Not at all
  - A little
  - A fair bit
  - Quite a lot
  - Very much
  - Not applicable

- Have you been worried that you could give the problem to a sexual partner?
  - Not at all
  - A little
  - A fair bit
  - Quite a lot
  - Very much
  - Not applicable

- Have you been worried a sexual partner will think they can catch the problem from you?
  - Not at all
  - A little
  - A fair bit
  - Quite a lot
  - Very much
  - Not applicable
Appendix 3.5 – Results of univariate analysis for primary & secondary outcomes by result groups (unweighted & using raw data only) for Study 2 (2 pages).

<table>
<thead>
<tr>
<th></th>
<th>Control (no HPV test)</th>
<th>HPV negative</th>
<th>HPV positive, normal cytology</th>
<th>HPV positive, abnormal cytology</th>
<th>HPV persistent at 12-months</th>
<th>HPV cleared at 12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD (95% CI)</td>
<td>ref</td>
<td>-2.0 (-4.5, 0.61)</td>
<td>3.4 (0.8, 6.0)</td>
<td>7.2 (4.4, 10.1)</td>
<td>1.9 (-0.9, 4.7)</td>
<td>2.1 (-1.8, 6.0)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.14</td>
<td>0.01</td>
<td>&lt;.001</td>
<td>0.19</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td><strong>Distress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD (95% CI)</td>
<td>ref</td>
<td>-0.4 (-1.0, 0.3)</td>
<td>0.4 (-0.2, 1.1)</td>
<td>1.0 (0.3, 1.7)</td>
<td>0.2 (-0.5, 0.9)</td>
<td>0.2 (-0.7, 1.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.26</td>
<td>0.16</td>
<td>&lt;.01</td>
<td>0.60</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td><strong>Very high anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>ref</td>
<td>1.0 (0.6, 1.7)</td>
<td>1.8 (1.1, 3.1)</td>
<td>3.5 (2.0, 5.9)</td>
<td>1.4 (0.8, 2.5)</td>
<td>1.4 (0.7, 3.1)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.96</td>
<td>0.02</td>
<td>&lt;.001</td>
<td>0.27</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td><strong>Case-level distress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds Ratio (95% CI)</td>
<td>ref</td>
<td>0.9 (0.6, 1.4)</td>
<td>1.2 (0.8, 1.8)</td>
<td>1.5 (0.9, 2.3)</td>
<td>1.2 (0.8, 2.0)</td>
<td>1.0 (0.5, 1.9)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.55</td>
<td>0.40</td>
<td>0.11</td>
<td>0.35</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
<td>Odds Ratio (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------------</td>
<td>---------</td>
<td>---------------------</td>
<td>---------</td>
<td>---------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Worry about cancer</td>
<td>ref</td>
<td>0.9</td>
<td>(0.5, 1.5)</td>
<td>0.69</td>
<td>4.6</td>
<td>(2.9, 7.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0</td>
<td>(3.0, 8.1)</td>
<td>4.6</td>
<td>(2.8, 7.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.2</td>
<td>(0.5, 2.5)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>High concern</td>
<td>0.07</td>
<td>(0.03, 0.2)</td>
<td>0.06</td>
<td>(0.03, 0.1)</td>
<td>ref*</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td></td>
<td>0.06</td>
<td>(0.03, 0.1)</td>
<td>ref*</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.1</td>
<td>(0.03, 0.3)</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>High reassurance</td>
<td>13.5</td>
<td>(7.9, 23.0)</td>
<td>12.1</td>
<td>(7.5, 19.7)</td>
<td>ref*</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>&lt;.001</td>
<td></td>
<td>12.1</td>
<td>(7.5, 19.7)</td>
<td>ref*</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.2</td>
<td>(3.2, 12.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

MD = mean difference; 95% CI = 95% confidence intervals; p = <.05 interpreted as statistically significant.

Ref = reference group. *The reference group for concern and reassurance is HPV positive with normal cytology due to very low and very high proportions (respectively) of positive responses in the control group for these two outcomes.
Appendix 4.1 - HRA approval letter for Studies 3 and 4 (3 pages).

Study title: HPV primary testing in cervical cancer screening; using behavioural science to understand anxiety and attendance
IRAS project ID: 236992
REC reference: 18/EM/0227
Sponsor: University College London

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales? You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should formally confirm their capacity and capability to undertake the study. How this will be confirmed is detailed in the “summary of assessment” section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a ‘green light’ email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland? HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.
If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document “After Ethical Review – guidance for sponsors and investigators”, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?

You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Emily McBride

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Yours sincerely

Email: hra.approval@nhs.net

Copy to:
List of Documents
The final document set assessed and approved by HRA and HCRW Approval is listed below.

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmation of any other Regulatory Approvals (CAG outcome/ s251 support)</td>
<td></td>
<td>07 January 2019</td>
</tr>
<tr>
<td>Copies of advertisement materials for research participants [Poster]</td>
<td>1</td>
<td>10 October 2016</td>
</tr>
<tr>
<td>Covering letter on headed paper</td>
<td>1</td>
<td>05 July 2018</td>
</tr>
<tr>
<td>Covering letter on headed paper</td>
<td></td>
<td>22 August 2019</td>
</tr>
<tr>
<td>Evidence of Sponsor insurance or indemnity (non-NHS Sponsors only)</td>
<td></td>
<td>25 July 2018</td>
</tr>
<tr>
<td>HRA Schedule of Events</td>
<td>2</td>
<td>20 September 2018</td>
</tr>
<tr>
<td>HRA Statement of Activities</td>
<td>2</td>
<td>20 September 2018</td>
</tr>
<tr>
<td>Interview schedules or topic guides for participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRAS Application Form [IRAS_Form_0000720178]</td>
<td></td>
<td>06 July 2018</td>
</tr>
<tr>
<td>Letter from funder [NHR]</td>
<td></td>
<td>25 August 2017</td>
</tr>
<tr>
<td>Letter from sponsor (Confirmation of sponsorship)</td>
<td></td>
<td>25 June 2018</td>
</tr>
<tr>
<td>Letters of invitation to participant</td>
<td>1</td>
<td>15 June 2018</td>
</tr>
<tr>
<td>Letters of invitation to participant [Invited for interview]</td>
<td>1</td>
<td>22 August 2018</td>
</tr>
<tr>
<td>Letters of invitation to participant [Not invited for interview]</td>
<td>1</td>
<td>22 August 2018</td>
</tr>
<tr>
<td>Non-validated questionnaire [Non-validated questions]</td>
<td>1</td>
<td>19 June 2018</td>
</tr>
<tr>
<td>Notice of Substantial Amendment (non-CTIMP)</td>
<td>1</td>
<td>10 November 2018</td>
</tr>
<tr>
<td>Other [Blog content]</td>
<td>1</td>
<td>19 November 2018</td>
</tr>
<tr>
<td>Other [ Tear-off slip with contact details]</td>
<td>1</td>
<td>22 August 2018</td>
</tr>
<tr>
<td>Participant consent form</td>
<td>1</td>
<td>15 June 2018</td>
</tr>
<tr>
<td>Participant information sheet (PIG) [Study 1]</td>
<td>4</td>
<td>09 January 2016</td>
</tr>
<tr>
<td>Participant information sheet (PIS) [Study 2]</td>
<td>2</td>
<td>08 January 2019</td>
</tr>
<tr>
<td>Referee’s report or other scientific critique report [NIHR summary reviews]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Research protocol or project proposal</td>
<td>1</td>
<td>08 June 2018</td>
</tr>
<tr>
<td>Summary CV for Chief Investigator (CI) [Jo Walker]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary CV for student [Emily McDowell]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary CV for supervisor [student research] [Laura Marr]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary, synopsis or diagram (flowchart) of protocol in non-technical language</td>
<td>1</td>
<td>20 June 2018</td>
</tr>
<tr>
<td>Validated questionnaire [Validated questionnaires]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 4.2 - Questionnaire used for Study 3 (6 pages).

Can you remember what your most recent cervical screening result was?  
You may have had an HPV test result or a cytology (smear) test result or both.

<table>
<thead>
<tr>
<th>HPV test</th>
<th>HPV was found</th>
<th>HPV was not found</th>
<th>No HPV test</th>
<th>Not sure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytopathology (smear)</td>
<td>Normal cytology (no cell changes)</td>
<td>Abnormal cytology (cell changes found)</td>
<td>No cytology test</td>
<td>Not sure</td>
</tr>
</tbody>
</table>

First, we’d like to know how you’re feeling at the moment

<table>
<thead>
<tr>
<th>Feeling</th>
<th>Not at all</th>
<th>Somewhat</th>
<th>Moderately</th>
<th>Very much so</th>
</tr>
</thead>
<tbody>
<tr>
<td>I feel calm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel tense</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel upset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel relaxed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel content</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel worried</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Since my cervical screening (smear) result I have been feeling...

<table>
<thead>
<tr>
<th>Feeling</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>In good general health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy about the way my body feels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In control of my body</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worried that I may have something seriously wrong</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerned about my fertility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In good gynaecological health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fearful about cervical cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interested in sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimistic about my future health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### How concerned do you feel about your screening result?

<table>
<thead>
<tr>
<th>Not at all concerned</th>
<th>Slightly Concerned</th>
<th>Somewhat concerned</th>
<th>Moderately concerned</th>
<th>Very concerned</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### How much do you agree with the following statements?

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am concerned about cervical cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am concerned about my sex life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am concerned about the impact of my screening result on my partner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am concerned about something else</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If you are concerned about something else, please indicate what:

- [ ]
- [ ]
- [ ]
- [ ]

### If you are concerned, please indicate what you are most concerned about? Please ONLY tick one.

- [ ] Cervical cancer
- [ ] My sex life
- [ ] The impact of my screening result on my partner
- [ ] Something else
- [ ] Not applicable - I am not concerned

### Have you told anyone about your screening result?

- [ ] Yes
- [ ] No
- [ ] I’d rather not say

### If yes, who did you tell?

<table>
<thead>
<tr>
<th>Partner</th>
<th>Friend</th>
<th>Family</th>
<th>Health professional</th>
<th>Someone else (please indicate who)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Page 2
### Thinking about what HPV means to you (please circle on a scale 1-10)...

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>How much does having HPV affect your life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much longer do you think you will have HPV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much control do you feel you have over your HPV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much do you think cervical screening can help?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much do you experience symptoms from your HPV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How concerned are you about your HPV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How well do you feel you understand HPV?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much does having HPV affect you emotionally?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Please list in order the three most important things that you believe caused your HPV

The most important causes for me are...

1.  
2.  
3.  

#### You will be invited back to cervical screening in around 12 months. Will you attend?

- Yes, definitely  
- Yes, probably  
- Probably not  
- Definitely not  

#### Is there anything that might stop you from attending your next cervical screen (smear test)?

...
Do you think any of the things below might stop you from attending your next screen (smear test)?
Please tick all that apply.

- [ ] No, nothing will stop me
- [ ] I might forget
- [ ] I don’t like being screened
- [ ] I find screening painful
- [ ] I find screening embarrassing
- [ ] It’s difficult to make an appointment at a time that suits me
- [ ] I don’t want to find out my test result
- [ ] I am at low risk of cervical cancer
- [ ] I might be too busy
- [ ] It’s not my main priority

Have you had any symptoms recently that you think might be related to your HPV? Please list any symptoms.

---

We’ve listed a number of general symptoms that you may or may not have experienced in the last 4 weeks...

<table>
<thead>
<tr>
<th>Symptom</th>
<th>I have experienced this symptom within the last 4 weeks</th>
<th>If yes, I think this symptom is related to my HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unusual bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breathlessness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiff joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sore eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain during sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upset stomach</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping difficulties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of strength</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Now please think about when you feel particularly stressed. Do you tend to...

<table>
<thead>
<tr>
<th>Activity</th>
<th>Not at all</th>
<th>A little bit</th>
<th>A fair amount</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turn to work or other activities to take your mind off things</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Get emotional support from others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Give up trying to deal with the situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do something to try to make the situation better</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit your GP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refuse to believe what is happening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Try to see the situation in a different light, to make it seem more positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Look for extra information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Try to come up with a strategy about what to do</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learn to live with the situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Criticise yourself</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speak to your partner, friends or family about it</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use alcohol or other drugs to help you get through it</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pray or meditate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Make fun of the situation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you have any comments about your NHS cervical screening test result letter or information leaflet that you received?

________________________________________________________________________

________________________________________________________________________

How could the NHS improve their screening result letters or information leaflets?

________________________________________________________________________

________________________________________________________________________

The NHS are thinking about ways they could inform women about their cervical screening test results in the future. Please tick all the ways you would be happy to receive your test results.

<table>
<thead>
<tr>
<th>Method</th>
<th>Letter</th>
<th>Text message</th>
<th>Email</th>
<th>Mobile app</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Finally, we’d like to ask you a few general background questions

How old are you? ____________

Please tick the box that best describes your ethnic group
- White (British or Other)
- Black/African/Caribbean/Black British
- Asian/Asian British
- Other ethnic group
- Mixed/multiple ethnic groups
- Prefer not to say

Are you currently diagnosed with an anxiety disorder or depression (or have you been previously)?

<table>
<thead>
<tr>
<th>Mental Health Diagnosis</th>
<th>Currently diagnosed</th>
<th>Previously diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other mental health diagnosis:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Do you know anyone who has ever been diagnosed with cervical cancer?
- No
- Yes, somebody close to me
- Yes, somebody I know but we’re not very close

What is the highest level of education you have completed? (Please tick one only)
- Degree or higher degree
- Higher education qualification
- ONC/BTEC
- No formal qualifications
- A-levels
- Below degree level
- O-levels

How would you describe your current relationship status? (Please tick one only)
- Single
- Married/in a civil partnership
- Widowed
- Living with partner
- Divorced
- Other (please specify): ____________________________

Thank you for taking the time to complete this questionnaire.

PLEASE RETURN THIS QUESTIONNAIRE TO UCL USING THE PRE-PAID ENVELOPE PROVIDED.
Appendix 4.3 - Participant Information Sheet for Study 3 (1 page).

Participant Information Sheet

Understanding anxiety and attendance in cervical screening (IRAS ref: 236982)

Purpose and background to the research

The aim of this study is to improve cervical screening attendance and the way screening results are delivered to women with the same test results as you. I was able to contact you because I am working closely with the NHS, who posed you this invitation pack. We hope to understand how women react to receiving their test result. We will do this by gathering information in a survey and through some 1:1 interviews. This information will be used to help the NHS decide how to word the test result letters they send to women. The research is part of a PhD being conducted at University College London (UCL). We plan to recruit around 260 women to take part in the survey and 40 women to take part in interviews.

Why have I been invited to take part in this study?

I am inviting you to take part because you recently attended NHS cervical screening, and you received the screening test result that I am interested in. The NHS is deciding how to word their letters for other women who get the same test result as you. My study is aimed at understanding how women react to their test result and I would like to hear your views.

What would taking part involve?

You simply need to fill in the short questionnaire and send it back to UCL within 3 weeks of receiving this letter. Using the pre-paid envelope provided (there is no need for a stamp). You can also let me know in your questionnaire whether you would like me to consider you for a confidential 1:1 interview in the next 2-8 weeks. If you select ‘yes’, I would like to be considered’ in your questionnaire, and you are chosen to take part, the interview will last for around 1-1.5 hours and will be audio-recorded. You will be asked about your views on your test result and cervical screening. You will also be asked about your opinion on information important to include in NHS test results letters. Unfortunately, I can’t invite everyone for an interview. I will select people based on their survey answers, so that I can hear a wide range of views.

Do I have to take part?

Taking part is completely voluntary. It is up to you to decide whether or not to take part. Your decision does not affect your medical care or legal rights. If you decide to take part and then change your mind, you can ask for your data to be withdrawn until 01/04/2020 by contacting us and quoting your study ID (found at the top of your survey), in which case it will be destroyed. You can also refuse to answer any question asked in the study – just leave the question blank.

What are the possible benefits of taking part?

There are no guaranteed benefits from taking part in this study. However, your participation will contribute to important research and may help to improve the quality of NHS services for women in the future. You may also find taking part in this research enjoyable and interesting.

What are the possible disadvantages and risks of taking part?

It is possible that you may feel uncomfortable answering some of the questions we ask you in the survey. If this is the case, you are free to leave those questions blank.

If you feel distressed and would like additional support you may wish to inform your GP or contact Jo’s Cervical Cancer Trust (Jo’s Cervical Cancer Trust is a charity which provides information on screening results, HPV and cervical cancer. Their website can be found at http://www.jostrust.org.uk/ and they provide a free helpline which is open Mon-Fri on 0800 802 8000).

The consent process

If you send back your completed survey to UCL, I will understand this to mean that you consent to taking part in this study. If you also tick ‘yes’, I would like to be considered for an interview and provide me with your contact details. I will understand this to mean that you consent to me using your details to invite you to potentially take part in an interview. If you are selected to take part in an interview and decide to go ahead with it, the person who conducts the interview will give you more information and take consent from you in writing.

Will my participation in this study be kept confidential?

Yes, your participation in this study will be kept strictly confidential. We will follow ethical guidelines and policies on data protection and information governance to ensure secure handling of your information. The information you give us in the questionnaires will not have any identifying information about you, unless you choose to provide these details to us (to be considered to take part in an interview). If you do provide these details, your questionnaire answers will be stored separately from any identifiable information. It is likely that the results of the study will be published, but no publications will contain information which identifies you or links back to you or your participation.

How will I use my personal data?

UCL is the sponsor for this study and is based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study. UCL will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will keep identifiable information about you for a maximum of 1 year after the study has finished. Your rights to access, change, or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible. You can find out more about how we use your information at https://www.ucl.ac.uk/privacy/participants-health-and-care-research-privacy-notice.

Individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. NHS England will pass these details to UCL along with the information collected from you. Your information could be used for research in any aspect of health or care, and could be combined with information you provide from other sources held by researchers, the NHS or government. Where the information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you. Where there is a risk that you can be identified, your data will only be used in research that has been independently reviewed by an ethics committee.

NHS England used your name and address to contact you about this research. They used a secure, approved marketing company called ‘OPTi’ to contact you by post. We will not use your contact information for anything other than this study. We will not share your contact information with any other company or organisation.

Cost and reimbursement

Your questionnaire should have come with a pre-paid envelope, so it won’t cost you anything to send back to UCL. If you are selected to take part in a 1:1 interview, I will offer you a £40 Amazon voucher for your time, and cover your travel expenses if you need to travel to London.

Who is organising and funding this study?

UCL are sponsoring this study. Their website can be found at http://www.ucl.ac.uk/ and they provide a free helpline which is open Mon-Fri on 0800 802 8000.

Participant Information Sheet – Version 5, 07.03.2019, IRAS number: 236982
Appendix 5.1 - Published Paper for Study 4 in Psycho-Oncology (9 pages).

Exploring reasons for variations in anxiety after testing positive for human papillomavirus with normal cytology: a comparative qualitative study

Emily McBride¹ | Laura A. V. Marlow² | Kirsty F. Bennett¹ | Selma Stearns¹ | Jo Waller²

¹Department of Behavioural Science and Health, Institute of Epidemiology and Health Care, University College London (UCL), London, UK.
²Cancer Prevention Group, School of Cancer and Pharmaceutical Sciences, King's College London (KCL), London, UK.

Correspondence
Emily McBride, Department of Behavioural Science and Health, Institute of Epidemiology and Health Care, University College London (UCL), London, UK.
Email: emcbride@ucl.ac.uk; Twitter: @EmilyMcBride; @UCL_BHC; LinkedIn: https://uk.linkedin.com/in/emily-mcbride-108425a

Funding Information
National Institute for Health Research, Grant/Award Number: DHR-2017-10-103; Cancer Research UK, Grant/Award Number: C74932/A17139; Medical Research Council, Grant/Award Number: MR/R033657/1;

Abstract
Objective: To explore reasons for variations in anxiety in women testing positive for human papillomavirus (HPV) with normal cytology at routine HPV primary cervical cancer screening.

Methods: In-depth interviews were conducted with 30 women who had tested HPV positive with normal cytology, including 15 with low-to-normal anxiety and 15 with high anxiety. Data were analysed using Framework Analysis to compare themes between low and high anxiety groups.

Results: Several HPV-related themes were shared across anxiety groups, but only highly anxious women expressed fear and worry, fatalistic cognitions about cancer, fertility-related cognitions, adverse physiological responses and changes in health behaviours, In comparison to those with low anxiety, women with high anxiety more strongly voiced cognitions about the 12-month wait for follow-up screening, relationship infidelity, a lower internal locus of control and HPV-related symptom attributions.

Conclusions: Receiving an HPV-positive result with normal cytology related to various emotional, cognitive, behavioural and physiological responses, some of which were specific to, or more pronounced in, women with high anxiety. If our observations are confirmed in hypothesis-driven quantitative studies, the identification of distinct themes relevant to women experiencing high anxiety can inform targeted patient communications and HPV primary screening implementation policy.

KEYWORDS
anxiety, cancer, cervical cancer, cervical screening, cytology, HPV, menal health, oncology, psychology, psycho-oncology
1 | BACKGROUND

Human papillomavirus (HPV) is a common sexually transmitted infection (STI) high-risk types of which are responsible for virtually all cervical cancers. In 2019, the English National Health Service Cervical Screening Programme (NHNSCP) fully implemented routine HPV primary screening, where cervical cell samples are first tested for HPV and cytology (microscopic cell examination) is used to triage HPV-positive results. Under HPV primary screening, women can test positive for HPV with normal cytology (HPV+/normal). Around 270,000 women in England (8.5% of those attending screening) are expected to receive this result each year.1,2 Due to the absence of cytological abnormalities, an HPV+/normal result carries a very low absolute risk of cervical cancer; however, given that HPV has been detected, relative risk is higher and women are recalled for repeat screening at 12 months. Most HPV infections clear naturally within 18 months (65%),2 and women are only referred to colposcopy after they test HPV+/normal three consecutive times at 12-month intervals.3

Despite the low cancer risk associated with testing HPV+/normal cytology, it is increasingly clear that, as a group, these women experience higher short-term anxiety than those with normal results1,4, as well as elevated psychosocial distress for up to 12 months.6,8 For many, anxiety remains in the normal range, but nearly a quarter experience clinically significant anxiety for reasons that remain largely unclear.2 Psychological responses have been well documented in women testing HPV-positive with abnormal cytology (where cancer risk is greater) but have been less well explored in women testing HPV+/normal at routine screening.6 Misinterpreting an HPV+/normal result could cause unnecessary anxiety if women overestimate their risk of cervical cancer. The positive (HPV+) and negative (cytology) terminology may also evoke confusion. In the absence of abnormal cytology, some women may focus more on the sexually transmitted aspects of HPV which could lead to concerns about sexual relationships. Importantly, the 12-month follow-up interval means no routine clinical contact in the interim, which could cause and/or intensify psychological consequences.

The aim of this study was to explore reasons for variations in anxiety in women testing HPV+/normal at routine HPV primary cervical screening. In-depth interviews were conducted with women purposively sampled from a larger quantitative study to compare those scoring low-to-normal versus high for anxiety, shortly after receiving an HPV+/normal screening result.

2 | METHODS

Women aged 24-63 who had tested positive for HPV with normal cytology were recruited to take part in a qualitative study through two NHNSCP HPV primary screening sites in England. The in-depth interviews were conducted with women who had taken part in a survey assessing their anxiety scores (see doi.org/10.14616/ISRCTN15111309), who did not report a current anxiety disorder. Women were purposively sampled to compare the experiences of those with low-to-normal versus high anxiety (indicated by a score of ≤38 vs. ≥49 on the 5-STA1-6, respectively). Where possible, they were also sampled to represent a range of demographics (e.g., age, ethnicity and education). Approvals were received from the Health Research Authority Research Ethics Group (18/EM/0227), Confidentiality Advisory Group (18/CAG/0113) and Cervical Screening Research Advisory Committee (ODR1819.005).

If women completed the survey, they could opt-in to be considered for an interview. The in-depth semi-structured interviews followed a topic guide (see Supporting Information 1) developed using the existing literature,12 and grounded in relevant psychology theory (including Lazarus’s Common Sense Model of Illness and Cognitive Behavioural Theory).23 Interviews took place face-to-face between 28th June and 31st August 2019, were audio-recorded and transcribed verbatim.

Data were coded using the qualitative analysis software NVivo 12 and a 10% check indicated good inter-rater reliability (Kappa = 0.91). The codes were summarized in a framework matrix to allow for theme comparisons between participants who had scored low-to-normal versus high for anxiety. Framework Analysis13 was chosen because it facilitates comparisons within and between cases.24 Greater methodological detail is available (see SI).

3 | RESULTS

Interviews were conducted with 90 women, including 15 with low-to-normal anxiety (median score of 26.7, range: 20.0–36.7) and 15 with high anxiety (median score of 53.3, range: 43.3–80.0). Table 1 displays a summary of participant characteristics.
TABLE 1  Participant characteristics and demographics overall and by anxiety group

<table>
<thead>
<tr>
<th></th>
<th>Overall sample (N = 30)</th>
<th>Low anxiety (N = 15)</th>
<th>High anxiety (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety score (median, range)</td>
<td>45.0 (20.0–80.0)</td>
<td>26.7 (20.0–36.7)</td>
<td>63.3 (53.3–80.0)</td>
</tr>
<tr>
<td>Age in years (median, range)</td>
<td>37.5 (24.0–63.0)</td>
<td>48.0 (26.0–63.0)</td>
<td>33.0 (24.0–63.0)</td>
</tr>
<tr>
<td>Education (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below degree</td>
<td>15</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Degree or higher</td>
<td>15</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Ethnicity (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>22</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Black</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mixed/multiple</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Relationship status (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partner</td>
<td>23</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>No partner</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Index of multiple deprivation (N)</td>
<td>19</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Least deprived (deciles 6–10)</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>HPV with normal cytology result (N)</td>
<td>21</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>1st result</td>
<td>9</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviation: HPV, human papillomavirus.

*Index of multiple deprivation is a multi-dimensional marker of area-level deprivation, based on residential postcode.

Women had tested HPV normal for a 2nd or 3rd consecutive time at their 12-month recall at HPV primary screening.

Interviews lasted on average 46 min (range: 24–75 min).
Women completed their anxiety questionnaire on average 11.5 days (range: 6–53 days) after receiving their test result and attended the interview on average 35.5 days after their result (range: 22–76 days).

3.1  Summary of themes

Women's reactions to receiving test results covered five themes: (1) emotional response, (2) cognitions related to HPV, (3) behaviours, (4) disclosure of result and (5) physiological response. Differences between low and high anxiety groups are highlighted throughout.

Quotes are reported with participant number (P) and by anxiety group (low as LA; high as HA).

See Figure 1 for an overview of the thematic comparisons between low versus high anxiety.

3.1.1  Emotional response

Women's reactions to receiving test results covered five themes: (1) emotional response, (2) cognitions related to HPV, (3) behaviours, (4) disclosure of result and (5) physiological response. Differences between low and high anxiety groups are highlighted throughout.

Quotes are reported with participant number (P) and by anxiety group (low as LA; high as HA).

Both anxiety groups described 'shock' or 'surprise' immediately after their result because they had no symptoms, had been vaccinated, or were unsure they were being tested for HPV. After the initial shock, some women in the low anxiety group reported little concern or 'relief and reassurance' (P6, LA).
Some women receiving an HPV+/normal result for the second or third time were 'more relaxed' because they knew what to expect, whilst others felt worse because their body was not successfully fighting HPV. After a third result, two women felt 'measured' to be offered further investigation (colposcopy).

3.1.2 | Cognitions about HPV

Cognitions about HPV covered six subthemes: (1) understanding of result, (2) cervical cancer and the aetiology of HPV, (3) 12-month screening interval, (4) sexual impact, (5) symptomatic attributions and (6) other cognitions.

Understanding of result

Few women were aware they had been tested for HPV prior to receiving their result. Many were 'confused', 'perplexed' or 'uncertain' about its meaning. There was particular confusion around the combined positive (for HPV and negative for cytology) aspect, as well as what 'cytology' or having an 'infection' meant.

So you’re thinking well I’ve not got cancerous cells, I’m okay for three years, so you think yeah, thumbs up. But then, you’ve got HPV so you might get cancerous cells. Do you understand what I mean? (P14, HA)

Cervical cancer and the aetiology of HPV

Most women were aware that sexual activity caused HPV. Others guessed that HPV was caused by poor hygiene or was a symptom of another condition. Most believed that HPV lasted 1–2 years; though a minority believed HPV would stay forever or had been there 'since birth'. Some women wanted to know whether they had 'high-risk' HPV in order to assess their cancer risk. Highly anxious women viewed themselves as medium-to-high risk of cervical cancer.

In the letter they obviously tell you that - that 50 per cent of the women carry the virus, but only 70 per cent of those women develop cervical cancer... so you’re thinking to yourself... basically I’ve got 70 per cent chance of developing cervical cancer. (P1, HA)

In contrast, most women in the low anxiety group reported feeling at 'low risk' of cancer and that their result was 'not serious'. Low perceived risk was related to not having abnormal cells in HPV, not being the direct cause of cancer; and HPV not causing problems when dormant or detected early.

Consequences related to developing cancer and its future impact were shared subthemes for both groups; however, these cognitions were prominent in highly anxious women. Some described thoughts about death and cancer treatment.
Because you start thinking, 'is my life sort of coming to an end? because I don't know, if I do get it, will my body be able to fight it, go through the therapy and will I, will I survive or not survive?' (P26, HA).

Several highly anxious women discussed the potential impact of cancer on their children or partner. In contrast, women in the low anxiety group explained that there was no point focusing on cancer because worrying about it isn't going to help' (P38, LA).

When the kids do something that makes me proud or, or something like that. And then I'll think oh, what if I wasn't here to see it? (P5, HA).

Several women wanted to find a cure for HPV and some had thought about treatments they could undergo to avoid cancer (e.g., hysterectomy).

Normally you have a virus, you take some medication and you kill the bloody thing. Why am I not being given any medication? (P21, HA)

Regardless of anxiety group, nearly all women reported 'no control' or a lack of control over HPV. Women with low anxiety expressed that they did not need to exert control because HPV clearance and transmission depended on external factors, so they were 'accepting' or 'coping' about it. Some of these women suggested that viral infections were inevitable or they took the fatalistic view, 'if your time's up, your time's up' (P28, LA).

At the moment I don't really feel like I've got any particular control. And I don't really feel like I need to have control of it. It just exists. (P21, LA)

In contrast, highly anxious women reported unease about their lack of control and described feeling 'lost'. One woman described HPV as a 'boiling time bomb' because she could not control its progression to cancer (P14, HA).

I also feel like it gives you that feeling of helplessness that you can't do anything to make it better. I don't really like that feeling. (P24, HA)

Most highly anxious women sought ways to exert control. Some searched for treatments or changed their behaviours (described under 'behaviours'). One woman highlighted that there was merit in trying to do something, regardless of whether it actually does anything' (P5, HA). A minority of women across both groups believed that they had a lot of control over HPV via attending their follow-up screen, monitoring themselves for cancer symptoms, and controlling the transmission of HPV to others. A couple were 'confident' their body would fight HPV.

12-Month screening interval
In the UK, women who receive an HPV test result for the first or second time at HPV primary screening are recalled for a 12-month follow-up screen. Whereas many women in the low anxiety group believed the 12-month wait was 'normal', nearly all highly anxious women wanted to re-attend earlier.

I think it's a long time to wait, twelve months. Yeah, maybe six months or three months, but I think twelve months is a long time to wait. (P4, HA)

Some wanted more information on the rationale for the interval and questioned the decision-making of doctors/policy-makers, with suggestions it could be a 'financial' decision. Many highly anxious women questioned whether cancer might develop before their next screen. In contrast, a few women in the low anxiety group believed the 12-month interval implied that HPV was not serious.

I feel like I've got the you know, sort of sword of Damocles or thing on top of my head. I'm waiting for 12 months to know if something wrong is happening or not so it's a bit...I find the 12 month wait, that's gonna be horrendous. (P1, HA)

I thought, 'if it's anything more serious than that, they won't, they'd invite me in sooner.' (P5, LA)

A few women had already requested an earlier screen from their GP or were considering getting screened privately. One explained that she was more 'accepting' of the wait after she was informed her body can take up to 2-years to clear HPV.

Sexual impact
Cognitions about the sexual impact of HPV mainly centered around the source of infection and transmission, the STI label and relationships/intimacy.

Several women reported feeling 'in a fix' (P6, LA) about who had given them HPV and when. Some were confused HPV was from their current partner whilst others were unsure.

Many questioned whether HPV was definitely an STI, whilst some believed HPV was 'not an actual STI' (P20, LA). Others wanted to know whether HPV could be passed on; condoms are needed; re-infection can occur between partners; and whether the act of sex as opposed to sexual contact caused HPV. The STI label was reported as 'dirty' by some women, as well as 'oppressive' (P4, HA) and 'nasty' (P28, LA). Some associated HPV with sexual promiscuity.

Thoughts about potential infidelity were common and appeared more pronounced in highly anxious women. Many women reported believing that their (ex)partner may have been unfaithful; though, most no longer believed this at the time of interview.
I think I know that he hasn’t been unfaithful. I think I do know that, I now appreciate this can happen and be in my body, I could have done this to myself 20 years ago.

(P20, HA)

Indecisively continued to be an issue for some highly anxious women by adding an element of mistrust or disruption to their relationship. A couple thought that their partner may not want to engage in sex if they know HPV was an STI.

If he thinks that he could give him something then he's... he can rightly not want to do it [sex], which is completely fine but then obviously that would affect our relationship. (P24, HA)

Symptom attributions
HPV was widely seen as asymptomatic but some highly anxious women attributed symptoms to the virus, including; the development of a fibroid in the womb; a urinary tract infection; breast milk production; previous genital warts; and thrush. One woman with low anxiety attributed flulike symptoms and weight gain to HPV. Some women across both groups mentioned symptoms but were unsure if they were connected to HPV, including irregular bleeding, cramp pain, cold sores, fallopian tube pain, cystitis, bleeding after sex, and bladder leaks.

Other cognitions
Fertility-related consequences were mentioned by younger women in the high anxiety group. The HPV vaccine was also discussed and was linked with annoyance about not being offered it by those with high anxiety. Two women discussed the consequences of HPV on their health and mortgage insurance. One had been advised by her insurer that she needed to declare her second HPV’s normal result on her mortgage.

And so he went back to the insurance company and said should he put this down... and their answer was if it was the first one, no - but now she’s had two yes. And we will not cover her for any treatment. (P28, LA)

3.1.3 | Behaviours
Only women with high anxiety reported changing their behaviour due to HPV. Some reported avoiding sexual intercourse or using condoms. A few attempted to boost their immune system with vitamin supplements, changes to diet, and exercise. One woman reported reducing smoking and another described vaping more to deal with the stress of HPV.

We’ve not had any sexual intercourse since I got the letter. (P18, HA)

For like the first month I was on this really healthy exercise and eating hype to boost my immune system!

That was purely the h-HPV because I thought, oh, my immune system needs to fight it. (P24, HA)

Women were also asked what they did immediately after they received their result. Many reported using the internet to search for information on HPV; and highly anxious women described this most extensively, stating it was often ’unhelpful’. Women with low anxiety usually reported putting their result letter to one side, ’skating reading’ it (P2, LA), or getting on with their day. Some women described using distraction (e.g., activities or work) to avoid thinking about their result.

3.1.4 | Disclosure of result
Seeking social support was described as a coping strategy to help deal with HPV. Nearly all highly anxious women reported disclosing their result to at least one person; though some delayed disclosure or did not tell certain individuals. Non-disclosure in this context was often because women did not want to burden loved ones.

I just don’t really want to worry her [sister] about this kind of thing. (P1, HA)

In the low anxiety group, the decision to disclose was mixed. A few women stated that they did not tell anyone because they were not concerned. Those who did disclose sometimes omitted certain information (e.g., the sexually transmitted aspect) due to embarrassment, not wanting to be viewed as ‘promiscuous’ (P22, LA), or viewing their result as ‘personal’ (P8, LA). Two women were contemplating whether to disclose their result to a partner.

I think I just tried to put it out of my head and I was a bit embarrassed so I never even discussed it with anyone. (P15, LA)

3.1.5 | Physiological response
Physiological responses were exclusive to highly anxious women. Soon after their result, some reported crying, sensations in their stomach, and/or sleepless nights. Others described bodily sensations such as shaking and increased heart rate, and nocturia. One reported that she lost her appetite due to her anxiety.

4 | DISCUSSION
Our findings advance the qualitative literature by exploring psychological response to testing HPV positive with normal cytology at routine HPV primary screening and identifying themes which may be
specific to women with high anxiety. Only highly anxious women expressed fear and worry, fatiguing cognitions about cancer, fertility-related cognitions, adverse physiological responses, and changes in behavior(s). In comparison to those with low anxiety, they more strongly voiced cognitions about the 12-month wait for follow-up screening, relationship infidelity, a low internal focus of control and HPV-related symptom attributions.

Similar to other studies, we found testing positive for HPV was linked to cognitions about cervical cancer and feelings of fear and worry. In our study, cancer-related cognitions appeared to be the most dominant theme and primary concern for highly anxious women. In particular, these women often focused on the consequences of cancer and expressed cognitions about undergoing cancer treatments or leaving loved ones behind. Further, many highly anxious women considered themselves to be at high risk of cervical cancer. In particular, the normal cytology aspect of an HPV-normal result indicates very low short-term cancer risk and should therefore, in theory, offer reassurance. However, nearly all women focused on the HPV-positive aspect of their result and gave little or no attention to normal cytology. Instead, some incorrectly believed that HPV was the direct precursor to advanced cervical cancer. These findings help to interpret recent cross-sectional research which found heightened anxiety associated with an HPV-negative result at HPV primary-screening. Targeted information in HPV-negative result letters emphasizing the very low short-term cervical cancer risk and explaining the relevance of normal cytology could improve women’s understanding and prevent unnecessary anxiety.

Linked to cancer-related cognitions, many highly anxious women voiced concerns about the 12-month wait for routine follow-up, questioning whether cancer may develop in the interim. Given that 12-month recall is specific to HPV primary screening, it is also important for screening policymakers to communicate the rationale for this interval in HPV-negative result letters to help reassure women.

The sexually transmitted nature of HPV has previously been linked to feelings of stigma, shame, and embarrassment. To date, most studies have assumed that sexual concerns play a central role in the development of anxiety following an HPV-positive result. Interestingly, however, we found that most sexual cognitions and related feelings of embarrassment were common to both anxiety groups. Relationship infidelity was the only subtheme which was more pronounced in women with high anxiety. Although they require confirmation using quantitative studies, our findings help to trace out nuances pertaining to cognitive versus emotional responses to HPV.

Longitudinal studies also support this notion given that psychosexual distress remains elevated for up to 12-month, whereas general anxiety diminishes within 3 months, indicating two distinct psychological pathways.

Typically, low perceived control is associated with poor health outcomes including adverse emotional response. In line with recent systematic review evidence for HPV, nearly all women in our study reported feeling that they had little or no control due to a lack of treatment or practical prevention methods for HPV. A novel finding was that highly anxious women appeared to focus on internal factors they could use to gain control (e.g., consuming multimixitamins), in contrast to women with low anxiety who linked external factors (e.g., fate) to acceptance of HPV. These findings point to individual differences in the interaction between locus of control and coping styles which, in the absence of a viable solution for HPV, may drive feelings of anxiety.

HPV is asymptomatic, yet highly anxious women believed or questioned whether certain dysynchronous symptoms may be HPV-related. Healthcare professionals and screening information materials should highlight the asymptomatic nature of HPV, while encouraging women to monitor for specific cervical cancer symptoms (e.g., unusual bleeding, pain from sex).

Fertility-related cognitions associated with an HPV-positive result have also been identified in previous studies. In our study, although a relatively minor theme, this was specific to younger women with high anxiety. Fertility practitioners could provide reassurance about fertility to younger women who have received an HPV-normal result.

Few studies have explored physiological and behavioural responses to HPV, with the exception of some general sexual behaviours. We incorporated these constructs into our topic guide, and several anxious women reported experiencing physiological sensations shortly after receiving their result (e.g., crying, shaking, stomach sensation), as well as changing their behaviour(s) due to HPV (e.g., stopping sex, vitamin consumption and avoiding cigarettes). Behavioural and physiological factors should be incorporated into future cervical screening evaluations to assess their relevance and the full psychological impact of receiving HPV-positive results.

4.1 Study limitations

Recruitment was linked to routine clinical management at HPV primary screening, ensuring a diverse and well-characterised sample. However, due to the relatively small numbers within each demographic group, we were unable to explore interactions between demographics and anxiety. We were able to calculate the time (days) between women receiving their result and attending interview, which ranged from 22–76 days. It is possible that this variability in time from result may have introduced heterogeneity in women’s recall of events and/or experiences of anxiety. Finally, although we excluded women who reported a current anxiety disorder, we did not measure anxiety scores prior to HPV primary screening, meaning we could not determine whether receiving an HPV-normal result was the primary source of their anxiety.

4.2 Clinical implications

To date, cervical screening patient communications and public health campaigns aimed at minimizing adverse psychological impacts have
5 | CONCLUSION

Revealing an HPV-positive with normal cytology: results related to various emotional, cognitive, behavioral, and physiological responses, some of which were specific to, or more pronounced in, women with high anxiety. To avoid unintended consequences for women attending HPV primary screening (e.g., unnecessary anxiety and/or adverse behavioral impacts), these distinct themes should be used in hypothesis-driven quantitative studies and used to guide the development of evidence-based patient communications and screening implementation policy.

ACKNOWLEDGEMENTS

We would like to thank the women who kindly gave up their time to take part in the interviews. Emily McBride was funded by a National Institute for Health Research (NIHR) Doctoral Research Fellowship for this project (DRF-2017-10-105). This publication presents independent research funded by the NIHR. The views expressed are those of the author(s) and not necessarily those of the NIHR, the NIHR or the Department of Health and Social Care. Jo Waller and Laura Marlow were funded by Cancer Research UK (C7492/AI/2139). Kirsty Bennett was funded by a Medical Research Council Studentship (MR/N013861/1).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Emily McBride conceived the study. Emily McBride and Selma Stearns collected the data. Emily McBride, Jo Waller, Laura A. V. Marlow and Kirsty F. Bennett analysed and interpreted the data. Emily McBride drafted the manuscript. All authors contributed to the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical interest.

ORCID

Emily McBride https://orcid.org/0000-0001-9928-429X
Laura A. V. Marlow https://orcid.org/0000-0003-1709-2397
Kirsty F. Bennett https://orcid.org/0000-0003-1448-3004

REFERENCES

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.


**Topic Guide**

1. **Introduction** – Have you taken part in a research project or interview before?  
   Information, Consent, Demographics, Introductions, Structure, Voucher, Confidentiality, Questions

2. Can you tell me a bit about yourself?

3. **You recently attended for cervical screening…**  
   a. Can you remember how long ago that was?  
   b. Have you been for cervical screening much in the past before that?  
   c. Thinking about your most recent result … When did you get it? Was there much of a wait between getting screened and the result arriving?  
   d. Can you remember what your test result said?

4. **How well do you feel you understand what your result means? HPV? With Normal cells?**

5. **I want you to think about when you opened your letter and saw your result. How did you react?**  
   a. How did you feel? What emotions?  
   b. What thoughts went through your head?  
   c. Did you notice any changes in your body? (e.g. butterflies, tense, heart rate)  
   d. What did you do immediately afterwards? …Anything else?

6. **Can you compare the way your felt when you saw your result to anything similar you’ve experienced?**

7. **What about now? Have your feelings changed much? More or less strong?**  
   a. If so, when did it change?  
   b. Why do you think that is?
8. If you had to compare the way you feel now about having HPV to a similar situation, what would it be?

9. Have you told anyone about your result?
   a. Do you usually talk to other people about your health? The same people? Health professionals?
   b. Do you find it helpful?

10. Has your result had an impact on any other areas of your life that we haven’t spoken about?

11. More generally, in your everyday life, how often would you say you feel stressed or anxious?

12. Beliefs about HPV:
   a. What do you think caused your HPV?
   b. How much control do you feel you have over your HPV?
   c. How long do you think you will have HPV for?
   d. How much do you think cervical screening can help?

13. Do you experience any symptoms that you think might be related to your HPV?

14. How likely are you to go back to cervical screening again in 12 months?

15. What did you think of the NHS letter and information that you received?
   a. Wording – anything that stuck out?
   b. Anything particularly good?
   c. Anything particularly bad?
   d. Anything that could have helped?

16. Anything that I’ve missed that you think is important or you want to add about anything we’ve discussed?
Appendix 5.3 - Participant Information Sheet for Study 4 (1 page).

Participant Information Sheet
Understanding anxiety and attendance in cervical screening (IRAS ref. 236982)

What is this study about?
The aim of this study is to improve cervical screening attendance and the way screening results are delivered to women with the same results as you. We plan to do this by gaining a better understanding about how women react to their test result and what it means to them. We are doing this by gathering information in a survey (which you previously completed) and through some 1:1 interviews. The results from this study will also be used to help the NHS decide how to word the test result letters they send to women.

Why have I been invited to take part in this study?
I am inviting you to take part because you recently completed and returned a survey to us, indicating that you might like to take part in an interview. I am interested in hearing your views about your recent cervical screening test result and understanding how your test result makes you feel.

What would taking part involve?
If you agree to take part, a female researcher will ask you some questions about your test result and cervical screening in the form of an interview. The interview will last for around 1.5 hours and it will be audio-recorded. Most interviews will take place at UCL in central London (we will cover your travel fare and meals), but if this isn’t suitable a researcher can come to your home or arrange a telephone interview. You will be asked questions about your views on your test result and cervical screening. You will also be asked for your opinion on what information is important to include in NHS test results letters.

Do I have to take part?
Taking part is completely voluntary. It is up to you to decide whether or not to take part. Your decision does not affect your medical care or legal rights. If you decide to take part and then change your mind, you can stop at any time. You can ask for your data to be withdrawn, up to the point that the data are analysed (01/04/2023), in which case it will be destroyed. You can also refuse to answer any questions in the study.

What are the possible benefits of taking part?
There are no guaranteed benefits from taking part in this study. However, your participation will contribute to important research and may help to improve the quality of NHS services for other women in the future. You may find taking part in this research enjoyable and interesting.

What are the possible disadvantages and risks of taking part?
It is possible that you may feel uncomfortable answering some of the questions we ask you. If this is the case, we are free to decline to answer or stop your participation. If you feel distressed and would like additional support, you may wish to inform your GP or contact Jo’s Cervical Cancer Trust. Jo’s Cervical Cancer Trust is a charity which provides information on screening results, HPV and cervical cancer. Their website can be found at http://www.jostrust.org.uk/ and they provide a free helpline which is open Mon-Fri on 0808 802 8000.

The consent process
If you agree to take part, you will be given a written consent form to read. If you agree to the points on the consent form, you will need to initial and sign it before the interview starts.

Will my participation in this study be kept confidential?
Yes, your participation in this study will be kept strictly confidential. We will follow ethical guidelines and policies on data protection and information governance to ensure secure handling of your information. Interviews will be audio-recorded and transcribed, but all identifiable information in the recordings will be removed so that your data is anonymous. It is likely that the results of this study will be published, but no publications will contain information which identifies you or links back to you or your participation.

Cost and reimbursement
As a thank you for taking part, you will receive a £40 amazon or boots voucher for your time (you can choose which one), and we will cover your travel expenses (travel fare and meals).

Who is organising and funding this study?
University College London (UCL) are sponsoring this study. The National Institute for Health and Research (the research arm of the NHS) are funding it. We are also working closely with Public Health England and the NHS cervical screening programme.

How will you use my personal data?
UCL is the sponsor for this study and is based in the United Kingdom. UCL will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will keep identifiable information about you for a maximum of 1 year after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study after the cut-off date (01/04/2023), we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information at https://www.ucl.ac.uk/legal-services/privacy/participants-health-and-care-research-privacy-notice.

NHS England make sure that relevant information about the study is recorded for your care, and oversee the quality of the study. Individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. NHS England will pass these details to UCL along with the information collected from you. Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government. Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of health and care research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you. Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee.

Thank you for taking the time to read this information sheet.
Appendix 5.4 – Consent form used for Study 4 (1 page).

CONSENT FORM

Understanding anxiety and attendance in cervical screening – IRAS 236982

Name of Researcher: ____________________________

1. I confirm that I have read and understand the information sheet dated 06.01.19 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the sponsor of the trial (University College London) and responsible persons authorised by the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I agree to my interview being audio-recorded and transcribed with all identifiable information removed. I agree to the possible use of verbatim quotation in publications, reports or presentations, with all identifiable information removed.

5. I agree to take part in the above study.

Name of Participant: ____________________________ Date: __________ Signature: ____________________________  
Name of Person taking consent: ____________________________ Date: __________ Signature: ____________________________  
Name of Chief Investigator (If different to the person taking consent): ____________________________ Date: __________ Signature: ____________________________

Consent form for Project 2 (interview study). Version 1, 15.06.18, IRAS number: 236982