

Current Urban Environment and Psychological
Pathways to Psychosis

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Thesis declaration form

I 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 in the thesis.

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Name:

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Overview

This thesis assesses the relationship between adversity and psychosis. Part one is a systematic review of empirical literature investigating gender differences in the association between interpersonal childhood adversity and psychosis. Females with psychosis had higher prevalence of composite abuse and females at ultra-high risk reported more sexual and emotional abuse (both vs. males). The association between childhood adversity and psychosis did not vary across gender. Potential mechanisms are considered and the need for further research is outlined, given the infancy of the literature.

Part two is a case-control study (134 first episode psychosis cases and 258 controls) investigating urban environment and psychological pathways to psychosis; specifically assessing, whether the relationship between psychosis and neighbourhood safety and social capital, is mediated and/or moderated by anxiety, schematic beliefs and a jumping to conclusions bias (JTC). Data collection consisted of assessments and interviews. Anxiety, schematic beliefs and JTC were associated with increased risk for psychosis; and higher levels of neighbourhood safety and social capital were associated with increased odds of psychosis, which was particularly evident within an intermediate social class. Positive other beliefs were shown to partially mediate the association between neighbourhood and psychosis. The complexity of the relationship between psychosis and urban neighbourhood is discussed and potential clinical implications regarding the protective benefit of positive beliefs are considered.

Part three is a critical appraisal of the thesis process, with reflections on the scientist-practitioner model, the assessment of complex causal pathways and the potential invisibility of wider societal inequalities within this research area.

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Part 2: Empirical Paper

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Part 1: Literature Review

**Gender Differences: A Review of Prevalence and Differential Impact on the
Association between Childhood Adversity and Psychosis**

Abstract

Background: Gender differences within psychosis have been evidenced in clinical presentations, outcomes and functioning. Given consistent findings of childhood trauma as a risk factor for psychosis and the differential report of abuse across gender in the general population; this review aimed to assess the prevalence of childhood adversity across gender in psychosis populations and gender differences in the association between interpersonal childhood adversity and psychosis or psychotic-like experiences.

Method: A systematic literature search was conducted within PsychINFO, EMBASE and Medline electronic databases, to identify all relevant empirical literature published up until April 2015. Interpersonal childhood adversity was defined as parental loss, bullying, neglect and physical, emotional/psychological and sexual abuse.

Results: A total of 33 eligible studies were identified using observational designs (cohort, cross-sectional, case-control), within non-clinical (n=7), ultra-high risk (UHR; n=6) and clinical-diagnosis samples (n=20). In psychosis populations, females had a higher prevalence of composite abuse compared to males. In UHR populations, females reported more sexual abuse and there was an indication for higher reports of emotional abuse. The association between childhood adversity and psychosis did not appear to vary across gender. However given the infancy of the literature, it is not possible to draw firm conclusions from the existing studies.

Conclusion: This review indicates a need for further empirical research on the relationship between childhood abuse and psychosis by gender, towards furthering etiological understanding to improve prevention and intervention treatment strategies.

Introduction

A renewed interest in gender differences within psychosis has led to an increase in literature over recent decades (Barajas, Ochoa, Obiola & Lalucat-Jo, 2015; Ochoa, Usall, Cobo, Labad & Kulkarni, 2012; Hafner et al., 2003; Leung & Chue, 2000). Gender being a stable, reliable and valid epidemiological parameter lends itself to being assessed as a possible explanatory factor for variation within psychosis, but often research has not looked at the role of gender. For example, many previous studies have failed to account for gender as a confounder, have not reported stratified gender analyses and used non-representative samples compared to naturalistic studies (Longenecker et al., 2010). However the recent surge of literature, has indicated differential clinical presentations, outcomes and functioning in psychosis, across gender. A large randomized clinical trial of first episode psychosis (FEP), comparing early intervention with standard treatment found that at baseline, males were more likely to have co-morbid substance use and negative symptoms, which are two factors significant in influencing course of psychosis (Thorup et al., 2014; Thorup et al., 2007). At a 2- and 5- year follow up, this study also reported gender differences in social functioning and symptomology. Females were more likely to be in remission, compliant with medication, have better social functioning, be employed and in education, whereas males were more likely to live alone and continue to experience co-morbid substance use and increased negative symptoms (Thorup et al., 2014). Similar results were also found within a longitudinal study of psychotic disorders (Grossman, Harrow, Rosen, Faull & Strauss, 2008).

An earlier onset for psychosis and higher incidence of schizophrenia in men, and better premorbid and social functioning in females have been consistently reported, which may partly explain better outcomes and milder course of illness for females (Thorup et al., 2014; Ochoa et al., 2012; Cotton et al., 2009; Grossman et al., 2008; Hafner et al., 2003; Leung & Chue, 2000). However, less conclusive findings for

gender differential patterns of symptomology and neuropsychological profiles have been indicated by a recent review (Ochoa et al., 2012). Literature has also begun to investigate this subject in individuals at ultra-high risk of psychosis (UHR), attempting to identify whether similar variance across gender is evident in subclinical phases, and therefore across the psychosis continuum. Although, definite conclusions cannot be drawn due to the infancy and limitations within this literature, a recent review of UHR suggested a similar pattern described above, with males experiencing higher levels of negative symptoms, longer durations of untreated illness and poorer social functioning (Barajas et al., 2015). Therefore studies have suggested the possibility of gender differences across various domains and along the continuum of UHR to psychotic disorder. This assessment of differences in the development of psychosis is vital in identifying possible putative risk factors, which could influence intervention strategies to improve illness prognosis.

Childhood adversity

One area less well researched in terms of gender differences within psychosis, is childhood adversity. There is now considerable evidence that childhood abuse is associated with a range of mental health problems (Spataro et al., 2004). This includes a growing body of literature linking early adversity to risk of psychosis (see Schafer & Fisher, 2011; Bendall, Jackson, Hulbert & McGorry, 2008; Morgan & Fisher, 2007; Read, van Os, Morrison & Ross, 2005); and to subclinical symptoms of psychosis (Arseneault et al., 2011; Morgan et al., 2009; Schreier et al., 2009). Additionally more systematic quantitative studies, synthesizing evidence using meta-analyses, have found a higher prevalence of childhood trauma in psychosis populations vs. controls (in sexual, physical and emotional abuse; Bonoldi et al., 2013) and found childhood adversity (neglect, parental death, bullying, sexual, physical and emotional/psychological abuse) to be 'strongly associated with higher

risk for psychosis' (OR= 2.78; Varese et al., 2012). The mechanisms between childhood trauma and psychosis are less well established but various theories have been proposed, which include, cognitive, affective and neurobiological pathways.

Cognitive models of psychosis suggest that trauma can lead to cognitive vulnerabilities for psychosis, via the development of negative core beliefs about the self and others and increasing later affective disturbance (e.g. depression and anxiety; Garety, Kuipers, Fowler, Freeman & Bebbington, 2001; Garety, Bebbington, Fowler, Freeman & Kuipers, 2007). These factors increase risk for psychosis, as well as contribute to symptom and distress maintenance, by biasing appraisals of anomalous experiences (Garety et al., 2001; 2007). For instance, anxiety and negative self beliefs partially mediated the relationship between childhood emotional and physical abuse and paranoia in adulthood (Fisher, Appiah-Kusi & Grant, 2012); and a longitudinal study found that affect (anxiety and depression), external locus of control and low self-esteem mediated the association between childhood victimisation (harsh parenting, bullying and domestic violence) and psychotic like experiences (PLE; Fisher et al., 2013). Furthermore, neurobiological pathways propose the adversity risk, via an increased sensitivity to stress, conceivably implicated within dysregulation of dopamine and the hypothalamic-pituitary-adrenal (HPA) axis (for reviews see, Holtzman et al., 2013; van Winkel, Stefanis & Myin-Germeys, 2008). The traumagenic neurodevelopmental model, incorporates biological, social and psychological factors, suggesting that trauma shapes neurodevelopmental abnormalities (e.g. enduring effects on the HPA axis) which then lead to heightened sensitivity to stress (Read, Perry, Moskowitz & Connolly, 2001). A core role for increased stress sensitivity has been identified within schizophrenia (Walker & Diforio, 1997) and studies using experience sampling methods have demonstrated intensified reactions to daily stress (e.g. increases in low-level psychotic symptoms and

affective responses) in people vulnerable to psychosis (Myin-Germeys & van Os, 2007; Myin-Germeys, Delespaul & van Os, 2005; Myin-Germeys, van Os, Schwartz, Stone & Delespaul, 2001). The integration of cognitive and neurobiological models has also been encouraged, for example, dopamine dysregulation may foster unusual salience towards particular stimuli and then the biased appraisal of these stimuli (i.e. via affective disturbance or negative biases) may lead to symptoms of psychosis (Heinz & Schlagenhauf, 2010; Garety et al., 2007). Over time, further dysregulation and adversity exposure may cause enduring psychotic-interpretations (Murray, 2011). This type of integration is also presented in recent aetiological models of psychosis (see Howes & Murray, 2014; Morgan, Charalambides, Hutchinson & Murray, 2010; van Os, Kenis & Rutten, 2010).

Gender differences and childhood adversity

Within the general population, the rates of overall childhood abuse appear to be similar across genders. The Department of Health statistics (2014) suggest that, of the total number of children in need for abuse or neglect (i.e. contact with social services), 49.9% were male and 47.8% were female. However differential rates across gender are apparent for categories of abuse. A national UK study reported differential rates for sexual abuse (21% female vs 11% male), physical abuse (12% female vs 15% male), a slight difference in emotional abuse (8% female vs 4% male) and no gender difference in neglect (May-Chahal & Cawson, 2005). This was similar to literature looking at data across countries, with females two-to-three times more likely to experience sexual abuse, both genders likely to experience physical abuse within the home and males more likely to experience supervisory neglect (May-Chahal, 2006).

Literature on psychosis, has indicated higher report of childhood abuse compared to the general population (Bonoldi et al., 2013; Kessler et al., 2010; MacMillan et al.,

1997); and a review by Morgan and Fisher (2007) indicated variation between the weighted prevalence of abuse (sexual abuse: 42% female vs 28% male; physical abuse: 35% female vs 38% male; sexual or physical abuse: 50% female vs 50% male; sexual and physical abuse: 26% female vs 18% male). However, Morgan and Fisher (2007) also note that calculating weighted prevalence may not be meaningful, given the disparity between articles on sample population and abuse measures.

Within other mental health difficulties there is evidence that across gender, the prevalence and impact of early abuse experiences on psychopathology varies (Hyman, Garcia & Sinha, 2006; Haatainen et al., 2003); but research on this topic within psychosis is very much within its infancy. Although, the findings on gender differences within psychosis and the possible disparity in abuse rates suggests a feasible hypothesis, that there may be different routes to psychosis and possibly the route from childhood abuse may be more frequent in females (e.g. the route from sexual abuse to psychosis may be more common in females). It is possible that childhood adversity may influence development differently in males and females, which may lead to varying vulnerabilities or pathways to psychosis.

Current literature review

Extensive research has indicated some consistent findings regarding gender differences within psychosis, although the etiological influence and possible putative interaction with other variables is still uncertain. The assessment of gender differences could provide further etiological understanding in psychosis and aid the development of more effective treatment, involving both prevention and intervention. There is evidence of a differential report of abuse across gender in the general population and given the consistent findings of childhood adversity as a risk factor for psychosis, it is possible that the relationship between psychosis and childhood

trauma, may differ between males and females. Previously however, it was reported that literature had not systematically assessed this relationship by gender (Bendall et al., 2008). Given the recent prominence of the gender topic within psychosis and a large body of literature on childhood abuse, this review aimed to systematically investigate the following questions on prevalence and association:

1. Does the prevalence of reported interpersonal childhood abuse differ across gender in psychosis/PLE samples?
2. Is there a gender difference in the association between interpersonal childhood abuse and psychosis or PLE?

Method

The methodology of this review followed the general outline for planning and conducting systematic reviews described in Petticrew and Gibley (2004).

Inclusion criteria

Studies were included in this literature review if they met the following criteria:

- Studies assessing proximal childhood interpersonal adversity experienced before age 18. Childhood interpersonal adversity was defined as abuse types (sexual, physical, emotional, psychological, neglect), parental separation or loss and bullying.
- Study sample consisting of both males and females with associated data for each.
- Study population or outcome measure related to psychotic disorders or PLE.

- Studies statistically assessing and explicitly reporting gender differences in either:
 - The prevalence of childhood interpersonal adversity among populations experiencing psychosis or PLE.
 - The association between childhood interpersonal adversity and psychosis or PLE.
- Any type of quantitative study design that incorporates the above criteria
- Peer reviewed journal articles
- English language
- Human participants

Exclusion criteria

Studies were excluded in this review if they met the following criteria:

- Studies assessing or reporting data on adversity that is not childhood specific, up to age 18 (e.g. lifetime adversity).
- Studies assessing or reporting data on childhood adversity that is not interpersonal in nature or specific to this type of proximal adverse experience (e.g. war, natural disasters).
- Study sample only including one gender, or no/insufficient information available on gender differences.
- Study population not psychosis/ PLE specific.
- Studies assessing gender differences in other areas of psychosis, where psychosis/ PLE were not the outcome measures or were not reported (e.g. cognitive factors, genetic or biological differences, duration of untreated psychosis, functioning).
- Studies not assessing gender differences in the report of adversity within a psychosis or PLE population; or not assessing gender difference in the

association between childhood adversity and psychosis/PLE.

- Studies not peer-reviewed, published in English or assessing humans.

Study selection

Search strategy

A comprehensive search was conducted within PsychINFO, EMBASE and Medline electronic databases, to identify all relevant empirical literature published up until April 2015. The key terms were generated from the inclusion criteria and Table 1 outlines the variety of gender, adversity and psychosis search terms used. Some of the adversity terms were combined with keywords of 'adol*', 'child' and 'early' to identify literature relevant to childhood adversity. References of recent, relevant systematic reviews (e.g. on childhood adversity or gender differences in psychosis) and some selected studies were examined to identify any additional publications.

Table 1. Overview of combined search terms used in the systematic literature search of three databases: PsychINFO, MEDLINE and EMBASE.

Childhood Adversity	Psychosis	Gender
Child Abuse (SH)	Psychosis (+SH)	Gender
child* adj2 abuse	First episode psychosis	Sex
	Schizo*	Human sex differences (SH)
Terms below were combined with 'child*;adol* and early'	Psychot*	
Adversity		
Life event*		
Trauma (+SH)		
Life experiences (SH)		
Psychological stress*		
Violence (SH)		
Bullied		
Bullying		
Victim*		
Victimization (SH)		
Parent* loss		
Parent* separati*.		
Parent* death*		
Parent* absence (+SH)		
Maltreat*		
Physical abuse		
Sexual abuse		
Emotional abuse		
Neglect		

Note. SH, term searched as a subject heading; +SH, the search term was also run as a subject heading.

Study identification

A total of 992 studies were identified after de-duplication, and the title, abstract and full texts were examined according to the inclusion and exclusion criteria. Queries regarding inclusion after full text review were discussed with another rater, a clinical psychologist, and a consensus decision was reached. A flowchart indicating the study selection process at each step and reasons for exclusion (for abstract and full-text phases) is presented in Figure 1.

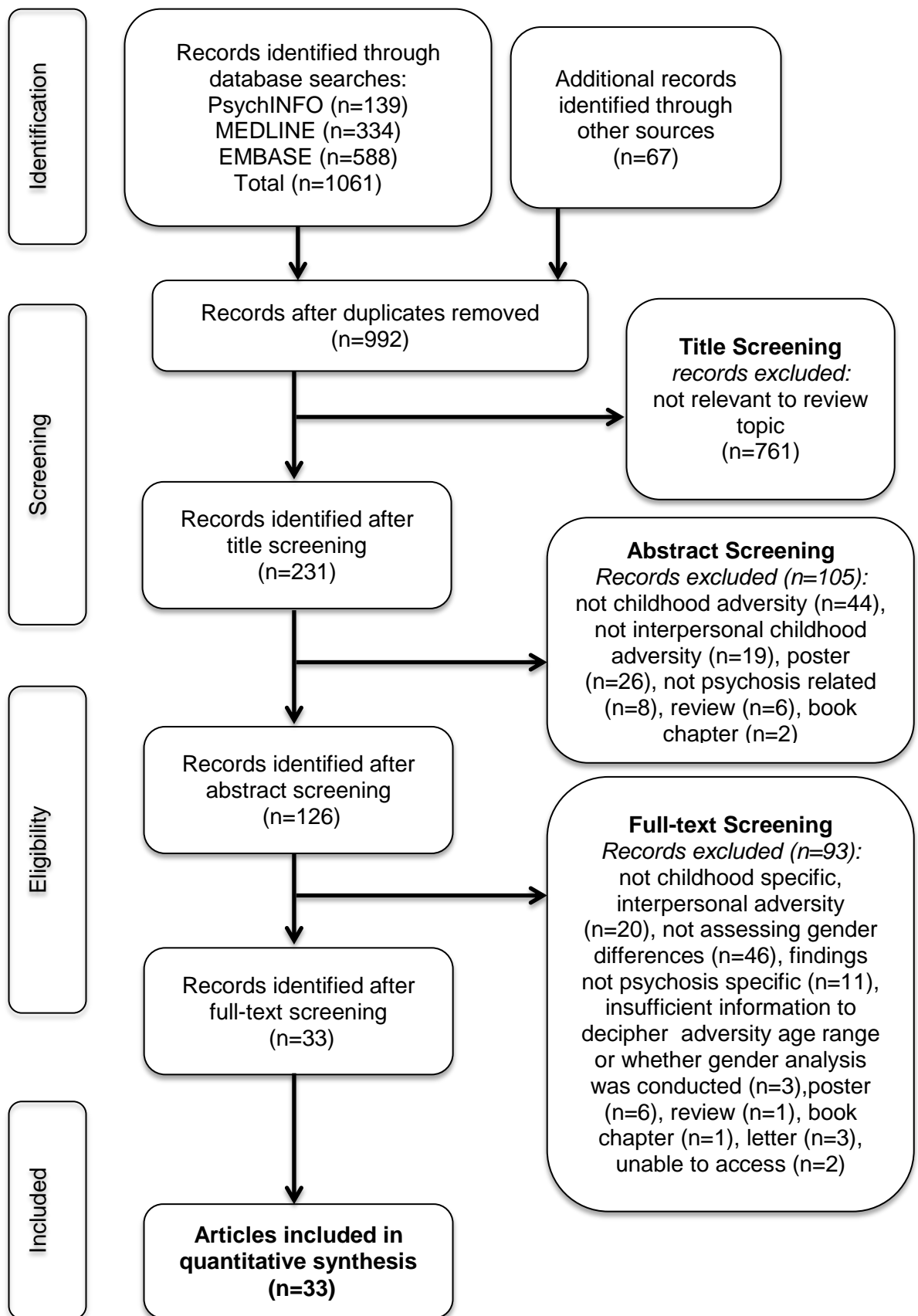


Figure 1. Flow diagram of the inclusion of articles for the literature review.

Quality ratings

The quality of the 33 included studies was assessed, using an adapted version of the rating tool for quantitative studies by Kmet, Lee and Cook (2004). This tool was modified to include only the general quality rating criteria relevant for the review, with some items re-worded to relate to the review aims. Two further items were also incorporated to assess the quality of the childhood adversity and psychosis/PLE measures, given their centrality within the review. This resulted in an 8-item quality rating tool (labeled A-G) as follows:

- A.** Is the study design evident and appropriate for assessing gender differences in childhood abuse and psychosis?
- B.** Is the method of subject/comparison selection OR source of information/variables described and appropriate?
- C.** Is the sample size appropriate?
- D.** Are the subject/ comparison group characteristics sufficiently described?
- E.** Are possible confounding variables controlled for (if applicable)?
- F.** Is the outcome measure used for psychosis or psychotic-like experiences, well defined and robust to measurement or misclassification bias?
- G.** Is the exposure measure used for childhood interpersonal adversity, well defined and robust to measurement or misclassification bias? Is it a valid and reliable?
- H.** Is the gender difference results described and analysed?

An anchoring system was developed, which outlined possible indicators relevant to rating each item (see Appendix 1). This was devised by reviewing various appraisal tools of observational studies (given this was the design of all the included articles) to create a review specific comprehensive overview to aid the quality scoring (e.g. CASP, 2013; STROBE, 2007; Kmet et al., 2004). In line with the quality rating tool

by Kmet et al. (2004), all studies were scored between 0-2 for each quality rating criteria (or n/a for item E, if appropriate), which reflected the extent to which they met the anchoring points for each item. The maximum points, which could be allocated, were 14 or 16, if Item E was applicable to the study, therefore a percentage was calculated for each study to permit a comparison on quality rating. These ratings were used as a general guide to the weight applied to the eligible studies, e.g. articles using standardized assessments of adversity were given more weight than studies using single questions within a general interview; or more importance was given to how results on gender difference were reported. Therefore this scoring system should be interpreted as a review specific guide of quality, rather than a general quality indicator.

Results

The quality ratings and characteristics of the 33 eligible studies are presented in Table 2 and Table 3, respectively. The main findings include only the results relevant for the review topic, regarding gender differences in adversity prevalence within psychosis or PLE populations and gender differences in the association between adversity and psychosis or PLE. Comparison or control groups within the studies are only included in Table 3 when relevant to the main findings reported (e.g. those that stratify results and assess differences in odds ratios between the male and female data).

Overview

As can be seen in Table 3, more articles were assessing gender differences in clinically related samples (i.e. UHR or psychotic disorders, n=26), compared to non-clinical samples/outcomes (n=7; van Nierop et al., 2014; Fisher et al., 2013;

Samplin et al., 2013; Barker-Collo & Read, 2011; Shevlin et al., 2011; Schreier et al., 2009; Walker et al., 1981). All of the eligible studies, except two (Spataro et al., 2004; Kitamura et al., 1993), found an overall association between different types of interpersonal childhood adversity and risk for psychosis/PLE. Of the two opposing results, Spataro et al. (2004) did not find an association between child abuse and schizophrenia, whereas Kitamura et al. (1993) did not assess this relationship but only compared gender differences within a psychosis population on the measured variables within the study. A higher prevalence of abuse was also reported in psychosis/PLE populations vs. controls (Gayer-Anderson et al., 2015; Traulsen et al., 2015; Addington et al., 2013; Samplin et al., 2013; McCabe et al., 2012; Aas et al., 2011; Bebbington et al., 2011; Heins et al., 2011; Fisher et al., 2009; Barker-Collo & Read, 2011; Agid et al., 1999); except for Furukawa et al. (1998) who found no difference in rate of parental separation in schizophrenia cases vs. controls.

Similar to a previous meta-analysis by Varese et al. (2012), the design of the studies was categorized in relation to how the results, pertinent to the current review, were analyzed. For example, a cohort study analysing the review relevant data in a cross-sectional manner was deemed 'cross-sectional within a cohort study'. Therefore only a minority of the studies used cohort/longitudinal designs (n=8), with the rest employing cross-sectional designs, of which six were case-control studies (see Table 3). Within the 33 studies, gender differences were only the main focus of six of the studies (Gayer-Anderson et al., 2015; Fisher et al., 2009; Samplin et al., 2013; Barker-Collo & Read, 2011; Kitamura et al., 1993; Walker et al., 1981).

Overall the majority of the eligible articles were allocated moderately-high to high quality ratings (ranging from 80-100%; see Table 2). There were only 7 studies with lower ratings, although this was still within a moderate range (60-79%; Bebbington et al., 2011; Thompson et al., 2009; Shevlin et al., 2007; Kilcommons & Morrison, 2005; Schenkel et al., 2005; Offen et al., 2003; Walker et al., 1981). This suggests that overall, there is very good review specific quality among the studies.

Measurement of psychosis/PLE

A range of measures was used within the studies to assess psychosis/PLE, including UHR/prodromal syndromes (n=6); FEP (n=5), psychotic disorders (n=9) and schizophrenic disorders (n=7). The quality rating of the measures used were high (criteria F; see Table 2), with the majority using a type of diagnostic interview schedule. For example, standardized measures within non-clinical studies, included specific PLE measures (e.g. Psychosis-like Symptoms Interview, Horwood et al., 2008; Community Assessment of Psychic Experience, Stefanis et al., 2002) or a diagnostic schedule to either assess the presence of at least one psychotic-experience or a specific symptom (e.g. hallucinations via Composite International Diagnostic Interview, Kessler & Ustun, 2004). These measures have been shown to have good psychometric properties (Mossaheb et al., 2012; Horwood et al., 2008; Spitzer, Williams, Gibbon & First, 1992). This was similar to articles within the clinical samples, with the majority of the studies using a standard diagnostic schedule to identify ultra-high risk prodromal states or psychosis, such as the Schedules for Clinical Assessment in Neuropsychiatry (SCAN, World Health Organization, 1992), Structured Clinical Interview for DSM-IV (SCID, Spitzer et al., 1992), Diagnostic Interview for Psychosis (DIP, Castle et al, 2006) and Comprehensive Assessment of At-Risk Mental States (CAARMS, Yung et al., 2005). The schedules used across clinical sample studies have also shown good

psychometric properties (e.g. Castle et al., 2006; Yung et al., 2005; Miller et al., 2003; Andreasen, Flaum, & Arndt, 1992; Spitzer et al., 1992; World Health Organization, 1992). Alternatively, some of the studies gathered the diagnostic information from national databases (Sorensen et al., 2014; Cutajar et al., 2010a; Cutajar et al., 2010b; Spataro et al., 2004) or patient inpatient or community mental health records (Kilcommons & Morrison, 2005; Schenkel et al., 2005; Offen et al., 2003).

Measurement of childhood adversity

A range of measures were used to assess different adversity types, with the majority of the studies using retrospective self-report of trauma. Although concerns about potential biases in retrospective reporting have been raised (Heinrichs & Zakzanis, 1998; Saykin et al., 1991), literature has indicated that those experiencing psychosis, are able to provide reliable and stable retrospective reports of childhood abuse, with good convergent reliability to clinical/medical records (Fisher et al., 2011). The self-reported measures of adversity ranged from standardized comprehensive schedules (e.g. Childhood Experiences of Care Abuse Questionnaire, Bifulco, Bernazzani, Moran & Jacobs, 2005; Childhood Trauma Questionnaire, Berstein et al., 2003); to single questions within other measures or as part of an interview; and self-reports identified on mental health records. The childhood specific standardized measures have shown good reliability and validity (Bifulco et al., 2005; Berstein et al., 2003; Smith, Lam, Bifulco & Checkley, 2002; Bremner, Vermetten & Mazure, 2000), which was reflected in quality ratings across studies within this domain (criteria G, see Table 2).

The operationalization for the scoring of childhood adversity, varied across articles. A total of 10 studies assessed a single adversity, 15 studies separately analysed adversity types and 8 studies only assessed composite scores combining different types of adversity into an overall category (e.g. total trauma score or categorical abuse vs. not abused; see Table 4 and 5 for studies). It is noted that whilst the composite scores are informative, it may also be limited in terms of comparison across studies due to the content being different for each composite (i.e. studies including different adversity types). Additionally, it may not enable the influence of each adversity type to be differentiated to understand whether the effect is generic or specific to a type of abuse. However, these scores are also important to assess due to literature on the cumulative effect of adversities on psychosis (Beards et al., 2013; Morgan et al., 2008; Shevlin, Houston, Dorahy, & Adamson, 2008).

Table 2. Quality rating of the included studies within the literature review. Quality rating tool adapted from Kmet et al. (2004).

Type	Study	Quality Rating Criteria ^a								Total	%
		A	B	C	D	E	F	G	H		
Non-clinical sample/ax	Fisher et al. 2013. (UK)	2	2	2	1	2	2	1	2	14/16	87.5
	Schreier et al. 2009. (UK)	2	2	2	2	2	2	2	1	15/16	93.8
	Walker et al. 1981. (Denmark)	2	2	2	1	0	1	2	1	11/16	68.8
	van Nierop et al. 2014. (The Netherlands)	2	2	2	2	2	2	1	2	15/16	93.8
	Barker-Collo & Read. 2011 (New Zealand)	2	1	2	2	2	1	1	2	13/16	81.3
	Shevlin et al. 2011. (USA)	2	2	2	2	n/a	2	1	2	13/14	92.9
Samplin et al. 2013. (USA)	2	1	2	2	n/a	2	2	1	12/14	85.7	
Clinical UHR sample/ax	Thompson et al. 2014. (Australia)	2	2	2	2	n/a	2	2	1	13/14	92.9
	Bechdolf et al. 2010. (Australia)	2	2	1	2	n/a	2	1	2	12/14	85.7
	Velthorst et al. 2013. (Australia)	2	2	2	2	n/a	2	1	2	13/14	92.9
	Addington et al. 2013. (North America)	2	2	2	2	n/a	2	1	2	13/14	92.9
	Thompson et al. 2009. (USA)	2	1	0	2	n/a	2	2	2	11/14	78.6
	Bebbington et al. 2011. (UK)	2	2	2	0	0	2	2	1	11/16	68.8
Clinical diagnosis sample/ax	Neria et al. 2002. (USA)	2	2	2	2	n/a	2	2	2	14/14	100
	Sorensen et al. 2014. (Denmark)	2	2	2	1	n/a	2	2	1	12/14	85.7
	Spataro et al. 2004. (Australia)	2	2	2	1	n/a	2	2	2	13/14	92.9
	Cutajar et al. 2010a (Australia)	2	2	2	2	0	2	2	2	14/16	87.5
	Cutajar et al. 2010b (Australia)	2	2	2	2	n/a	2	2	2	14/14	100
	Ucok & Bikmaz. 2007. (Turkey)	2	1	2	2	n/a	2	2	1	12/14	85.7
	Kitamura et al. 1993. (Japan)	2	1	2	2	n/a	2	1	2	12/14	85.7
	Shah et al. 2014. (Australia)	2	2	2	2	2	2	2	2	16/16	100
	Shevlin et al. 2007. (USA)	2	2	2	0	2	2	1	1	12/16	75
	Schenkel et al. 2005. (USA)	2	1	1	2	n/a	2	1	2	11/14	78.6
	Offen et al. 2003. (UK)	2	1	0	2	n/a	2	1	2	10/14	71.4
	Kilcommons & Morrison. 2005. (UK)	2	1	0	1	n/a	2	2	2	10/14	71.4
	Aas et al. 2011. (UK)	2	2	2	2	n/a	2	2	2	14/14	100
	McCabe et al. 2012. (Australia)	2	1	2	2	n/a	2	2	2	13/14	92.9
	Fisher et al. 2009. (UK)	2	2	2	2	2	2	2	2	16/16	100
	Gayer-Anderson et al. 2015. (UK)	2	2	2	2	2	2	2	2	16/16	100
	Furukawa et al. 1998 (Japan)	2	2	2	0	n/a	2	2	2	12/14	85.7
	Heins et al. 2011. (The Netherlands)	2	2	2	1	1	2	2	2	14/16	87.5
	Trauelsens et al. 2015. (Denmark)	2	2	1	2	0	2	2	2	13/16	81.3
	Agid et al. 1999. (Israel)	2	1	2	2	n/a	2	1	2	12/14	85.7

Note: Ax, assessment; Scoring: 2=fully met criteria, 1=partially met criteria, 0=did not meet criteria, n/a=not applicable to the study in relation to the pertinent results for the review.

^a Short hand summary of criteria: A, design; B, recruitment, C, sample size; D, sample characteristics described; E, confounders if applicable; F, psychosis measure; G, childhood adversity measure; H, reporting of results.

Table 3. Characteristics of the studies included in the literature review on gender differences in the relationship between interpersonal childhood adversity and psychosis.

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Non-clinical sample/ax								
Fisher et al. 2013. (UK)	Birth Cohort	6692 children from ALSPAC forming a birth cohort (3286 M, 3406 F; mean age 12.9 at assessment of PLE symptoms)	None	PLIKSi (derived from the DISC-IV and SCAN 2.0) assessing symptoms: broad (any suspected or definite symptoms) and narrow (definite symptoms only).	Questionnaires completed by mothers indicating harsh parenting before age 7 and DV before age 6. Bullying and Friendship Interview Schedule with Ps, Bg before age 8.5.	Harsh parenting (including hitting and hostility) DV, Bg	The direct effects in the stratified gender meditational analysis for the different types of abuse on PLE indicated that the effect of harsh parenting, DV and Bg was similar for males and females, for both narrow and broad PLE symptoms.	I
Schreier et al. 2009. (UK)	Birth Cohort	6437 children from ALSPAC forming a birth cohort (3173 M, 3264 F; mean age 12.9 at assessment of PLE symptoms)	None	PLIKSi (derived from the DISC-IV and SCAN 2.0) assessing symptoms: broad (any suspected or definite symptoms) and narrow (definite symptoms only).	Bullying and Friendship Interview Schedule with Ps (ax at age 8.5 and 10). Parental and teacher reports on individual question within the SDQ (across childhood)	Peer Victm. (incl. overt and relational Bg)	No interaction between gender and Peer Victm. (reported by ps, parent or teacher) on PLE symptoms, indicating similar associations between gender.	I
Walker et al. 1981. (Denmark)	Cohort (baseline and 10 year follow-up)	207 genetically- at risk young people (i.e. mothers were diagnosed with schizophrenia; 121 M, 86 F; age 10-20; age 20-30 at follow up)	None	Follow-up Clinical interview on psychiatric symptoms; PSE & CAPPs. Pathology groups analysed resulting in five factors (with hebephrenic traits and thought disorder).	Baseline assessment included parental absence (and substitute care) up to age 10 gathered from parent/ guardian interview and checked in official Danish population records.	ParLoss (maternal and paternal). Substitute care	In high-risk males maternal absence leading to institutionalization was more strongly associated with thought disorder and hebephrenic traits, whereas being cared for by other family members led to less symptomology. No significant pathway was found for high-risk females. Father's absence not somatology for either gender.	I
van Nierop et al. 2014. (The Netherlands)	Cross sectional within a cohort study	Multi-stage random sampling of 6295 general population participants (age 18-65; including EPP, n=384)	5868 general population participants from the overall sample not reporting PLE	EPP ascertained via CIDI 3.0 (with sections from version 1.0 & 2.0) and SCID-I (ps with at least one psychotic experience)	Trauma Questionnaire from previous study (NEMESIS-1) including seven negative life events before age 16	Trauma (inclu. ParLoss, EN, PA, PsyA, SA)	There was no interaction between gender and trauma associated with EPP severity.	I

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Barker-Collo & Read. 2011 (New Zealand)	Cross sectional	338 non-representative sample of general population (91 M, 247 F; age 17-87)	None	SCL-90-R, assessing various symptom scales (incl. Paranoid Ideation and Psychoticism)	Individual yes or no questions (one for each abuse type), before age 16.	PA, SA, Any abuse (PA or SA) Both abuse types (PA+SA)	<i>Abuse groups and Psychoticism:</i> For both genders they were more likely to meet psychoticism caseness if they experienced both types of abuse vs. any abuse, no abuse or PA. For female this was also true for SA, whereas males were most likely to meet psychoticism caseness if they reported SA. <i>Stratified gender analysis: Both</i> genders showed an increased rate for paranoid ideation when experiencing both abuse types (vs.non abused counterparts). Only males showed an association between SA and paranoid ideation (vs. non-abuse males). No association with PA. Both genders showed an association between SA or both abuse types and psychoticism (vs. non-abuse counterparts). No association with PA. <i>Interaction:</i> Significant interaction between gender and abuse type, where males reports of psychoticism increased more than females when abuse had been experiences (highest SA).	I
Shevlin et al. 2011. (USA)	Cross Sectional	Stratified, multistage, area probability sample: 2353 general population ps (988 M, 1365 F; mean age 44.35)	None	CIDI assessing psychosis (relating to DSM-IV) and symptomatology of auditory and visual hallucinations.	Posttraumatic Stress Disorder module of CIDI included three questions relating to childhood adversity before age 16.	Physical assault, Rape Other sexual assault.	Gender did not moderate the association between the different types of childhood adversity and visual or auditory hallucinations.	I
Samplin et al. 2013 (USA)	Cross Sectional	67 general population ps (30 M; 37 F; mean age 39.9)	None	PLE ascertained via CAPE and SCID-I/NP to rule out psychopathology	CTQ, before age 17.	EA	There was no interaction between sex and EA on PLE.	I

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Clinical UHR sample/ax								
Thompson et al. 2014. (Australia)	Cohort (mean follow up 7 years)	233 UHR (96 M, 137 F; age 15-30)	None	CAARMS interview assessing presence of at least one UHR criteria: i) Attenuated Psychotic Symptoms ii) BLIPS iii) TG	CTQ (self-report)	PA, SA, EA PN, EN, Total abuse (composite score of all the above)	UHR females reported significantly more EA, SA and total abuse vs. males. There was no difference between genders on scores of EN, PN and PA. No data provided on the other childhood abuse domains in the article.	P
Bechdolf et al. 2010. (Australia)	Cross sectional within a cohort study	92 ultra-high risk patients (32 M, 60 F; age 15-24)	None	CAARMS interview assessing presence of at least one UHR criteria: i) Attenuated Psychotic Symptoms ii) BLIPS iii) TG	GTQ (no explicit age stated, one yes or no question with the word 'child' for each abuse type)	PA, Ng	No gender difference in the reports of PA or N.	P
Velthorst et al. 2013. (Australia)	Cross sectional within a cohort study	127 UHR (53 M, 74 F; age 14-26)	None	CAARMS interview assessing presence of at least one UHR criteria: i) Attenuated Psychotic Symptoms ii) BLIPS iii) TG	Records from medical files, experiencing one or more traumatic event before age 18.	PA, EA, SA Other (e.g. verbal abuse, DV, witness of shooting) Total Trauma (composite measure of above)	There was no difference between genders in the prevalence of total trauma. UHR females were more likely to report experiencing SA vs. UHR males. No data provided on the other childhood abuse domains in the article.	P
Addington et al. 2013. (North America)	Cross-sectional within a cohort study	N = 360 UHR (210 M, 150 F; age 13-34)	Article was case-control within a cohort but control n/a for main findings	COPS diagnosis assessed using the Structured SIPS	Childhood Trauma and Abuse Scale, before age 16 (semi-structured interview)	Psychological Bg, Physical Bg, EN, PA, PsyA, SA	COPS females reported more childhood trauma for each type (EN, PA, PsA, SA) vs. COPS males. No gender difference for bullying abuse types between COPS cases.	P
Thompson et al. 2009. (USA)	Cross Sectional	30 UHR (25 M, 5 F; age 13-25)	None	Identification as prodromal to psychosis ascertained using SIPS/SOPS	ETI (semi-structured interview), adversity before age 18.	Total trauma (incl. general trauma e.g. ParDth, PA, EA and SA)	There was no association between gender and total trauma scores.	P

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Bebbington et al. 2011. (UK)	Cross sectional	43 individuals with 'probable psychosis', identified from general population (age 16+, no gender breakdown)	None	SCAN (providing ICD-10 diagnosis; 23 ps) and meeting at least two psychosis-screening criteria (on anti-psychotics, positive response to 5a on PSQ, self-report diagnosis or inpatient for MH in previous 3 months, 20 ps)	Adult Psychiatric Morbidity Survey providing information (about levels of childhood sexual abuse before age 16 (three individual questions))	SA (incl. contact abuse and non-consensual sexual intercourse)	No statistical analysis on reported rates of abuse (contact SA; 1/13 males and 7/21 females; non-consensual sexual intercourse: 0/13 males and 5/21 females). Gender moderated the effect of SA on psychosis, with the association being stronger in female probable psychosis cases (vs. male cases).	I
Clinical diagnosis sample/ax								
Neria et al. 2002. (USA)	Cohort (baseline to 24 month follow-up)	426 FEP cases (255 M, 171 F; age 15-60)	None	DSM-III-R Diagnosis of PD ascertained from SCID at baseline and DSM-IV consensus research diagnosis at 24-month follow-up.	Research/clinical interviews: trauma module of National Comorbidity Survey (24-mnth), trauma reports (6-mnth), collateral from family hospital records, all before age 16.	Victm. (incl. SA, PA, and Ng)	Female cases were more likely to report childhood victimization vs. male cases (OR: 2.43).	P
Sorensen et al. 2014. (Denmark)	Cohort (Data linkage)	2,486,646 million people born in Denmark 1955–1993, followed from age 15 to diagnosis, death, emigration or study ending in 2009 (age 15-53)	None	Danish Psychiatric Central Register to assess SczD using Danish modification ICD-8 (from 1969-1993) and then ICD-10 (from 1994+).	Danish Civil registration System	ParLoss (maternal and paternal)	Stratified gender analysis: For both genders there was an association between early maternal and paternal loss and higher risk of schizophrenia (males ParLoss vs. alive & females ParLoss vs. alive) at similar order of magnitude to IRR of population. Male IRR: 1.05, Female IRR: 1.35. No analysis to assess whether this effect was moderated by gender.	I
Spataro et al. 2004. (Australia)	Historical cohort (9 year follow-up, Data-linkage)	1612 sexually abused children (1327 F, 285 M, mean age at abuse: 9)	General population controls (N= 3 139 745) matched on age	Diagnosis of SczD (ICD-10) ascertained by Victorian Psychiatric Case Register.	Record of SA before age 16, ascertained from Victorian Institute of Forensic Medicine.	SA	There was no the association between SA and SczD, when comparing male SA cases vs. controls or when comparing female SA cases vs. controls. There was no difference in rate of SczD between SA males vs. SA females.	I

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Spataro et al. 2004. (Australia)	Historical cohort (9 year follow-up, Data-linkage)	1612 sexually abused children (1327 F, 285 M, mean age at abuse: 9)	General population controls (N= 3 139 745) matched on age band.	Diagnosis of SczD (ICD-10) ascertained by Victorian Psychiatric Case Register.	Record of SA before age 16, ascertained from Victorian Institute of Forensic Medicine.	SA	There was no the association between SA and SczD, when comparing male SA cases vs. controls or when comparing female SA cases vs. controls. There was no difference in rate of SczD between SA males vs. SA females.	I
Cutajar et al. 2010a. (Australia)	Historical cohort (13 to 44-year follow-up, Data-linkage)	Cohort of sexually abused children (N=2759, 2201 F, 558 M; mean age at abuse 10)	General population sample (N= 2677) matched on gender and age band.	Diagnosis of PD (ICD-10) ascertained by Victorian Psychiatric Case Register (SCz, other PD, all PD)	Record of SA before age 16, ascertained from Victorian Institute of Forensic Medicine.	SA (penetrating and non-penetrating)	Stratified gender analysis: Both male and females SA cases show increased rates of all PD associated with SA vs. controls (male OR 2.3, female OR 2.0). Only female CSA cases (vs controls) showed elevated rates of Scz (OR: 3.2). When assessing only penetrating SA, both genders showed elevated rates of PD and Scz vs controls (male OR 3.6, female OR 2.3). SA males vs. SA females indicated no difference in the rates of Scz There was no interaction between SA or penetration SA, gender and all PD.	I
Cutajar et al. 2010b. (Australia)	Historical cohort (12 to 43-year follow up; Data-linkage)	Cohort of sexually abused children (N=2759, mean age at abuse 10)	General population (n= 2677) matched on gender and age band.	Diagnosis of PD (ICD-10) ascertained by Victorian Psychiatric Case Register	Record of SA before age 16, ascertained from Victorian Institute of Forensic Medicine.	SA	Stratified case-control analysis indicated that both males and females showed a significant association between SA and PD (vs. controls; male OR 2.5, female OR 2.04). There was no significant difference in rates of PD between SA males vs. SA females.	I
Ucok & Bikmaz. 2007. (Turkey)	Cross-sectional within a Cohort Study	57 FEP cases (29 M, 28 F; age range not stated)	None	FEP ascertained via patient records and SCID (DSM-IV diagnosis)	Childhood Abuse Questionnaire and CTQ, before age 18.	PA, EA, SA, PN, EN,	There were no gender differences in reported rates of each abuse type between FEP females vs. FEP males.	P
Kitamura et al. 1993. (Japan)	Cross Sectional	53 cases of Scz from an inpatient population (21 M, 32 F; mean age 26.7)	None	Definite or probable criteria for Scz ascertained by Research diagnostic criteria.	Ad hoc interview on life-history incl. PArLoss types separately for both parents, before age 16.	ParSep (12-mnth+) PArDth PArLoss (composite score).	Females were more likely to have any PArLoss than males. No gender differences in the individual types of parental loss.	P

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Shah et al. 2014. (Australia)	Cross sectional	1825 cases of PD (1087 M, 738 F; age 18-64)	None	PD diagnosis ascertained from DIP (ICD-10) Interviews also incl. psychopathology items (symptoms, age of onset and course of PD)	Childhood adversity module (before age 18) in SHIP survey. Presence of abuse had to meet the standard national Australian definitions.	Abuse (incl Ng, PA, SA and EA)	Female cases were more likely to report abuse vs. male cases (OR: 2.8). For both genders, those who reported child abuse were more likely to report lifetime subjective thought disorder. There was no association between abuse and PD type, PD course or PD symptoms for males or females.	P&I
Shevlin et al. 2007. (USA)	Cross Sectional	Stratified, multistage, area probability sample of 5877 general population ps (age 15-54)	None	Modified version of CIDI assessing lifetime prevalence of non-affective PD (DSM-IV diagnosis)	The National Comorbidity Survey (individual questions, no age limit explicitly stated in study but questions used the word 'child')	Ng, PA	There was no interaction between gender and N or PA in the association with PD.	I
Schenkel et al. 2005. (USA)	Cross sectional	40 SczD cases from an inpatient population (15 M, 25 F; age 20-62)	None	SczD ascertained from clinical interview, patient records and hospital staff consultation.	Clinical interview questions and patient medical records.	Abuse (composite score of PA, SA and Ng)	There were no gender differences in childhood abuse reports between male vs. females cases.	P
Offen et al. 2003. (UK)	Cross sectional	26 PD cases (19 M, 7 F; age 18-60)	None	PD diagnosis (DSM-IV) from patient records.	Individual yes/no question within a broader questionnaire.	SA	Female PD cases reported more SA vs. male PD cases.	P
Kilcommons & Morrison. 2005. (UK)	Cross sectional	32 PD cases (25 M, 7 F; age 23-67)	None	PD diagnosis (DSM-IV) from patient records.	Trauma History Questionnaire (childhood section-experiences before age 16)	PA, SA, Sudden loss, GA (incl. witnessing killing). Total trauma (composite of all)	There were no differences between female vs. male cases on reporting of the different types of abuse.	P
Aas et al. 2011. (UK)	Cross sectional within Case control	138 FEP (73 M, 65 F; age 16-65)	n/a for main finding.	FEP via patient records and SCAN (ICD-10 diagnosis)	CECA.Q, data before age 16 (administered by researchers)	Trauma (composite score of PA and SA)	FEP females experienced higher levels of trauma vs. FEP males.	P

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
McCabe et al. 2012. (Australia)	Cross sectional within a Case control study	408 Scz cases (264 M, 144 F; age 18-65)	n/a for main finding	SczD diagnosis ascertained via DIP (ICD-10 diagnosis)	Modified version of Childhood Adversity Questionnaire, before age 18.	2 composite scores (incl. PA, Ng, EA, SA and ParLoss) - Any abuse (binary: at least one abuse) Total abuse (continuous: number of events)	There were no gender differences in the in reports of experiencing any abuse between Scz females vs. Scz males (categorical variable). Scz females were more likely to report a greater number of childhood trauma vs. Scz males (continuous variables).	P
Fisher et al. 2009. (UK)	Case-Control	181 FEP (97 M, 84 F; age 16-64)	246 controls from the same geographical area.	FEP via patient records and SCAN (ICD-10 diagnosis) In controls: PLE ascertained via PSQ.	CECA.Q, data before age 16 (administered by researchers)	PA, SA, Either abuse (composite score PA or SA) Both abuse (composite score PA and SA)	^b Female FEP more likely to report PA (OR: 3.33) and SA (OR: 1.88) vs female controls. No association found in males. There was an interaction between gender and PA, and gender and SA (weaker interaction) on FEP. Either Abuse: Female FEP more likely to report either abuse (OR: 2.5) vs female controls. No association found in males. There was an interaction between gender and reporting either abuse (SA or PA) on FEP. Both abuse: Female FEP more likely to report both abuse (OR: 3.37) vs female controls. No association found in males. No interaction between gender and reporting both abuse (PA and SA). PLE: A trend for female controls with PLE to report more PA vs controls without PLE (OR: 3.09). No increased rate of PLE among males for PA/SA or females for SA.	I
Gayer-Anderson et al. 2015. (UK)	Case-Control	202 FEP cases (100 M, 102 F; age 16-65)	266 controls from the same geographical area.	FEP via patient records and SCAN (ICD-10 diagnosis)	CECA.Q, data before age 16 (administered by researchers)	PA, SA	^b Female FEP more likely to report PA (OR: 3.31) and SA (OR: 2.21) vs. female controls. No association found in males. There was a significant interaction between gender and PA; and gender and SA, on FEP.	I
Furukawa et al. 1998. (Japan)	Case-Control	Scz diagnosis (N=225; 114 M, 111 F, age 16+)	122 healthy controls (52 M, 70 F)	SczD diagnosis and symptoms via PISA interview administered by a psychiatrist (DSM-III-R diagnosis)	PISA for cases and TOSHI for controls (identical individual questions on ParLoss types before age 16)	ParDth ParSep ParLoss (composite score of both)	Article unable to identify increased or decreased incidence of Scz across gender for cases vs. controls due to CI including 1.0. Female Scz cases with paternal ParLoss were more likely to experience hallucinations (OR: 3.52) No association in males Scz cases.	I

Table 3 continued

Study (country)	Design	Sample	Comparison Group	Psychosis measure	Childhood Adversity Measure	Childhood Adversity Type	Relevant Findings	Result: P, I or P&I ^a
Heins et al. 2011. (The Netherlands)	Case-Control, Case-Sibling	272 cases non-affective PD (189 M, 83 F; age 16-55)	258 healthy siblings of cases (117 M, 141 F); 227 healthy controls (69 M, 158 F)	Non-affective PD, ascertained via the Comprehensive Assessment of Symptoms and History (DSM-IV diagnosis)	CTQ, prior to age 17	Trauma (composite score EA, PA, GA, EN and PN)	Gender did not moderate the association between psychosis and trauma, in the case-control, case-sibling or sibling-control analyses.	I
Trauelson et al. 2015. (Denmark)	Case-Control	101 FEP (75 M, 26 F; age 18-34)	101 healthy population controls mated for gender, age and parental education (75 M, 26 F; age 18-33)	FEP ascertained via OPCRIT scored on patient records and PANSS interview (ICD-10 diagnosis)	CTQ, prior to age 17	SA	No significant interaction between gender and SA on psychosis.	I
Agid et al. 1999. (Israel)	Case-Control	76 Scz cases (36 M, 40 F; mean age 42.5).	76 Healthy controls matched on age band, gender and ethnicity.	SczD ascertained via SCID (DSM-III-R). Ax of other diagnosis in other case sample but n/a to main findings.	Hebrew University Database Questionnaires (incl. past and recent life events, before age 17)	ParLoss (incl. ParSep and ParDth)	Stratified gender analysis: There was a trend for higher ParLoss reports in female Scz cases vs female controls (OR: 4). There was no difference in ParLoss reports between male Scz cases vs male controls (OR3.5).	P

Study type was defined on how the article analysed the main finding reported, e.g. a cohort study analysing data in a cross-sectional manner was deemed 'cross-sectional within a cohort study'

^a P, study result on prevalence of abuse between gender reported; I, study result on differential impact of gender on the association between childhood abuse and psychosis; P&I, study reports both prevalence and impact results on gender differences..

^b study reported the use of a more liberal p-value of 0.01 due to difficulty in detecting interaction effects.

Note: *Gender acronyms:* M, male; F, female; *Psychosis diagnosis acronyms:* BLIPS, Brief Limited Intermittent Psychotic Symptoms; COPS, criteria of prodromal syndromes; FEP, first episode psychosis; EPP, extended psychosis phenotype; PLE, psychotic-like experiences; PD, psychotic disorder; SczD, schizophrenic disorder. TG, trait group with either schizotypal personality disorder or first degree relative with a of psychotic disorder; UHR, ultra-high risk for psychosis.

Childhood Abuse acronyms: Bg, bullying; DV, domestic violence; EA, emotional abuse; EN, emotional neglect; GA, general abuse; Ng, neglect; PA, physical abuse; ParDth, parental death; ParSep, parental separation; ParLoss, parental loss or absence; PN, physical neglect; PsyA, psychological abuse; SA, sexual abuse; Vitm, victimization.

Other: ALSPAC, Avon Longitudinal Study of Parents and Children; Ax, assessment; CAARMS, Comprehensive Assessment of At-Risk Mental States; CAPE, Community Assessment of Psychic Experience; CAPPs, Current and Past Psychopathology Scales; CECA-Q, Childhood experiences of Care Abuse Questionnaire; CIDI, Composite International Diagnostic Interview (version 1.0, 2.0, or 3.0); CTQ, Childhood Trauma Questionnaire; DIP, Diagnostic Interview for Psychosis; DISC-IV, Diagnostic Interview Schedule for Children version IV; DSM-III-R/ DSM-IV, Diagnostic and Statistical Manual (3rd edition revised or 4th edition); ETI, Early Trauma Inventory; GTQ, General Trauma Questionnaire; ICD-8/ICD-10, International Classification of Diseases (8th or 10th revision); IRR, Incidence risk ratio; NEMESIS-1, Netherlands Mental Health Survey and Incidence Study 1; OPCRIT, operational criteria checklist for psychotic and affective illness; OR, odds ratio; PANSS, Positive and Negative Symptom Scales; PILKSi, Psychosis-like Symptoms Interview; PISA, Psychiatric Initial Screening for Affective disorders; Ps, participants; PSE, Present State Examination; PSQ, Psychosis screening questionnaire; RR, risk ratio; SCAN, WHO Schedules for Clinical Assessment in Neuropsychiatry (version 1.0 or 2.0); SCID, Structured Clinical Interview for DSM-III-R; SCID-I, Structured Clinical Interview for DSM-IV; SCID-I/NP, Structured Clinical Interview for DSM-IV Non-patient version; SCL-90-R, Symptom Checklist-90-Revised; SDQ, Strengths and Difficulties Questionnaire; SHIP, Survey of High Impact Psychosis; SIPS, Structured Interview for Prodromal Syndromes; SOPS, Scale of Prodromal Symptoms; TOSHI, Time-Ordered Stress and Health Interview.

Prevalence of interpersonal childhood adversity

Overall there were 16 studies, which assessed differences in reports of interpersonal childhood adversity among psychosis/PLE populations (with Shah et al., 2014 also reporting on differential gender effects). The results are summarized in Table 4. Within these studies, only Samplin et al., (2013), assessed a non-clinical sample (finding no gender difference in report of emotional abuse), therefore making it difficult to draw conclusions on prevalence within PLE populations.

Adversity Types: For sexual abuse, four out of six studies described a higher report among females compared to males (Thompson et al., 2014; Addington et al., 2013; Velthorst et al., 2013; Offen et al., 2003), whereas two reported no gender differences (within psychosis populations, Ucok & Bikmaz, 2007; Kilcommons & Morrison, 2005). Of the studies with positive findings, Offen et al. 2003, was the only article using a psychosis sample (with the other three articles on UHR), and was scored with a lower quality rating (71.4%); due to small sample size between groups and a single childhood adversity question as part of a measure, with a report of no psychometric data. However, this type of measure does fall under the category of a retrospective report in general, which has been shown to be reliable (Fisher et al., 2011). The other studies with differential gender findings (Thompson et al., 2014; Addington et al., 2013; Velthorst et al., 2013), were all rated 92.9%, indicating high review specific quality, suggesting that in those within an at risk mental state, there is higher report of sexual abuse in females. The results also indicate another possible differential reporting between UHR and psychosis population, when assessing emotional and psychological abuse. Thompson et al. (2014) and Addington et al. (2013) found a higher prevalence of emotional abuse among females within an UHR sample; whereas no gender difference was found for this abuse type in psychotic-disorder samples (Ucok & Bikmaz, 2007; Kilcommons & Morrison, 2005).

In terms of other abuse types, it appears that there are no gender differences in the reported rates of physical abuse (Bechdolf et al., 2010; Ucok & Bikmaz, 2007; Kilcommons & Morrison, 2005) or neglect (Bechdolf et al., 2010; Ucok & Bikmaz, 2007). Addington et al. 2013 was the only article indicating a gender difference within both of these abuse types, with greater prevalence among females in UHR. Similarly, it was indicated that the rate of parental loss (one study assessing loss of a loved one, Kilcommons & Morrison, 2005) did not differ between genders on articles within clinical diagnosis populations (Kilcommons & Morrison, 2005; Agid et al., 1999; Kitamura et al., 1993). However Agid et al. (1999) did find a trend for female schizophrenia cases, to report more parental loss than female controls; whereas no difference was found between male cases vs. controls (Agid et al., 1999). There was also no gender difference in bullying, although it is not possible to draw any conclusions on prevalence from a single study (Samplin et al., 2013).

Adversity Composite Measure: The majority of studies reported on a composite score of adversity (see Table 4). Within UHR samples, Thompson et al. (2014) found that females report a higher total CTQ score compared to males; whereas two other studies reported no gender difference on composite scores of abuse (Velthorst et al., 2013; Thompson et al., 2009). However, Thompson et al.'s (2009) null findings is within the context of a lower quality rating (78.6%), mostly due to the uneven sample size for gender (25 males vs. 5 females) which limits the validity of their findings; (whereas the other two studies scored a high quality rating across domains, 92.9%; Thompson et al., 2014; Velthorst et al., 2013). For the clinical diagnosis samples, five studies out of seven indicated that females report higher rates of overall combined trauma compared to males (Shah et al., 2014; McCabe et al., 2012; Aas et al., 2011; Neria et al., 2002; Kitamura et al., 1993). The studies with null results had lower quality ratings (Kilcommons & Morrison, 2005; Schenkel et al., 2005), due to small sample size and uneven gender distribution. Whereas the

other studies scored within the moderately-high to high quality rating, with three articles scoring 100% (Shah et al., 2014; Aas et al., 2011; Neria et al., 2002). The majority of these studies used a categorical composite measure (e.g. trauma vs no trauma; Shah et al., 2014; Aas et al., 2011; Neria et al., 2002; Kitamura et al., 1993), whereas McCabe et al. (2012) found no gender difference for a categorical composite score, but did find that females scored higher on the total number of traumas experienced. Overall this suggests that there is higher prevalence of overall abuse in females who experience a psychotic disorder.

Table 4. Summary of study prevalence findings: rates of childhood adversity between gender in psychosis/psychosis-like experience populations.

Type	Study	SA	PA	Lack of nurturing environment			Bg ^a	Composite ^a
				EA/ PsyA ^a	Ng ^a	Parental Loss ^a		
Non-clinical sample/ax	Samplin et al. 2013. (USA)			0				
Clinical UHR sample/ax	Thompson et al. 2014. (Australia)	+f		+f				+f
	Bechdolf et al. 2010 (Australia)		0		0			
	Velthorst et al. 2013. (Australia)	+f						0
	Addington et al. 2013. (North America)	+++	+f	+f	+++		0	
	Thompson et al. 2009. (USA)							0
Clinical diagnosis sample/ax	Neria et al. 2002. (USA)							+f
	Ucok & Bikmaz. 2007. (Turkey)	0	0	0	0 ^b			
	Kitamura et al. 1993. (Japan)					0		+f
	Shah et al. 2014. (Australia)							+f
	Schenkel et al. 2005. (USA)							0
	Offen et al. 2003. (UK)	+f						
	Kilcommons & Morrison. 2005. (UK)	0	0	0 ^c		0 ^c		0
	Aas et al. 2011. (UK)							+f
	McCabe et al. 2012. (Australia)							+f ^d ; 0 ^d
	Agid et al. 1999. (Israel)					0		

Note: Ax, assessment; Bg, bullying; EA, emotional abuse; N, neglect; PA, physical abuse; PD, psychotic disorder; PsyA, psychological abuse; SA, sexual abuse; UHR, ultra high risk. +, p<0.05 or study report of significance with no p value given statistics used or no raw data state; ++, p<0.01, '+' p<0.1; 0, no gender difference found; (+), non-significant trend; blank, association not assessed or not reported explicitly in study; m or f, indicates direction of gender difference.

^a EA/PsyA includes studies assessing EA, PsyA and variables on parental relationship; Ng includes studies assessing general, emotional or physical neglect and parent-child relationship; Parental Loss includes studies assessing parental death or separation; Bg includes studies assessing general, psychological or physical bullying; Composite includes studies which combined scores of any childhood abuse types in assessing gender differences.

^b Association for physical neglect and emotional neglect assessed separately.

^c Association for general abuse such as witnessing a killing (EA) and association for sudden loss of a loved one (parental loss).

^d Significant difference for a higher number of adversities reported (+f) and no difference between any loss reported vs no loss reported (0).

Gender differences in childhood adversity and psychosis

Overall there were 19 studies, which assessed the possibility of gender differences in the association between interpersonal childhood adversity and psychosis/PLE.

The results are summarized in Table 5. Within these studies, only Bebbington et al. (2011) assessed an UHR sample, making it difficult to draw conclusions on this relationship solely within UHR populations.

Adversity Types: The associations relating to sexual abuse indicated no differential impact on psychosis/PLE outcome, as six out of ten studies found no gender difference (Trauelsen et al., 2015; Shevlin et al., 2011; Cutajar et al., 2010a; Cutajar et al., 2010b; Fisher et al., 2009; Spataro et al., 2004). These studies were scored between a moderate-high to high rating (81.3%-100%), suggesting good review specific quality. Within the non-clinical samples, Barker-Collo and Read (2011) found a gender interaction, where males reports of psychoticism were higher than females, across abuse types, with the highest difference for sexual abuse. However this study's ratings were relatively low, due to poorer gender distribution in the sample and use of individual items both, on a checklist to assess PLE (Symptom Checklist-90-Revised) and to assess abuse. Alternatively, two other studies assessing sexual abuse reported no gender differences (Shevlin et al., 2011; Fisher et al., 2009).

For the clinical samples, three studies found the effect of sexual abuse on psychosis to be stronger in females; one within an UHR sample (Bebbington et al., 2011; although quality rating was only 68.8% given relatively poorer description of sample characteristics and insufficient report of statistical information to infer precision of results); and two on FEP (Gayer-Anderson et al., 2015; Fisher et al., 2009). Gayer-Anderson et al. (2015) and Fisher et al. (2009) used a case-control design, within the UK, to assess the relationship (female OR: 1.88-2.21) and had excellent review specific quality (100%); although, they also applied a more liberal

p-value due to interaction effects being harder to detect. Similarly for psychological abuse, only Gayer-Anderson et al. (2015) and Fisher et al. (2009) found that females had higher odds of FEP (approx. 3.3 times more likely) after experiencing physical abuse compared to males (after adjusting for confounders); and Fisher et al. (2009) found a similar trend for female controls reporting PLE (not reaching significance due to the small sample). However, three other studies found no suggestion of moderation by gender on this relationship across PLE (Barker-Collo & Read, 2011; Shevlin et al., 2011) or psychosis-diagnosis populations (Shevlin et al., 2007; this study had relatively lower quality ratings, 75%, for not including confounders, no age explicitly described within the adversity measure and no report of statistical information on non-significance).

Fisher et al. (2013), was the only study to investigate the association between bullying and emotional abuse on PLE symptoms, finding no gender differences in this relationship, from assessing the direct effects of the mediation analysis (e.g. Bullying: broadly defined PLE male OR: 1.08; female OR: 1.09; narrowly defined PLE male OR: 1.10; female OR: 1.09). Similarly no differential impact for gender was found between neglect and PLE (Fisher et al., 2013) or psychotic disorder (Shevlin et al., 2007). For parental loss, two studies indicate no gender difference (Sorensen et al., 2014; Schreier et al., 2007); whereas Walker et al. (1981) found males to be more likely to experience thought disorder and hebephrenic symptomology after experiencing maternal absence which led to insituationalisation; while this association was not found in females and was lower in males looked after by family members following maternal absence. Contrastingly, Furukawa et al. (1998) indicated that female cases with a schizophrenic disorder were more likely to experience hallucinations following paternal loss compared controls; with this association not present in males. This suggests that there are no conclusive

findings on the differential impact of gender on psychosis/PLE after experiencing neglect, bullying, parental loss or emotional abuse.

Adversity Composite Measure: Five studies used a composite measure of childhood adversity, with three high quality rated articles finding no effect of gender on the association with psychosis (Shah et al., 2014; Heins et al., 2011) or PLE (van Nierop et al., 2014; only study using a continuous composite scoring). Within a non-clinical population, Barker-Collo and Read's (2011) study found a significant gender interaction, where both genders showed an association between abuse (categorical composite measure: both physical and sexual abuse) and psychoticism, but males reported higher scores following these adverse experiences. Alternatively, in a FEP population, Fisher et al. (2009) found no gender moderation with a composite measure of both sexual and physical abuse; although this study did find a stronger association in females, between an either abuse composite score (either sexual or physical) and FEP. The overall results suggest no conclusive evidence for the relationship between combined abuse experiences and psychosis/PLE to be moderated by gender.

Table 5. Summary of study findings on differential impact: gender differences in the associations between type of adversity and psychosis or psychosis-like experiences.

Type	Study	Lack of nurturing environment					Composite ^a	
		SA	PA	EA/ PsyA ^a	Ng ^a	Parental Loss ^a		Bg ^a
Non-clinical sample/ax	Fisher et al. 2013. (UK)			0 ^b	0 ^b		0	
	Schreier et al. 2009. (UK)					0		
	Walker et al. 1981. (Denmark)					++m ^c		
	van Nierop et al. 2014. (The Netherlands)							0
	Barker-Collo & Read, 2011 (New Zealand)	+m	0					+m
	Shevlin et al. 2011. (USA)	0 ^d	0					
	Fisher et al. 2009. (UK)	0	(+)f					
Clinical UHR sample/ax	Bebbington et al. 2011. (UK)	+f						
Clinical diagnosis sample/ax	Sorensen et al. 2014 (Denmark)					0		
	Spataro et al. 2004. (Australia)	0						
	Cutajar et al. 2010a. (Australia)	0						
	Cutajar et al. 2010b. (Australia)	0						
	Shah et al. 2014. (Australia)							0 ^e
	Shevlin et al. 2007. (USA)		0		0			
	Fisher et al. 2009. (UK)	'+f' ^e	'+f' ^e					+f ^g ; 0 ^g
	Gayer-Anderson et al. 2015. (UK)	'+f' ^e	'+f' ^e					
	Furukawa et al. 1998 (Japan)					+f ^h		
	Heins et al. 2011. (The Netherlands)							0
Trauelsen et al. 2015. (Denmark)	0							

Note: Ax, assessment; Bg, bullying; EA, emotional abuse; N, neglect; PA, physical abuse; PD, psychotic disorder; PsyA, psychological abuse; SA, sexual abuse; UHR, ultra high risk.
+, p<0.05 or study report of significance with no p value given statistics used or no raw data state;
++, p<0.01, '+' p<0.1; 0, no gender difference found; (+), non-significant trend; blank, association not assessed or not reported explicitly in study; m or f, indicates direction of gender difference.

^a EA/PsyA includes studies assessing EA, PsyA and variables on parental relationship; Ng includes studies assessing general, emotional or physical neglect and parent-child relationship; Parental Loss includes studies assessing parental death or separation; Bg includes studies assessing general, psychological or physical bullying; Composite includes studies which combined scores of any childhood abuse types in assessing gender differences.

^b Association for domestic violence (EA/PsyA) and harsh parenting (N).

^c Association for maternal loss leading to institutionalization.

^d Separate associations conducted for rape and for other sexual assault.

^e Association with type of PD and PD symptoms.

^f Study reported the use of a more liberal p-value of 0.01 due to difficulty in detecting interaction effects.

^g Association with composite score of either abuse (PA or SA; +f) and association with composite score of both abuse (PA and SA; 0).

^h Association for paternal parental loss on hallucinations.

Discussion

As reported in the wider literature (Varese et al., 2012; Arseneault et al., 2011; Schafer & Fisher, 2011; Morgan et al., 2009; Bendall et al., 2008; Morgan & Fisher, 2007; Read et al., 2005), the eligible studies indicated an overall association between childhood adversity and psychosis, as well as higher prevalence of adversity reported in psychosis populations compared to the general population. In relation to review specific aims, females reported a higher prevalence of overall abuse compared to males in clinical samples. Additionally, there was suggestive evidence of UHR females experiencing more sexual and emotional/psychological abuse compared with UHR males. There were no other gender differences in reports for other types of adversity (bullying, physical abuse, neglect and parental loss) and not enough articles to ascertain conclusions within non-clinical samples. The current literature also suggests no gender difference in the relationship between interpersonal childhood adversity and psychosis/PLE.

Prevalence

The results within clinical samples, suggest more overall trauma experienced by females, whereas there was very little evidence of differential prevalence for specific types of adversity. Most of the studies used a categorical composite measure of trauma (Shah et al., 2014; Aas et al., 2011; Neria et al., 2002; Kitamura et al., 1993); although Aas et al. (2011), used the CTQ which dichotomized results into severe and non-severe categories, suggesting higher levels of abuse in females; and McCabe et al. (2012), indicated a higher number of cumulative traumas in females. Plausibly, females experienced a variety of adversities (i.e. reflected in the combination of trauma measures) and possibly more severe or cumulative experiences. It may therefore be the range of traumas that are associated with a diagnosis of psychosis, which is reflected in a review specifying a heightened risk

after the experience of cumulative childhood adversity (Shevlin et al., 2008). Childhood adversity, with a range of adverse experiences, may be an indicator of an early impact on attachment relationships, which could have lasting effects on psychopathology and interpersonal functioning (Gumley, Taylor, Schwannauer & MacBeth, 2013; Berry, Barrowclough & Wearden 2008). This may also foster the development of enduring cognitive bases (e.g. negative thoughts about the self, world and others; hostility attribution biases), which culminate into a vulnerability to psychosis, reflected in cognitive models of psychosis (Garety et al., 2001, 2007). Coupled together, it is possible that these individuals are lacking the protective resources in adulthood, which provide some resilience to risk of psychosis. For example, less social support combined with more severe abuse was found to be associated with increased odds of psychosis in females (Gayer-Anderson et al., 2015).

Furthermore UHR females reported higher prevalence of specific types of adversities, namely sexual and emotion/psychological abuse. Linking these findings, it is plausible that these single types of abuse are associated with a risk of subclinical-symptoms but possibly not severe enough for a full-episode of psychosis, unless additional adverse events are experienced. This would connect with research on adult adversity, which suggests that life events and lifetime adversity are associated with psychosis or PLE (Shevlin et al., 2013; Wigman et al., 2011; Bechdolf et al., 2010; Shevlin et al., 2007). Early trauma has also been shown to predict adversity in adulthood and interact with adult adversity to escalate the risk of psychosis onset (Morgan et al., 2014a; 2014b; Lataster, Myin-Germeys, Lieb, Wittchen & van Os, 2012). The experience of childhood abuse (sexual or physical) increases risk for further childhood victimization (Casey & Nurius, 2005) and for adult victimization, especially among females (sexual, physical, psychological; Coid

et al., 2001; Schaaf & McCanne, 1998; Cloitre, Tardiff, Marzuk, Leon & Portera, 1996; Messman & Long, 1996). Therefore for UHR individuals, further exposure to traumatic experiences could lead to the development of psychosis; whereas the composite abuse indicated in the clinical samples, could possibly indicate a range of early adversity which lead to a higher risk for psychosis or even re-victimization. Alternatively, within the clinical samples there was less literature on individual types of adversity by gender, which indicates a need for further research to elucidate the possible influence of each adversity type and facilitate understanding on whether the effect is generic or specific to a trauma type.

Association between childhood adversity and psychosis

Gender was not found to be a moderator in the association between interpersonal childhood adversity and the continuum of psychosis. There were only two studies, which indicated that females exhibited a stronger association, between adversity (sexual, physical) and FEP (Gayer-Anderson et al., 2015; Fisher et al., 2009) and sexual abuse and UHR classification (Bebbington et al., 2011). All of these studies were within the UK, with the FEP studies based in London (Bebbington et al., 2011 was a national survey within England). The studies with null findings, were based within coterminous United states (Shevlin et al., 2008; 2011), the state of Victoria Australia (Cutajar, 2010a, 2010b; Spataro et al., 2004) and the Region Zealand in Denmark (Trauelsen et al., 2015), which are either covering a range of areas (urban and more rural) or possible localities in contrast to that in London, UK. These gender differential findings may therefore also be in the context of other interacting variables, such as urbanicity which varies across the study samples. This may be relevant as there is growing literature connecting risk of psychosis with urban compared to rural living and apparent differences in rates of psychosis across urban neighbourhoods (Deserno & Reininghaus, 2013). Although some studies indicate

higher incidence rates for males in urban areas (Kelly et al., 2010; Marcelis, Navarro-Mateu, Murray, Selten & van Os, 1998), it is possible that, the childhood trauma risk interacts with adult adversities associated with urban exposure, faced by females. For example, abused females may be more likely to experience re-victimisation in adulthood which may be heightened in urban areas; and other related stressors such as single parenthood and isolation (e.g. Fisher et al., 2015; Gayer-Anderson et al., 2015; Mann et al., 2014; Shevlin et al., 2013; Bengtsson-tops & Ehliasson, 2012; Elklit & Shevlin, 2011; Ministry of Justice, 2011; Tricket, Noll & Putnam, 2011; Fearon et al., 2006; Briere & Jordan, 2004; Bhugra et al., 1997).

Another important factor to consider is whether the research design and statistical approaches were optimal to detect the possible subtle effect between genders. More sophisticated analyses require more power to identify effects and therefore it is suggested that interaction effects are difficult to detect (although a number of the articles consisted of large general population samples). There is a possibility that the moderation was not present within conventional p-values, reflecting the more liberal p-value approach implemented with Gayer-Anderson et al. (2015) and Fisher et al. (2009). Additionally more case-control designs (compared to other observation designs in the review), found positive results, with three indicating stronger associations in females between sexual abuse, physical abuse, paternal loss and a composite score on psychosis/PLE (Gayer-Anderson et al., 2015; Fisher et al., 2009; Furukawa et al., 1998). However, it was evidenced that the cohort studies were more likely to use measures assessing childhood adversity that was either, closer to specific age range of the trauma pertinent to the study (Fisher et al., 2013; Schreier et al., 2007; Walker et al., 1981) or using historical data-linkage from national records (Sorensen et al., 2014; Cutajar et al., 2010a; Cutajar et al., 2010b;

Spataro et al., 2004). These methods did not find a differential gender impact between adversity and psychosis/PLE outcome (except Walker et al., 1981), which possibly suggests differential findings between the use of records vs. self-report methods, used within the studies described above. This may reflect the critique of possible bias in retrospective reporting, such as memory or recall bias from cognitive appraisals of an event (Susser & Widom, 2012). Although, other cohort studies did report differences in prevalence, using the CTQ (Thompson et al., 2014) and multiple sources of information across various time-points (Neria et al., 2002). Overall, there were limited studies assessing the differential association between genders, with articles also investigating a small range of adversity types, which restricted the current reviews ability to make comparisons and draw firm conclusions within this area.

Possible mechanisms

This current review highlights some gender differences within the association between childhood adversity and psychosis; and the wider literature proposes gender as a possible factor to explain some of the heterogeneity within psychosis (Barajas et al., 2015; Thorup et al., 2014; Ochoa et al., 2012). Females experienced a higher prevalence of interpersonal childhood abuse, and this may suggest that a route to psychosis from childhood trauma may be more frequent in females. The stress-vulnerability model states that mental health difficulties may occur, if the stress experienced surpasses an individual's vulnerability level (Zubin, Magaziner & Steinhauer, 1983), which encompasses both cognitive models and stress sensitivity hypotheses about the development of psychosis. The cognitive model of psychosis, suggested that cognitive and affective processes in predisposed individuals, can lead to biased appraisals of anomalous experiences which influence the development of psychosis (Garety et al., 2001, 2007). Differences in cognitive and

affective pathways between genders, has not been extensively assessed. However, although Fisher et al. (2013), found similar meditational pathways (anxiety, depression, external locus of control, low self-esteem) between genders from childhood victimization to PLE, they also indicate some gender differences, when assessing pathways from victimization to definite PLE. For example, females had a stronger meditational pathway between harsh parenting and definite PLE, but a weaker pathway from domestic violence, compared to males. This is suggestive of different cognitive or affective process between genders, but requires further investigation.

Stress sensitivity is another possible explanation for gender differential patterns in psychosis, possibly a route for females from trauma. Childhood adversity is proposed to effect neurodevelopmental processes and behavioral outcomes which influences stress response (Read et al., 2005). The possible biological mechanisms implicated are deregulated HPA axis or dopamine transmission (van Winkel et al., 2008; Myin-Germys & van Os, 2007; Read et al., 2005). Increased stress sensitivity, has been shown in individuals vulnerable to psychosis using report (Trotman et al., 2014; Lataster, 2009) and experience sampling methods (Myin-Germeys & van Os, 2007; Myin-Germeys et al., 2005; Myin-Germeys et al., 2001); as well as, in those who have experienced childhood adversity (Glaser, van Os, Portegijs & Myin-Germeys, 2006). There is also a suggestion of possible differential stress sensitivity across gender. For instance, in females, increased stress sensitivity mediated the relationship between life events and PLE (Gibson et al., 2014); and females with a diagnosis of psychosis (vs. male cases) demonstrated heightened emotional reactivity to daily stressors (Myin-Germeys & van Os, 2007; Myin-Germeys, Krabbendam, Delespaul & van Os, 2004). Furthermore, females with a history of sexual and physical abuse displayed higher 'pituitary-adrenal and autonomic

responses to stress' vs. female controls, indicative of HPA axis sensitivity (Heim et al., 2000). Other literature has also indicated HPA dysregulation, in sexually abused females (vs. female controls; Putnam & Trickett, 1997; De Bellis et al., 1994). Therefore it is possible that differences in gender are not just evidenced in features of psychosis but in underlying etiology, with females following a more affective pathway to psychosis and affective symptom expression (Barajas et al., 2015; Ochoa et al., 2012; Myin-Germeys & van Os, 2007; Leung & Chue, 2000; Castle, Sham, Wessely & Murray, 1994). Increased stress sensitivity in females, may be consequential to the experience of childhood adversity, which is further compounded by daily stress and other activating events for cognitive and affective processes, subsequently leading to psychosis (Myin-Germeys & van Os, 2007). However these mechanisms require further exploration in empirical research, especially in comparing etiology and association between male and female participants.

Limitations, implications and future directions

There are several limitations to be considered. This review is a narrative account of the eligible literature, which provides a useful overview on the area, but it would also be useful for more systematic quantitative studies to synthesize the evidence (e.g. meta-analyses), to provide further critical analysis and additional statistical information from combining findings of comparable studies. For instance, one of the exclusion criteria for the current review was insufficient information on gender differences, i.e. articles only using gender as a confounder or covariate, whereas in a meta-analysis it may have been possible to request this data from researchers to increase the size of the reviewed literature. The articles' strengths include large sample sizes, good-to-excellent quality rating and many articles with reliable and valid exposure and outcome measures. However, a variety of studies investigated

individual abuse types, only three out of twelve studies indicated a gender difference across three different types of adversity (two for sexual abuse and physical abuse, Gayer-Anderson et al., 2015; Fisher et al., 2009; one for parental loss, Furukawa et al., 1998); while the other nine were dispersed across adversity types. This disparity in childhood adversity measures makes it hard to compare across types of trauma experienced. This coupled with the limited studies across trauma or sample population, makes it difficult to draw firm conclusions about gender differences in prevalence and association between adversity and psychosis.

Another factor which the findings should be interpreted within, is the cross-sectional nature of most of the articles. From this design causation cannot be implied and it is also tied with critiques of retrospective reports, such as potential of recall bias particularly in those with severe mental health difficulties (Susser & Widom, 2012; Heinrichs & Zakzanis, 1998; Saykin et al., 1991). However, given the time and cost of longitudinal data, cross-sectional studies are an efficient way of investigating multiple exposures, with the potential of assessing a variety of putative confounders, moderators and mediators. They are especially important when investigating rare disorders, such as psychosis, given it is not always feasible to conduct studies with the number of participants needed to identify enough cases of psychosis for a sufficiently powered analysis (Mann, 2003). Retrospective reports are also therefore a feasible research tool, and reliability has been indicated in the reports of childhood abuse within psychosis populations (Fisher et al., 2011). Additionally, case-control studies can be well designed to assess possible causality, using criteria such as reducing selection and information bias and attempting to establish temporal order of exposure and outcome to try to reduce the possibility of reverse causality (Susser, Schwartz, Morabia & Bromet, 2006).

This review indicates a need for more literature to be conducted on the gender differences in the association between childhood adversity and psychosis. The future research should endeavour to identify gender differences, as well as expand and clarify the potential modification. Important questions can be assessed, in regards to whether there is a larger impact of abuse on a certain gender, whether the trauma route to psychosis is more frequent in females due to higher prevalence of abuse, or whether there is a differential impact of abuse across gender (e.g. different presentation in terms of symptoms, functioning and course of illness). It would also be important to assess additive interactions between childhood and adulthood adversity, across gender, given the research on the cumulative impact of adversity and childhood adverse experiences predicting re-victimisation (Shevlin et al., 2012; Shevlin et al., 2008; Casey & Nurius, 2005; Coid et al., 2001; Cloitre et al., 1996).

Given these limitations, feasibility issues and the necessity of large populations, especially in terms of detecting interaction or mediation effects, it suggests that the exploration of these associations could be conducted with general population samples on PLE. Thus, permitting large enough sample sizes to assess complex interactions along the continuum of psychosis. This also mirrors the focus in assessing early differences and mechanisms in psychosis, to promote wellbeing and recovery by providing successful treatment strategies within early intervention services (EIS). For example, new developments have indicated more effective strategies for early intervention, which include psychological therapy for the individual and family; and optimal psycho-social and pharmacological treatment (Tempier, Balbuena, Garety & Craig, 2014; Onwumere, Bebbington & Kuipers, 2011; Bird et al., 2010; Petersen et al., 2005; Craig et al., 2004). The need for more assessment of the multifaceted relationship between childhood adversity and

psychosis for males and females may provide early gender-specific interventions to prevent onset or improve prognosis. Furthermore, this review reiterates the importance of enquiring about trauma history in clinical practice, to develop comprehensive formulations which enable individualized treatment plans; as well as an option for effective trauma specific therapy for psychosis (Conus, Berk, & Schäfer, 2009; Read et al., 2005). For instance, if the trauma route to psychosis is more prevalent in females, then intervention may include a trauma-related focus, due to history of adversity, and the associated risk of further adversity (Morgan et al., 2014a; Lataster et al., 2012; Shevlin et al., 2008; Briere & Jordan, 2004; Coid et al., 2001; Schaaf & McCanne, 1998; Harris, 1994). Other interventions, may also include areas such as parenting support for individuals with psychosis who may experience difficulties with attachment relationships and isolation, given the impact from childhood adversity (Gumley et al., 2013; Campbell et al., 2012). This may be important as offspring of parents have been shown to experience increased risk of psychopathology and an early intervention may improve outcomes for both parent and offspring (Uher et al., 2014; Rasic, Hajek, Alda & Uher, 2013; Campbell et al., 2012; David, Styron & Davidson, 2011).

Conclusion

This review of the present literature evidences few gender differences, with females reporting higher levels of abuse across the psychosis continuum. Renewed attention on assessing possible gender differences in psychosis has highlighted differences from sub-clinical to clinical psychosis, across a variety of symptomology and functioning domains. Detecting putative risk factors, how they interact and possible underlying mechanisms are essential for the development of new intervention and prevention treatments. The establishment of EIS initiatives has fostered developments and knowledge regarding useful treatment for psychosis and

much recent literature on gender differences has been within FEP populations. This focus on understanding early difference aims to provide optimal interventions and improve illness prognosis and quality of life. Overall, this current review indicated that within clinical samples, females experience more adversity than males, but from the limited available evidence, firm conclusions cannot be drawn about gender differences in the relationship between interpersonal childhood adversity and the onset of psychosis PLE. Therefore this current literature review indicates a need for further empirical research on this association, towards furthering etiological understanding to improve prevention and intervention treatment strategies.

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Part 2: Empirical Paper

Current Urban Environment and Psychological Pathways to Psychosis

Abstract

Background: Urban environment is a risk factor for psychosis, with literature assessing various conceptualisations of urbanicity, from deprivation to social capital. Cognitive models (Garety et al., 2007), propose the importance of affective and cognitive processes in the development and maintenance of psychosis; however research investigating the potential psychological pathways from urbanicity to psychosis are limited. The current study aims to assess the interplay between urban neighbourhood and psychological processes, on risk of psychosis.

Method: This case-control study (134 first episode psychosis cases and 258 population controls), used the social environment assessment tool to elicit participant's perceptions of their current neighbourhoods safety and social capital. The assessment of psychological variables included, anxiety, schematic beliefs and a jumping to conclusions bias (JTC). The interplay between the variables was assessed using logistic regression and multiple mediation and moderation analyses.

Results: Anxiety, schematic beliefs and JTC were associated with increased risk for psychosis; and area safety and social capital was associated with a 1.71 increase in odds for psychosis, although this relationship appeared present for individuals within an intermediate social class. Positive other beliefs partially mediated the association between neighbourhood safety and social capital and psychosis, by reducing risk. Lastly an exploratory three-way interaction indicated the possible importance of a JTC bias in increasing odds for psychosis, in the context of low anxiety, within an environment with low safety and social capital.

Conclusion: Similarly to wider literature, the importance of affective and cognitive processes in psychosis is reiterated. This study highlights the complex relationship between psychosis and urban neighbourhood safety and social capital, which is likely to interact with other individual variables in increasing risk. The clinical implications of the protective benefit of positive other beliefs is discussed, in relation to bolstering social support and the field of Community Psychology.

Introduction

The impact of social and environmental factors is evident in the development and maintenance of psychotic disorders (McGrath, 2004, 2007), from unexplained variance in genetic twin studies indicating an environmental component (Uher, 2014; Cardno et al., 1999) to literature on environmental adversities at the level of structural factors (e.g. characteristics of the wider environment, position in social hierarchies) and social factors (e.g. interpersonal and individual level experiences). Some structural factors associated with a higher risk of psychosis include more social disadvantage, isolation and areas with higher crime and victimisation (Bhavsar, Boydell, Murray & Power, 2014; Morgan et al., 2008; Reininghaus et al., 2008; Lögdberg, Nilsson, Levander & Levander, 2004). In relation to social factors, poor social networks and loneliness are risk factors evident prior to onset of psychosis (Sundermann, Onwumere, Kane, Morgan & Kuipers, 2014; Gayer-Anderson & Morgan, 2013); and adverse adult life events and childhood trauma has also been associated with an increased risk (Howes & Murray, 2014; Varese et al., 2012; Hultman, Wieselgren & Ohman, 1997; Bebbington et al., 1993). Accumulating literature indicates a clear association between childhood adversity and development of adulthood psychosis/psychotic like experiences (Fisher, 2013; Varese et al., 2012), and an indirect effect on symptoms via psychological mechanisms has been shown (cognitive and affective pathways; Fisher, 2013; Fisher et al., 2013; Fisher, Appiah-Kusi & Grant, 2012). The psychological pathways between some specific adult adversities and onset of psychosis have been less well researched and more based on theoretical conceptualisations. One such expanding area is urbanicity.

Urbanicity and psychosis

Area of residence can effect mental health across the lifespan (Ludwig et al., 2012) and living in an urban environment has been associated with higher rates of

psychosis in a number of countries (Heinz, Deserno & Reininghaus, 2013; Kelly et al., 2010; Sundquist, Frank & Sundquist, 2004). This relationship with urbanicity has been found along the continuum of psychosis, including increased risk for sub-clinical psychosis (van Os, Hanssen, Bijl & Vollebergh, 2001) and transition in ultra-high risk individuals (Dragt et al., 2011). The evidence of temporal effects of urbanicity on risk of psychosis (e.g. exposure to urban environment at birth and during upbringing) and a dose-response relationship (Heinz et al., 2013; Harrison et al., 2003; Pedersen & Mortensen; 2001a, 2001b; Marcelis, Navarro-Mateu, Murray, Selten & van Os, 1998); suggest that this effect cannot be fully explained by social drift (movement to urban areas consequent to the prodrome or onset of a disorder). Comparison of urban and rural areas, indicate that urbanicity is associated with approximately a 1.5-to-4 fold increase in the rates of psychosis (Kirkbride, Jones, Ullrich & Coid, 2014; Heinz et al., 2013; Vassos, Pedersen, Murray, Collier & Lewis, 2012; Kelly et al., 2010; March et al., 2008; McGrath et al., 2004;). Furthermore, the incidence varies substantially across urban neighbourhoods, with the size of this effect estimating that 'neighbourhood' may account for between 2-12% of the variation in incidence rates of psychosis (van Os, Kenis & Rutten, 2010; Zammit et al., 2010; Kirkbride et al., 2007a, 2007b; van Os, Driessen, Gunther & Delespaul, 2000).

Conceptualisation and assessment of urbanicity

Assessment of urbanicity and the proposed explanatory factors, includes a variety of conceptualisations and measures across the literature. There are numerous environmental factors associated with urban living that have been suggested to explain the variation, which include factors at an individual level (environmental exposures of individuals in urban areas) and an area level (exposure to area characteristics). This includes a range of social adversity factors across the lifespan at the individual level. For example, a recent review indicated childhood adversity

factors such as parental unemployment, poor parental education, single-parent households, poor housing and socio-economic status; and adulthood disadvantage factors included single marital status, poor education and low socio-economic status (Heinz et al., 2013). At the area-characteristic level a range of variables are assessed to indicate urbanicity. Area factors shown to have an association with psychosis, include population density/size, area deprivation, area crime rates, income inequality, ethnic density and voter turnout as a proxy for social capital (Bhavsar et al., 2014; Kirkbride et al., 2014; Lofors & Sundquist, 2007; Kirkbride et al., 2007b; Allardyce & Boydell, 2006). However, the complexity of the conceptualisation of risk within urban social environments is further indicated by the interactions between area- and individual level factors. Increased risk of psychosis and psychotic like experiences, has been found where individuals with a certain characteristic represent a smaller proportion of the area population; such as migrant or ethnic minority populations and single individuals (Das-Munshi et al., 2012; Schofield, Ashworth & Jones, 2011; Kirkbride et al., 2007b; Allardyce & Boydell, 2006; Boydell et al., 2001; van Os et al., 2000). Additionally, the effect of discrimination was also buffered by ethnic density of the area (Becares, Nazroo & Stafford, 2009) and perceptions of disadvantage mediated the relationship between ethnicity and psychosis (Cooper et al., 2008). Therefore these more subtle interactions and the range of concepts and assessments linked with urbanicity, suggest a need for research on possible putative constructs within the environment and potential mechanisms, to further understand the complex impact of social context on psychosis.

Urbanicity and psychosis: theoretical accounts

A number of overlapping explanatory theories have been used to explain the higher risk and incidence of psychosis across geographical location, described briefly below:

1. Social fragmentation, (operationalised using multiple variables such as single-households, population turnover, rented households, marital status), which suggests that higher fragmentation is associated with more conflict and less social cohesion, integration, communication and supportive networks (Zammit et al., 2010; Allardyce et al., 2005).
2. Social integration, which associates risk with more isolation and exclusion (e.g. ethnic density literature; Bosqui, Hoy & Shannon, 2014).
3. Social defeat, which links risk to feelings of reduced value and being an outsider, which may be triggered by a stressful urban environment (van Nierop et al., 2014; Stowkowy & Addington, 2012; Selten & Cantor-Graae, 2005).
4. Social deprivation, which associates factors related to area deprivation and social adversity to increased odds for mental health difficulties. For example, socio-economic deprivation, population density, victimization and crime (Purcell, Harrigan, Glozier, Amminger & Yung, 2015; Bhavsar et al., 2014; Lorenc et al., 2012; Kirkbride et al., 2007a, 2007b; Lögdberg et al., 2004).
5. Social Capital, which hypothesizes that less community aid and cohesion is linked with increased risk (Kirkbride et al., 2007b, 2008; Lofors & Sundquist, 2007; Allardyce & Boydell, 2006; Krabbendam & van Os, 2005).

All these theories overlap in suggesting that the risk associated with urban environment, relates to complex links around safety and less stable community ties, which may make people more vulnerable to isolation, discrimination and exclusion (Allardyce & Boydell, 2006; Krabbendam & van Os, 2005). Potentially these influential explanatory factors are intertwined. For example, social capital

encompasses features in the environment, such as interpersonal trust, community networks and density, reciprocity and mutual aid, civic engagement and a sense of belonging (Putnam, 1993). Social capital is thought to buffer social stress via the provision of a sense of cohesion, safety and protective resources, thereby reducing risk for psychosis in vulnerable individuals (Kirkbride et al., 2007b; 2008; Boydell, McKenzie, van Os & Murray, 2002; Putnam, 2001). However it also has potential to exert a negative impact, where cohesion may be a risk or protective factor depending on whether someone belongs to the social group or not (Whitley & McKenzie, 2005). It is possible that social capital depends on other explanatory variables, such as less social fragmentation, which would provide more neighbourhood stability to enable more social cohesion and trust (McCulloch, 2003). Alternatively it can interact with other proposed concepts, such as neighbourhood deprivation (Wickham, Shryane, Lyons, Dickens & Bentall, 2014a) because experience of victimisation, areas with higher disorder/crime and fear of crime are associated with psychosis (Fisher et al., 2015; Bhavsar et al., 2014; Lögdberg et al., 2004); and literature indicates that more neighbourhood cohesion is associated with less area violence (Sampson, Raudenbush & Earls 1997). The overlapping explanatory accounts of urbanicity appear to encompass over-arching factors including deprivation (e.g. crime, inequality) and a sense of community cohesion and connection. Measures assessing the combination of these factors will aid the understanding of these constructs and the effect of urbanicity.

Potential psychological pathways

Although there is evident association between psychosis and urbanicity, clearly not all people who experience urban living, develop psychosis. Therefore other social, psychological and biological factors must also be of influence, which is proposed in both recent aetiological models (Howes & Murray, 2014; Morgan, Charalambides, Hutchinson & Murray, 2010; van Os et al., 2010) and cognitive models of psychosis

(Garety, Bebbington, Fowler, Freeman & Kuipers, 2007; Freeman, Garety, Kuipers, Fowler & Bebbington, 2002; Garety, Kuipers, Fowler, Freeman & Bebbington, 2001). Plausibly, urban adversity could interact with proposed psychological mechanisms underlying symptoms of psychosis, whereby in vulnerable individuals (biopsychosocial vulnerability), stress activates cognitive and emotional changes leading to an anomalous experience (e.g. hallucination; Garety et al., 2001, 2007). Following this, various biased cognitive processes, affective disturbances, social factors (e.g. adversity, isolation) and existing core beliefs (about self and other) influence the appraisal of this experience (Garety & Freeman; 2013). It is these biased appraisals, rather than just the anomalous experience, that are important in the development of psychotic symptoms and the accompanying distress and disability (Garety et al., 2001; 2007). These similar processes then also contribute to symptom and distress maintenance. Other internal appraisals possibly associated with some exposures in urban living have also mediated the association between childhood relative deprivation and paranoia (mediators: perceptions of a low social rank and an unjust world towards the self; Wickham, Taylor, Shevlin & Bentall, 2014b). However research on possible putative interactions between urbanicity and individual psychological mechanisms is within its infancy (Morgan et al., 2014; Kelly et al., 2010; van Os et al., 2010).

Psychological Factors and Psychosis

Affective disturbance, a jumping to conclusions bias (JTC) and core beliefs are all influential factors evidenced in transition to psychosis, persistence and severity of symptoms (Falcone et al., 2015; Dudley et al., 2013; Fisher et al., 2013; Fisher et al., 2012; Garety et al., 2007; Gracie et al., 2007; Peters & Garety, 2006; Freeman & Garety, 2003).

Schematic beliefs: Core beliefs about self and other have been associated with psychosis and psychotic symptoms in clinical and non-clinical populations (Thomas, Farhall & Shawyer, 2015; Freeman & Garety, 2014; Fowler et al., 2011; Steel, Marzillier, Fearon & Ruddle, 2009; Gracie et al., 2007; Fowler et al., 2006; Smith et al., 2006; Freeman & Garety, 2003; Chadwick & Trower, 1997). In particular, negative schemas about self (e.g. bad, worthless and vulnerable) and other (e.g. other people are punitive and dangerous), are said to be implicated in the core themes of mistrust, threat and suspiciousness involved in paranoid and delusional cognitions (Freeman et al., 2002), as well as also influencing appraisals of anomalous experiences and increasing negative affect, theoretically increasing risk of psychosis (Oliver, O'Connor, Jose, McLachlan & Peters, 2012; Garety et al., 2001, 2007; Freeman et al., 2002). There is less of a picture on the potential impacts of positive beliefs, with some studies indicating no difference or some potential influence of positive self and other beliefs in chronic psychosis, but less is known about these beliefs in early psychosis or at-risk populations (Thomas et al., 2015; Fowler et al., 2006).

Affect: Negative affect is linked with an increased risk for psychosis (Krabbendam et al., 2005; Owens, Miller, Lawrie & Johnstone, 2005; Jones, Rodgers, Murray & Marmot, 1994) and anxiety is seen to have a fundamental role in positive psychotic symptoms (especially paranoid fears and delusions; Freeman et al., 2007; Garety et al., 2007). Anxiety is thought to be associated to symptomology as it prompts threat content and distress via increased use of safety behaviours and affective psychological processes (e.g. threat anticipation, negative interpretation bias and worry; Freeman, 2007; Garety et al., 2001; Garety & Freeman, 1999). Additionally the anxious and depressive worries about one's own vulnerability is said to extend into persecutory beliefs (Freeman et al., 2002).

Cognitive bias: The JTC bias is associated with positive symptoms (most notably delusions) in first episode and longstanding psychosis (Garety & Freeman, 2013; Freeman, Pugh & Garety, 2008; Fine, Gardner, Craigie & Gold, 2007; Freeman, 2007; Garety et al., 2005). Besides a proposed involvement in symptom maintenance, given the relationship with delusion severity (Falcone et al., 2015; Freeman & Garety, 2014; Peters & Garety, 2006), the presence of JTC is also exhibited in an attenuated form in people recovered from delusions and in those at risk and with delusion proneness in the general population (Freeman et al., 2008; Broome et al., 2007; Colbert & Peters, 2002). This suggests that the data gathering bias might represent a vulnerability to psychosis (Falcone et al., 2015; Garety & Freeman, 2013; Freeman et al., 2008; Fine et al., 2007; Freeman, 2007).

Mechanisms of influence: work in progress

Potentially the urban environment can act as a stressor, interacting with the cognitive and affective processes implicated in psychosis. This is implied by research using experience sampling methods that show individuals vulnerable to psychosis have heightened reactions to daily stress, with increases in low-level psychotic symptoms and affect (Myin-Germeys & van Os, 2007; Myin-Germeys, Delespaul & van Os, 2005; Myin-Germeys, van Os, Schwartz, Stone & Delespaul, 2001). Additionally core beliefs and anxiety have been shown to mediate the association between adverse exposures (e.g. childhood trauma, loneliness, assault and lifetime stressors) and the development of psychotic symptoms (Sundermann et al., 2014; Fisher et al., 2013, Freeman et al., 2013; Fisher et al., 2012; Freeman & Fowler, 2009; Gracie et al., 2007). Specifically related to urban environment, the immediate effect of exposure to a deprived city street increased anxiety and JTC in individuals with delusions (Ellett, Freeman & Garety, 2008). Similarly this type of exposure, led to increases in paranoia, voices, anxiety, negative self and other beliefs and a decrease in positive self-beliefs (Freeman et al., 2015). It was

suggested that affective states and negative other beliefs, partially mediated the effect of environment on increased paranoia (Freeman et al., 2015). Additionally, more stress and low trust was shown to mediate the association between neighbourhood deprivation and paranoia (Wickham et al., 2014a), which suggests the influence of trust and beliefs about others. This connects with other research on social support, which indicates an influence of poor networks and perception of support on psychosis (Gayer-Anderson & Morgan, 2013). Individuals with perception of better support from others experienced less psychotic symptoms than those who perceived their social support more negatively (Sundermann et al., 2014). It is proposed that support is important in recovery for psychosis, as it can influence the affective and cognitive processes implicated in psychosis (Sundermann, Onwemere, Bebbington & Kuipers, 2013). Therefore, this suggests a potential role for both negative beliefs about the self, others and the world, in increasing risk, and positive beliefs about the self and others, reducing risk (although literature on positive schema is more limited). Overall this literature suggests that there are potential pathways from urban adversity to risk of psychosis, via key psychological processes (cognitive and affective) in psychosis.

There is also probable interplay between cognitive and affective processes. For example experimentally increasing anxiety led to an increase in paranoia and JTC, with this increased JTC mediating the association between anxiety and paranoia (Lincoln, Lange, Buro, Exner & Moritz, 2010). The JTC bias was also shown to be stronger with emotionally salient material (Dudley, John, Young, & Over, 1997; Young & Bentall, 1997); and anxiety related fears might escalate with negative beliefs and reasoning biases, which then increase the susceptibility to psychotic symptoms (Freeman et al., 2013; Lincoln et al., 2010; Garety et al., 2001, 2007). This is suggestive of one possible interacting relationship, between anxiety and a JTC bias, which potentially could be heightened with the context of urban adversity.

Literature is moving towards assessing the complexity of causal paths, using mediation, interaction (synergy) and mediated synergy (Morgan et al., 2014). However urbanicity literature is within the early stages, so before research assesses complex pathways, such as mediated synergy, it should identify possible mediation and interaction (moderation) pathways separately. Importantly, literature is needed to investigate whether the urban environment interacts with or is mediated by key psychological processes in psychosis. Previous literature has identified that processes implicated in the cognitive model, have been both mediators and moderators in a relationship with psychosis (e.g. affect, reasoning biases, adversity, schematic beliefs; Freeman et al., 2015; Morgan et al., 2014; Fisher et al., 2012). Therefore questions arise as to whether urban environment has a differential influence on risk with certain groups/characteristics – ‘moderation’; and secondly, whether this urban setting leads to other processes which then increases risk – ‘mediation’ (e.g. via mediating and/or moderating factors such as stress, anxiety, negative beliefs, minority status, impact on biological systems; Freeman et al., 2015; Wickham et al., 2014b; Fisher et al., 2012; Ellet et al., 2008; Kirkbride et al., 2007b; Myin-Germeys & van Os, 2007). There are also possible additive interactional relationships that can be investigated, suggested by some research on psychological processes implicated in psychosis, such as research on a JTC bias being amplified by anxiety (although this relationship is inconsistent).

The current study

Researching beyond individual factors to assess putative interactions and underlying mechanisms, is important, as it is indicative of more complex causal pathways evident in mental health difficulties. Literature on pathways between urbanicity and risk of psychosis is within its infancy, so it is not clear whether an adverse environment also exerts an effect on psychosis via other mediating variables; and/or whether the impact of the urban adversity, further increases risk, in

context of the presence/absence of certain moderators. Assessing these complex interactions advances aetiological understanding, which also facilitates the development of potentially targeted interventions for psychosis. Therefore this thesis plans to assess cognitive models of psychosis, by investigating some psychological pathways between current urban environment and psychosis. It will separately assess the association between urbanicity, psychological variables and psychosis (main effects). Then in separate analyses, it will examine whether psychological variables (a JTC bias, schematic beliefs and anxiety) mediate and/or moderate the relationship between urban environment and psychosis. An additional exploratory three way interaction, potentially suggested in early experimental studies on anxiety and a JTC bias, will also be assessed.

The research aims are as follows:

Main effects:

1. To assess whether the odds of psychosis will be greater in those who experience: a) greater urban adversity b) higher levels of anxiety, c) greater negative schematic beliefs and d) a presence of a JTC bias.
2. To assess whether the odds of psychosis will be lower in those with higher levels of positive schematic beliefs.

Mediation:

3. To separately assess whether the association between psychosis and urban environment is mediated by each psychological variable (affect, reasoning bias and schematic beliefs).

Moderation:

4. To separately assess whether urban environment interacts with affect, a reasoning bias or negative schematic beliefs, to increase the odds of psychosis; or interacts with positive schematic beliefs to reduce odds of psychosis.

Additional exploratory three-way interaction:

5. To conduct an exploratory three-way interaction, to assess whether a presence of the JTC bias additively interacts with anxiety and urban adversity to further increase the odds of psychosis.

Method

Design

This study uses data from a larger research project on first episode psychosis (FEP): 'Childhood Adversity and Psychosis study, (CAPsy; funded by the Wellcome trust). The CAPsy study aimed to explore associations between FEP and child adversity, adult adversities and other psychological, social and biological processes. This was an incidence and case-control study, which recruited 303 cases and 301 controls, over a four-year period (2010-2014). The ethical approval for the study was granted by the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) and South London and Maudsley NHS Foundation Trust (SLaM) Research Ethics Committee (Ref: 321/05, including amendments 1 to 9).

Participants

Participants were recruited from two boroughs in South-East London (Lambeth and Southwark). This current study is constituted of a subset of participants from the wider CAPsy Study who completed the measure on safety and social capital in the current urban environment, a total of 392 participants (134 cases and 258 controls). There was a reduction in the number of participants completing the measure of current environment, as it was not a high priority within a total of 26 assessments of varying lengths (with priority assessments also including possible distressing interviews on life events and child abuse). This meant that the measure was more likely to be completed in later appointments, which increased rate of drop out or

non-completion, as follow-up appointments were first focused on ensuring priority assessments were completed.

Cases

The case sample consisted of a cohort of individuals who presented with psychotic symptoms for the first time, to adult inpatient and outpatient mental health services within the catchment area. The mental health services were part of SLaM. The study implemented a comprehensive screening method to detect eligible cases, involving a weekly screen across secondary and tertiary services (general adult inpatient, specialist inpatient services and specialist community mental health teams). This screening process involved checking all points of contact with services, the review of clinical notes and regular liaison with staff. Clinical notes were screened for any report of psychotic symptoms for potential cases (e.g. positive or negative psychotic symptoms via the Screening Schedule for Psychosis, Jablensky et al., 1992) and any queries were followed up via clinical notes and staff liaison to ascertain whether inclusion criteria was met (see below for criteria). This strategy aimed to increase recruitment rates, reduce selection bias and provide a representative FEP sample presenting to SLaM services within the study catchment area. Figure 1 illustrates the process of recruitment for the case sample. After agreement with eligible cases' clinical teams, a researcher would approach them to describe the details of the study, answer questions and provide the information and consent forms (Appendix 2). Following this, written informed consent was sought.

The inclusion criteria were:

- Aged 18 to 64
- Resident within the specified catchment area (Lambeth or Southwark).

Residency was defined as: a) at least a one night stay at a residential

address within the catchment areas or b) detained in Brixton prison, irrespective of address pre-sentencing.

- Presence of an untreated first episode of psychosis, even if long-standing (ICD-10: F20-29; F30-33) during the study period (1st January 2010 - 1st January 2014). This did not mean that cases had to be untreated at the point of recruitment only that treatment (as defined below) did not begin prior to the study commencing.
- Sufficiently fluent in English to ensure informed consent and understanding of assessment measures.

The exclusion criteria were:

- Aged under 18 or over 64.
- Not resident within the catchment area of the study.
- Treatment for an episode of psychosis outside of the study period.

Treatment was defined as: a) contact with mental health services for an episode of psychosis (i.e. accepted as a referral by mental health services; disclosed to services symptoms we deemed to be psychotic, even if the mental health team did not); b) Prescription of anti-psychotic medication for one month or more (including prescribing by a GP, prison doctor, or private psychiatrist even in the absence of contact with or pending referral/transfer to secondary mental health services).

- Evidence of psychotic symptoms precipitated by an organic cause.
- Transient psychotic symptoms resulting from acute intoxication, as defined by ICD-10.
- Severe learning disabilities (defined by an IQ of less than 50 or a diagnosis of mental retardation)
- Not sufficiently fluent in English to understand consent process and complete assessments.

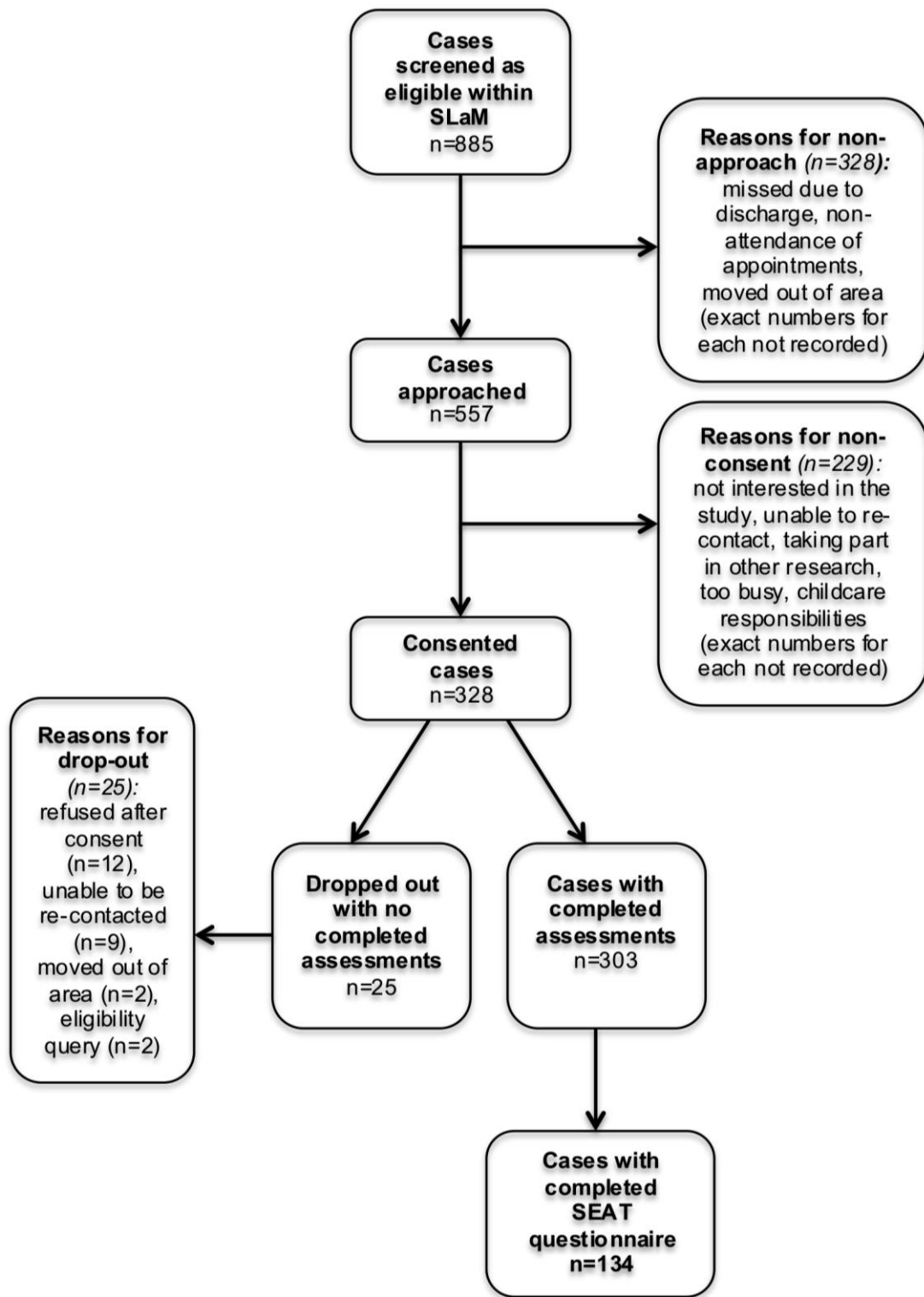


Figure 1. Flow chart for the process of case recruitment

Note. Reduction in the number of final cases because of drop-out or non-completion of SEAT measure due to lower priority in a battery of 26 assessments. Exact numbers for reasons not available.

Controls

A general population control sample was drawn from the study catchment areas. Quota sampling, based on the 2011 census data, was implemented to provide a sample representative of the local population in regards to age (18-65), ethnicity and gender. With these quotas the control sample was then recruited via two methods:

1) GP surgeries.

Twelve GP surgeries recruited via the Primary Care Research Network, helped with control recruitment. Practice managers searched their GP lists to identify individuals who met the inclusion criteria, and they were subsequently sent study invitation letters and an information pack (a follow-up letter was sent after no response within 2-weeks).

2) An ongoing community study- the Biomedical Research Centre (BRC) South East London Community Health Survey (SELCoH).

SELCoH was an epidemiological cohort study of randomly selected households assessing the health needs of this community (Hatch et al., 2011). For recruitment they used the Royal Mail Small Users Postal Address File (PAF; Jenkins & Meltzer, 1995) to randomly sample addresses within the catchment areas. Participants within the SELCoH study who met our inclusion criteria were contacted and invited to participate.

There was identical inclusion and exclusion criteria for cases and controls, except that cases had psychosis. Additional exclusion criteria for potential controls were if they had a history of or current psychosis. All eligible controls in each household were invited to take part, and a modified Kish grid was used to randomly select one member of the household when more than one occupant offered to participate.

Written informed consent was sought after full explanation of the study and having read the information sheets (as described above). Those who consented to participate were screened with the Psychosis Screening Questionnaire (Bebbington & Nayani, 1995; Appendix 3), and individuals who met criteria for a psychotic disorder or reported any history of treatment for psychosis were excluded.

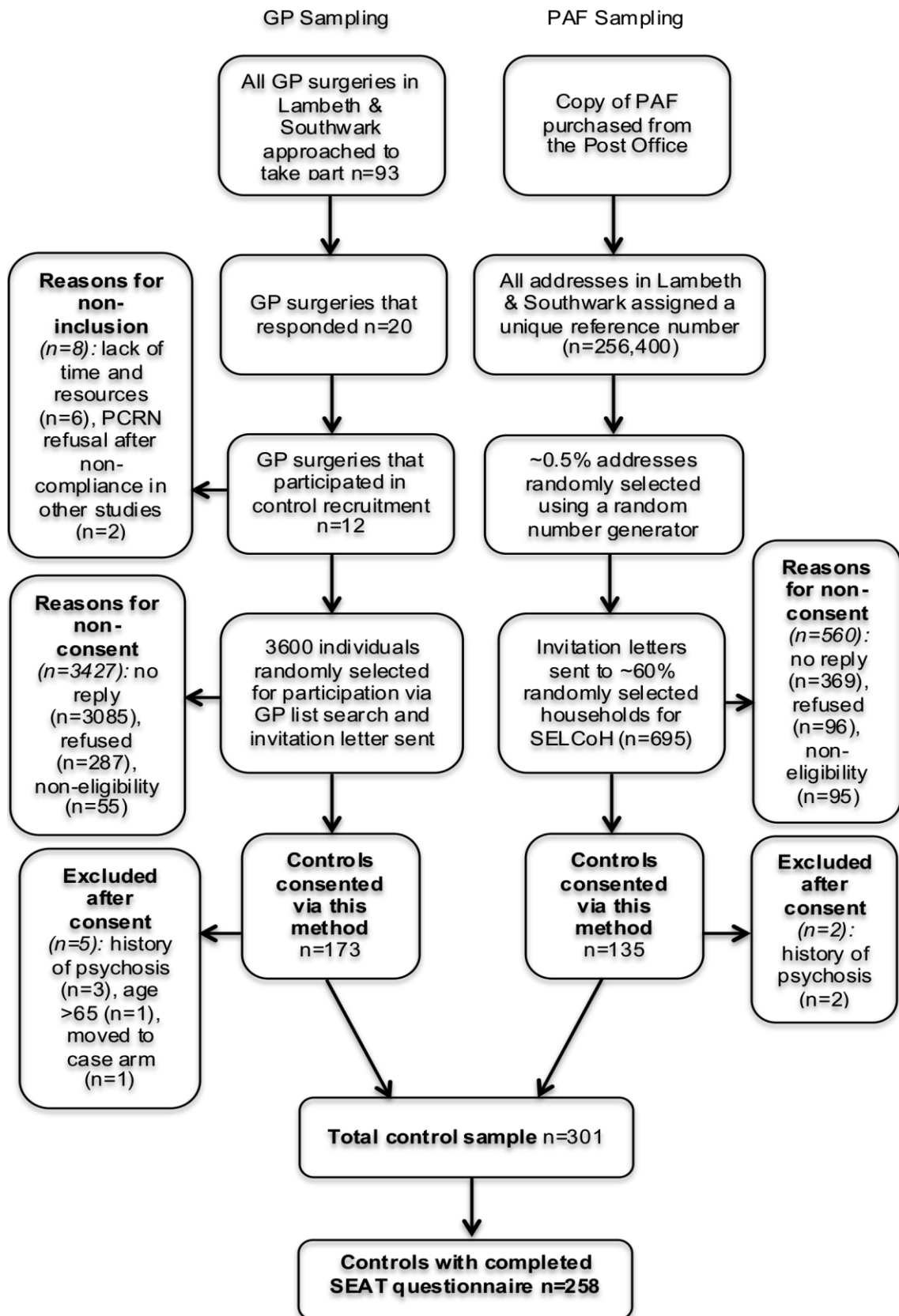


Figure 2. Flow chart for the process of control recruitment

GP, General Practice; PAF, Postal Address File; PCRN, Primary Care Research Network; SELCoH, South East London Community Health Survey.

Note. Reduction in the number of final controls because of drop-out or non-completion of SEAT measure due to lower priority in a battery of 26 assessments. Exact numbers for reasons not available.

Data collection

Consented participants completed an average of 5 hours of assessments and interviews, over an average of three appointments. For cases, the median length of time from first contact with services to first appointment for the study was 92 days (inter-quartile range: 40-252 days); interviews/assessments were not conducted with individuals who were floridly psychotic (study only conducted when individuals were well enough) so this could account for the wide time frame described. The appointments were held at the participant's home or an interview room in either the IoPPN, on the psychiatric ward or the community team location. Participants were compensated up to £30 for partaking in the study. The CAPsy study included a large assessment battery (diagnostic instruments, neuropsychological testing, biological measurements and psychological and social interviews/questionnaires), but only the measures used for the current thesis are described below. The relevant measures outlined were completed by cases and controls.

Assessment measures

Socio-demographics

- *Medical Research Council Socio-demographic Schedule (Mallett, 1997).*

An amended version of the MRC Socio-demographic Schedule was used to collate various socio-demographic characteristics of participants. The demographics used in the current thesis were age (calculated from participants' date of birth), gender, ethnicity, education level, employment status and their main social class. The following describes the scoring, for analysis of these variables.

Ethnicity: Participants described their ethnicity according to the 18 categories employed by the 2011 UK Office of National Statistics census (clinical notes/ and/or medical staff were referred to, if the question was not completed). For analysis the

18 categories were recoded into six main ethnic groups: White British; White Other (grouping the smallest categories of White Irish, White Gypsy and White Other); Black Caribbean; Black African; Asian (grouping categories of Indian, Pakistani, Bangladeshi, Chinese and Other Asian) and Other (grouping categories of Mixed groups, Black Other and Other).

Education: Participants were asked about their highest level of education. For analysis the six categories were collapsed into three categories: School – left with no qualifications or with qualifications (grouping categories of compulsory education: ‘school no qualifications’ and ‘school with qualifications’); Further Education (grouping categories of ‘tertiary/further first level of non-compulsory education’ and ‘vocational - job related education’) and Higher Education (grouping categories of ‘higher undergraduate education’ and ‘higher postgraduate education’).

Employment: Participants were asked about current employment status. For analysis the six categories were recoded into three categories: Employed (grouping categories of ‘part-time employee, full-time employee and self-employed’); Unemployed; Student and Economically Inactive (e.g. house person, carer, retired, physical illness/disability).

Social Class: For this study participants main social class was assessed by the main job held across their lifespan, using the European Socio-Economic Classification system (ESeC). The ESeC contains ten options to classify social class and for analysis they were collapsed into six categories:

- ‘Salarial’ (grouping categories: ‘1- Large employers, higher grade professional, administrative and managerial occupations; and 2 - Lower

grade professional, administrative and managerial occupations and higher grade technician and supervisory occupations’).

- ‘Intermediate’ (grouping categories: ‘3 - Intermediate occupations; 4 - Small employer and self-employed occupations, excluding agriculture; 5- Self-employed occupations and 6- Lower supervisory and lower technician occupation’).
- ‘Working Class’ (grouping categories: ‘7- Lower services, sales and clerical occupations; 8- Lower technical occupations and 9- Routine occupations’).
- ‘Never Worked/Long-Term Unemployed’ (category ‘10 - Never worked and long-term unemployed for six months or more’).
- Then additional codes were used for ‘Student’ (full time students) and ‘Non-classifiable’ (which included the economically inactive, such as carers, housewives, retirees, and any unknown occupations that did not fall into the ESeC categories). For this current study, there were no full time students within the sample, so this category was omitted from the analysis.

Current urban environment

- *Social Assessment and Environment Tool (SEAT; see Appendix 4).*

The SEAT is a multiple item questionnaire administered by the researcher, focusing on the current neighbourhood an individual lives in. The SEAT questionnaire was developed as part of the CAPsy study and a paper on the scoring and validation of the measure is in preparation (Kirkbride, in prep). It aims to assess reports of neighbourhood safety and social capital. In particular, crime and disorder, impact of crime and disorder, community action and intervention, neighbourhood identity, networks and co-operation, and the individual’s engagement in the neighbourhood. For every category, there are various statements and the individual must provide a rating on a 5-point likert scale for each. For example:

- 1. Crime and Disorder (4 items)
 - 'Please rate how common the following events or problems are in your neighbourhood': e.g. People attempting to break into houses or cars.
- 2. Impact of Crime and Disorder (4 items)
 - 'Please rate how much the following events or issues concern you in general (even if not common in your neighbourhood)': e.g. People attempting to break into houses or cars.
- 3. Community Action and intervention (4 items)
 - 'Please rate how likely people are to take action in your neighbourhood if they observed': e.g. People attempting to break into houses or cars.
- 4. Neighbourhood identity, networks and co-operation (6 items)
 - 'Please rate how much you agree with the following statements about your neighbourhood': e.g. People share similar values and beliefs.
- 5. An individual's engagement in the neighborhood (4 items)
 - 'Please rate how much you agree with the following statements about your neighborhood': e.g. I feel part of this neighborhood.

The scoring consists of the sum total for each category (including reverse coding for category 2 and 3). This procedure culminates into four sub-domains: Civic Disorder (category 1 above), Impact of Civic Disorder (category 2 above), Informal Social Control (category 3 above) and Social Cohesion and Trust (category 4 and 5 above). These subdomains then combine into an overall score of neighbourhood Safety and Social Capital (via z-standardizing the subdomain totals and then calculating a weighted sum of these z-scores). For a detailed description of the scoring procedure, see Appendix 5. For the SEAT, a higher score indicates a higher level of neighbourhood safety and social capital. The current study uses the overall Safety and Social Capital score for the analysis.

This measure also identifies the participant's current postcode, which enables

comparisons and multi-level analyses between reported characteristics of a neighbourhood with objective area measures, such as national statistics collected by governments. The current study used the postcode data to identify the Index of Multiple Deprivation 2010 scores (see description below).

- *Index of Multiple Deprivation 2010 (IMD; Department for Communities and Local Government, 2011).*

IMD is an objective, relative measure of deprivation for small area-levels across England. The IMD provides a score and a ranking on seven domains of deprivation ('income deprivation; crime deprivation; health deprivation and disability; barriers to housing and services deprivation; education deprivation; employment deprivation; and living environment deprivation') and an overall composite score of multiple deprivation (Department for Communities and Local Government, 2011). The participant postcode (from the SEAT) enabled the identification of their lower super output area (LSOA) level, which are small geographic administrative areas that range between 1000-3000 in population and have a mean population of approximately 1630 people (Office for National Statistics, 2012). These geographic areas (LSOA) link to demographic information, which enable statistical analysis. Therefore this study identified participants IMD score (the overall composite score of multiple deprivation) via their corresponding LSOA. For this measure a higher IMD score indicates more area deprivation.

Psychological variables

- *Brief Core Schema Scales (BCSS; Fowler et al., 2006).*

The BCSS assess participant's schematic beliefs about the self and others. It is a 24 item, 5 point- self-report rating scale (0-4) that identifies four dimensions: negative self (6 items), positive self (6 items), negative other (6 items), and positive

other (6 items). Participants were asked whether they held each belief statement in a No/Yes format, and if they answered positively they rated their degree of belief conviction on a 4-point scale ('1-4' corresponding to believe it slightly, believe it moderately, believe it very much, or believe it totally). If they answered negatively, it was scored as '0'. The sum total of each dimension is calculated, with higher scores indicating greater levels of the belief. The researchers administered the BCSS in a question format. This scale is considered to be a useful measure of schema in psychosis and shown to have good psychometric properties across various constructs (including high internal consistency, stable test-retest reliability and some moderate-strong convergent validity with other measures; Fowler et al., 2006).

- *Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959, 1969).*

The HAM-A assesses the severity of anxiety symptoms (over the past 7 days), via a semi-structured interview conducted by the researchers. It is a 14-item assessment that measures somatic anxiety (physical complaints related to anxiety) and psychic anxiety (mental agitation and psychological distress), including observations of the participant from the interview. Each item is scored on a scale from '0-4' (not present to very severe) and the sum of the items generates an overall total (maximum of 56), with higher scores representing more anxiety. This assessment is considered to have good psychometric properties, with adequate to strong internal consistency (Kobak et al., 1993; Moras, Di Nardo & Barlow, 1992), strong test-retest reliability (Maier, Buller, Philipp & Heuser, 1988) and acceptable to strong inter-rater reliability (Bruss, Gruenberg, Goldstein & Barber, 1994; Moras et al., 1992). A structured interview guide for interviewers to use when conducting HAM-A has also shown adequate reliability and validity (Shear et al., 2001).

- *Beads Task (Garety et al., 2005; Garety, Hemsley & Wessely, 1991)*

The Beads Task is a probabilistic reasoning task measuring the JTC bias (tendency to make decisions with limited information) and was administered by researchers. Participants are shown a jar of coloured beads on a computer screen with either: 60 blue beads and 40 red beads ('the mainly blue jar') or 40 blue beads and 60 red beads ('the mainly red jar'). The jars are then removed and the participant is told that one of the jars has been selected at random by the computer. The participant task, was to ask for as many coloured beads as they would like before deciding which of the two jars the beads had come from. The beads requested are visible on the screen to act as memory aids. The number of beads requested before a decision is made is the main variable, with two beads or less categorised as the JTC bias, creating a dichotomous variable (JTC present and JTC absent). The beads tasks are the most commonly used assessment of JTC (Fine et al., 2007; Freeman 2007; Garety & Freeman, 1999).

Analysis

Analyses were conducted using Stata version 11 (Stata, 2009). Analysis commenced with data cleaning and normality assessment for each continuous variable within the study (by inspecting histograms and assessing skewness and kurtosis). The core sample consisted of participants who completed the SEAT measure (n=392). The sample size in some analyses (e.g. mediation and moderation) reduces due to missing data from the anxiety and schema measures, as Stata only includes participants with full data on the variables included in each analysis.

Power

A power analysis was conducted using Stata to assess the capacity of the sample size to detect an effect using logistic regression (Preacher, Rucker, & Hayes, 2007; Preacher & Hayes, 2004). Two studies suggest an OR=2 for an association found between both child and adult social adversity and risk for psychosis, and psychosis-like experiences (Morgan et al., 2009; Morgan et al., 2008). This is similar to the measure of adversity within this study, as it includes factors that would fall under urban adversity, such as social isolation and area of living. Therefore from a power analysis, with level of alpha of 0.05 and power of 80%, the study would need 87 participants (across groups) to detect an effect size of OR=2. Therefore the sample size should be able to detect an effect at this level. If then controlling for other predictors in the model, and assuming the squared multiple correlation amongst the predictors is $r^2=0.4$, then at 80% power level the study would need 146 participants (across groups).

Furthermore, a calculation was performed using a more conservative odds ratio (OR 1.5), and found that in the simple logistic regression with level of alpha of 0.05 and power of 80%, the study would need 219 participants (across groups) to detect an effect size of OR=1.5. If then controlling for other predictors, with a squared multiple correlation of $r^2=0.4$, the study would require 364 participants (across groups).

Socio-demographics

For the demographic comparisons between the case-control sample, mann-whitney U tests and chi-squared tests were implemented (chi-squared: if cell count of >5 was not reached fisher's exact test was employed).

Composition for main analyses - binary variables

From examining the normality of the variables, most data displayed a non-normal distribution: *non-normal distribution*: anxiety (HAM-A; Hamilton, 1959, 1969), negative self and other beliefs (BCSS; Fowler et al., 2006), continuous JTC score (Beads Task, Garety et al., 1991, 2005); *borderline*: positive self beliefs (BCSS; Fowler et al., 2006); *normal distribution*: SEAT (Kirkbride, in preparation) given the use of a standardised scoring method and positive other beliefs (BCSS; Fowler et al., 2006). Therefore to examine the relationships between current urban environment (SEAT), psychological variables (anxiety, schematic beliefs, JTC) and psychosis, the continuous scores for: SEAT (-8.86-7.08), anxiety (0-56) and schema categories (0-24) were recoded into binary variables. To dichotomise the scores for the new variable the total sample median was calculated and median-splits were used. Table 1 presents the median-split ranges for each binary variable.

Table 1. The range of scores for the median-split variables (SEAT, anxiety and schematic beliefs) and the range for the JTC scoring.

		Range of Scores
SEAT Scores		
	Low	-8.86 – 0.05
	High	0.06 – 7.08
Anxiety Scores		
	Low	0 – 5
	High	6 – 33
JTC Scores		
	Present	0 – 2
	Absent	3 – 20
Negative Self Scores		
	Low	0 – 0
	High	1 – 24
Positive Self Scores		
	Low	0 – 14
	High	15 – 24
Negative Other Scores		
	Low	0 – 3
	High	4 – 24
Positive Other Scores		
	Low	0 – 12
	High	13 – 24

Rationale for creating binary variables using median splits

It is recognised that dichotomising variables may reduce the studies statistical power and that using median-splits on the overall sample may limit comparisons due to varying cut points for cases and controls (DeCoster, Iselin & Gallucci, 2009; MacCallum, Zhang, Preacher & Rucker, 2002). However, using this method reflects other literature in this area, examining affective and cognitive pathways between adverse experiences and odds of psychosis (Fisher et al., 2012); and the scoring system provided for the SEAT identifies categorisation of the scores as a possibility for this measure (Appendix 5). Secondly, the median-split method also seems to be reasonable because dichotomisation is suggested to work better when the variables are skewed, and it can be useful for potential non-linear relationships between variables and outcomes (Farrington & Loeber, 2000). An additional consideration when using dichotomisation, is whether the measures used have high reliability (DeCoster, Gallucci & Iselin, 2011; DeCoster et al., 2009), and this is observed in the current study as the measures assessing anxiety and schemas are said to be stable across time and have good psychometric properties (Fowler et al., 2006; Moberg et al., 2002; Maier et al., 1988). Furthermore grouping variables can be suggested to make research outcomes easier to interpret and understand, thereby improving the communication of findings (Farrington & Loeber, 2000).

SEAT: preliminary validation checks

The developer of the SEAT provided a scoring procedure for the questionnaire, which is in process of publication (see Appendix 5 for scoring system). Given that the validation and scoring paper is in preparation, this study conducted some analyses as a preliminary check of the SEAT. The relationship between the four subdomains were assessed via correlations (using the continuous total scores), to see if they performed in the same way as suggested in the scoring document (i.e.

less civic disorder will be associated with less impact of civic disorder, more informal social control and more social cohesion and trust; Kirkbride, in preparation).

The SEAT was also examined against the IMD via a correlational analysis with the continuous overall SEAT score, to assess the association with an objective area-level measure. The IMD score also produced a binary variable via the median-split procedure described above (low range: 9.2-31.9; high range: 32-54.2) to assess against the binary SEAT variable (using a chi-square analysis).

Main effects

To assess the main effects of urban environment (SEAT), anxiety, JTC and schematic beliefs on odds of psychosis: each variable was explained via their median and interquartile range (IQR; due to the non-normal distributions and median-split variables created) and group comparisons were made using chi-square analyses. To assess the main aims, logistic regressions were conducted to separately investigate the associations between SEAT, the psychological variables (anxiety, schematic beliefs, JTC) and case-control status. These analyses used the binary median-split variables for the SEAT, anxiety symptoms and schematic belief categories and the binary variable for the scoring of the JTC bias. The logistic regression analysis was conducted both unadjusted and adjusted for *a priori* confounders: gender, age, ethnicity and participant's main social class, which is in line with protocol for this study and other papers by the research team with similar populations (e.g. Gayer-Anderson et al., 2015). The confounders did differ between cases and controls and social class was selected over education and current employment, due to potential confounding with intelligence and current FEP status, respectively. Additionally, confounders were kept to a minimum due to potential power reduction related to more parameters included within analyses.

To be comprehensive and for additional information of possible interest the appendix also includes the wilcoxon rank-sum or t-test analyses of the continuous data, investigating group differences between SEAT, anxiety, JTC bias, schematic beliefs and case-control status (Appendix 6).

Psychological pathway analyses

To assess the interplay between social environment and psychological variables on psychoses, the study examined whether urban environment (measured via safety and social capital) was mediated and/or moderated by a) anxiety, b) a JTC bias c) schematic beliefs about self and others.

Mediation

Simple mediation assesses the effect of one independent variable (X) on a dependent variable (Y), via a possible third variable, the mediator (M; see figure 3). In mediation analyses variable X's relationship with Y is divided into its direct effect on Y and its indirect effect on Y via M. Figure 3 illustrates a mediation model, where the *a* path is the effect of X on M, the *b* path is the effect of M on Y and the *c'* path is the direct effect of X on Y. In this model the indirect effect of X on Y via M, is the product of the paths *a* and *b*; and the *c* path is the total effect of X on Y (which is the sum of the indirect and direct effects).

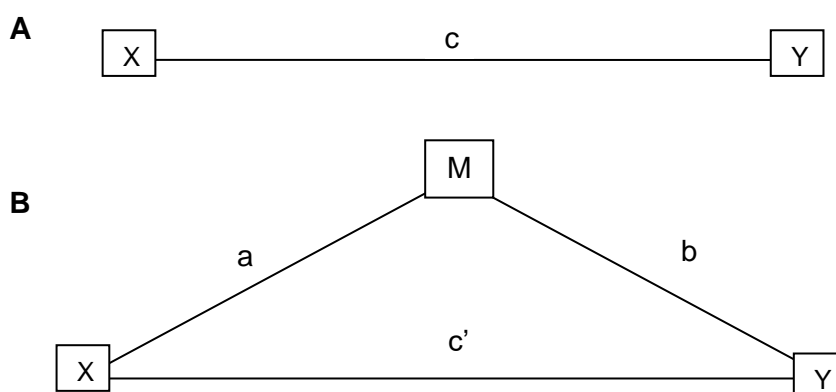


Figure 3. Illustration of a simple mediation model. (A) represents a direct effect. (B) represents a mediation model, where X has an indirect effect on Y via M.

The study used the binary mediation command in Stata (which uses the product of coefficients approach; Kenny, 2008; MacKinnon & Dwyer, 1993) to examine possible mediating effects of each psychological variable (anxiety, schematic beliefs, JTC). In line with Preacher & Hayes (2008), the total effect of SEAT on case-control status was portioned into a direct effect and indirect (mediating) effect through anxiety, JTC bias and beliefs about self and others (in separate analyses). This analysis also implemented the bootstrapping command with 500 bootstrap replications to obtain bias-corrected confidence intervals, which provide more robust estimates of direct, indirect and total effects (Morgan et al., 2014; MacKinnon, 2008; Preacher & Hayes, 2008). Therefore this study reports the standardised coefficient and bias-corrected confidence intervals, where confidence intervals that do not contain zero are significant. This analysis was also conducted both unadjusted and adjusted for *a priori* confounders (gender, age, ethnicity and social class).

Moderation and exploratory three-way interaction

To assess an interaction between SEAT and either of the psychological variables (anxiety, schematic beliefs, JTC) on the odds of psychosis, this study used a likelihood ratio test to compare the models with and without the interaction term. The p-value of this test was examined to assess the presence of an effect modification at the level $p < 0.05$. For significant results, an odds ratio and confidence interval for psychosis given the significant interaction was calculated using the `lincom` command in Stata. The same method described was also used to assess an exploratory analysis of a potential three way interaction between SEAT, JTC bias and anxiety on odds of psychosis. For a significant three-way interaction result the `lincom` command was used to examine the direction of the interaction, by obtaining odds ratios, confidence intervals and p-values for all the potential group combinations in the interaction. These analyses were conducted both unadjusted and adjusted for *a priori* confounders (gender, age, ethnicity and social class).

Results

Participant demographics

A comparison of the current socio-demographic characteristics between cases (n=134) and controls (n=258) indicated the following (see Table 2): compared with controls, cases were younger, were more likely to be of non-White ethnicity (Black Caribbean, Black African and Other ethnicity), and more likely to be male. Additionally compared to controls, cases were more likely to be currently unemployed and more often had a lower level of education (cases 31.5% vs. controls 12.5%), whereas a higher proportion of controls had completed higher education (cases 20.2% vs. controls 56.4%). In terms of main social class over lifetime, cases were more likely to be categorized as working class (cases 42.5% vs. controls 11.6%), whereas controls were more likely to be classified into the professional category (cases 8.2% vs. controls 51.6%).

Table 2. Current socio-demographic characteristics by case-control status

	Controls (n=258)	Cases (n=134)			
	Mean (SD)	Mean (SD)	U	df	p
Age (years)	35.1 (12.4)	28.4 (8.6)	5.40	-	<0.001*
	n (%)	n (%)	χ^2	df	p
Gender					
Female	126 (48.8)	50 (37.3)	4.73	1	0.030*
Male	132 (51.2)	84 (62.7)			
Ethnicity					
White British	120 (46.1)	40 (29.9)	15.7 ^b	5	0.007*
White Other	29 (11.2)	12 (9)			
Black African	40 (15.5)	37 (27.6)			
Black Caribbean	34 (13.2)	24 (17.9)			
Asian	11 (4.3)	4 (3)			
Other	24 (9.3)	17 (12.7)			
Highest Education Level^a					
School	32 (12.5)	42 (31.3)	50.12	2	<0.001*
Further	80 (31.1)	65 (48.5)			
Higher	145 (56.4)	27 (20.2)			
Current Employment^a					
Employed	169 (65.5)	30 (22.6)	89.90	3	<0.001*
Student	34 (13.2)	12 (9)			
Unemployed	34 (13.2)	71 (53.4)			
Economically inactive	21 (8.1)	20 (15)			

Table 2 continued

	Controls (n=258)	Cases (n=134)			
	n (%)	n (%)	χ^2	df	p
Social Class (main)					
Salariat	133 (51.6)	11 (8.2)			
Intermediate	63 (24.4)	41 (30.6)			
Working class	30 (11.6)	57 (42.5)	100.12 ^b	4	<0.001*
Long-term unemployed	1 (0.4)	10 (7.5)			
Not classifiable	31 (12)	15 (11.2)			

Note. U, Mann-Whitney Test; df, Degrees of Freedom. (Percentages may not add up due to rounding)

*Significant at p<0.05

^a Some missing values (education: 1 missing control value; employment: 1 missing case value)

^b Indicates Fishers Exact test, all other values are χ^2

Psychological variables and case-control status

This section addresses study aims 1 and 2, assessing the associations between the psychological variables and psychosis. Please see Table 3 and 4, reporting inter-quartile range and group differences, respectively. Appendix 6, has the supplementary group differences analysis on the continuous data.

Aims:

1. To assess whether the odds of psychosis will be greater in those who experience: higher levels of anxiety, greater negative self beliefs, greater negative other beliefs and a presence of a JTC bias.
2. To assess whether the odds of psychosis will be lower in those with higher levels of positive self and other beliefs.

The main analyses using logistic regression described below, are reported in Table 4.

- Anxiety (HAM-A; Hamilton, 1959, 1969).

There was evidence that higher levels of anxiety (cut at the median) were associated with a 3.13 increase in the odds of psychosis after controlling for *a priori* confounders (age, gender, ethnicity and social class).

- *JTC bias (Beads Task, Garety et al, 1991, 2005).*

A presence of the JTC bias was associated with a 1.89 increase in the odds of psychosis after controlling for *a priori* confounders.

- *Beliefs about self and other (BCSS; Fowler et al., 2006).*

After controlling for *a priori* confounders, an increased level of negative self beliefs (cut at the median) was associated with a 2.72 increase in the odds of psychosis and greater negative other beliefs (cut at the median) was associated with a 2.14 increase in the odds of psychosis. There was no association between positive self beliefs (cut at the median) and case-control status (p=0.801). For positive other-beliefs, there was some evidence that the presence of greater positive other beliefs was associated with lower odds of psychosis (unadj. OR 0.58). However this result did not hold after adjustment for *a priori* confounders (see Table 4).

Table 3. Median scores on psychological variables (anxiety, JTC and schematic beliefs) in cases and controls

	Controls	Cases
	Median (IQR)	Median (IQR)
Anxiety Scores (n= 386)	3 (2-7)	7 (4-12)
JTC Score (n= 392)	4 (1-9)	2 (1-5)
Negative Self Scores (n= 387)	0 (0-1)	2 (0-5)
Positive Self Scores (n= 379)	14 (10-17)	13 (7-17)
Negative Other Scores (n= 387)	2 (0-6)	6 (2-12)
Positive Other Scores (n= 382)	13 (10-16)	11 (7-15)

Note. IQR, Interquartile Range. n varies for anxiety and schema due to missing data.

Table 4. Association between psychological variables (anxiety, JTC and schematic beliefs) and case-control status

	Controls	Cases	x^2	df	p	Unadjusted		Adjusted ^a	
	n (%)	n (%)				OR (95% CI)	p	OR (95% CI)	p
Anxiety (n= 386)									
Low (0-5)	181 (70.2)	51 (39.8)	32.78	1	<0.001*	3.55 (2.28-5.53)	<0.001*	3.13 (1.84-5.32)	<0.001*
High (6-33)	77 (29.8)	77 (60.2)							
JTC (n= 392)									
Absent (3-20)	173 (67.5)	54 (40.3)	25.90	1	<0.001*	3.02 (1.96-4.64)	<0.001*	1.89 (1.11-3.23)	0.020*
Present (0-2)	85 (33)	80 (59.7)							
Negative Self (n= 387)									
Low (0-0)	158 (61.5)	48 (36.9)	20.91	1	<0.001*	2.73 (1.76-4.22)	<0.001*	2.72 (1.20-4.61)	<0.001*
High (1-24)	99 (38.5)	82 (63.1)							
Positive Self (n= 379)									
Low (0-14)	125 (49.2)	63 (50.4)	0.05	1	0.828	0.95 (0.62-1.46)	0.828	1.07 (0.63-1.82)	0.801
High (15-24)	129 (50.8)	62 (49.6)							

Table 4 continued

	Controls	Cases	χ^2	df	<i>p</i>	Unadjusted		Adjusted ^a	
	n (%)	n (%)				OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Negative Other (n= 387)									
Low (0-3)	161 (62.4)	47 (36.4)	23.33	1	<0.001*	2.90 (1.87-4.49)	<0.001*	2.14 (1.25-3.66)	0.005*
High (4-24)	97 (37.6)	82 (63.6)							
Positive Other (n= 382)									
Low (0-12)	122 (47.8)	78 (61.4)	6.26	1	0.012*	0.58 (0.37-0.89)	0.013*	0.74 (0.44-1.25)	0.260
High (13-24)	133 (52.2)	49 (38.6)							

Note. df, Degrees of Freedom; OR, Odds ratio; CI, Confidence Interval. The n for each variable differs due to missing data relating to those measures (total sample n=392). (Percentages may not add up due to rounding)

^a Adjusted for age, gender, ethnicity and social class

*Significant at $p < 0.05$

Safety and social capital in the current urban environment: SEAT

SEAT: preliminary checks

- *Correlations between the SEAT subdomains.*

Correlations were conducted between the subdomains of the whole sample (n=392). Examining Table 5, suggests that less civic disorder (CD; i.e. higher score due to reverse scoring), relates to less impact of civic disorder (ICD; i.e. higher score due to reverse scoring), more informal social control (ISC) and more social cohesion and trust (SCT). Also higher ISC is associated with more SCT; and less ICD (i.e. higher score due to reverse scoring) correlates with less ISC. As a preliminary check this appears to be in line with the scoring system provided, which stated that 'less civic disorder will be associated with less impact of civic disorder, more informal social control and more social cohesion and trust' (Kirkbride, in preparation).

Table 5. Correlations between the four subdomains of the SEAT: civic disorder, impact of civic disorder, informal social control and social cohesion and trust.

	CD	ICD	ISC	SCT
CD	-	-	-	-
ICD	0.409***	-	-	-
ISC	0.109*	-0.234***	-	-
SCT	0.250***	-0.071	0.368***	-

Note. CD, Civic Disorder; ICD, Impact of civic disorder; ISC, Informal social control; SCT, social cohesion and trust.

*significant at p<0.05 **significant at p<0.01 ***significant at p<0.001

- *Association between SEAT and index of deprivation (IMD).*

The SEAT (continuous variable) was negatively correlated with the total score of the IMD (r= -0.13, p=0.009), which suggests that higher neighbourhood safety and social capital was associated with areas of lower multiple deprivation (see Figure 4). Similarly, when analysing the binary composition of these variables, it suggests a

small indication that individuals living in neighbourhoods with high safety and social capital were more likely to live in an area of low deprivation (low SEAT: 45.7% vs. high SEAT: 55.6%), although this did not reach statistical significance (Table 6).

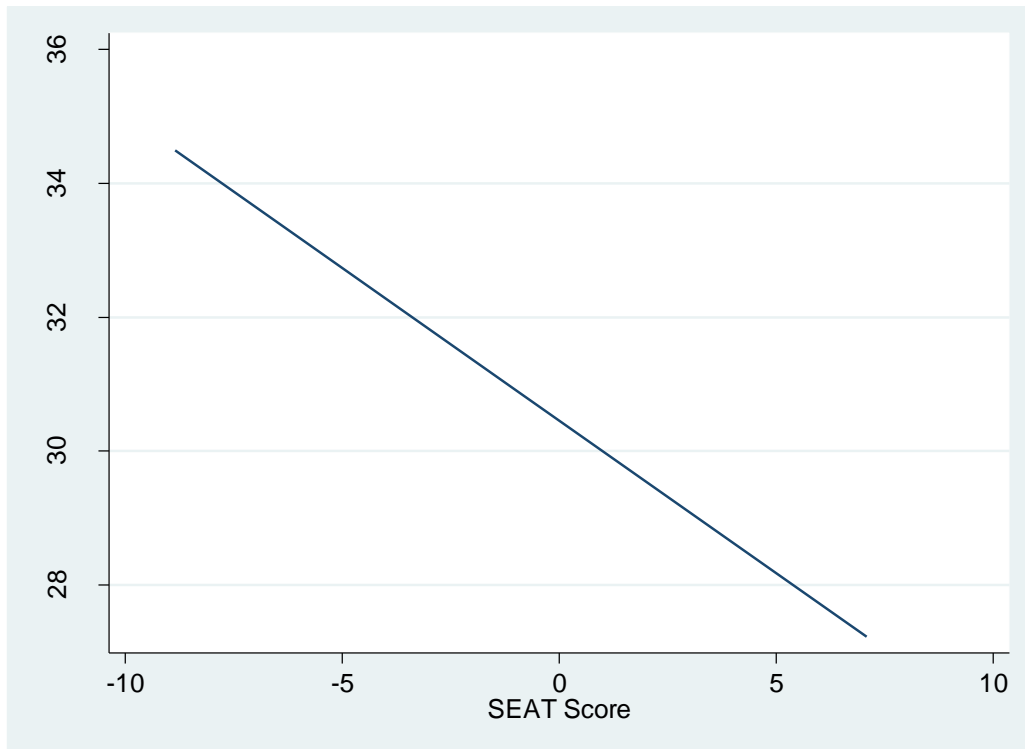


Figure 4. Correlation between continuous neighbourhood safety and social capital (SEAT) and index of multiple deprivation (IMD) scores.

Table 6. Comparison of the binary SEAT variable and the binary index of multiple deprivation (IMD) variable.

	SEAT		x^2	df	p
	Low (n=184)	High (n=197)			
IMD					
Lower Deprivation	84 (45.7)	104 (55.6)	3.68	1	0.055
Higher Deprivation	100 (54.5)	83 (44.4)			

Note. df, Degrees of Freedom. Missing data due to missing postcodes from SEAT questionnaire. (Percentages may not add up due to rounding.)

Safety and social capital (SEAT) and case-control status

This section addresses study aim 1, assessing the associations between the SEAT and psychosis. See Table 7 for output on binary variable group differences and Appendix 6 for the supplementary analysis on group differences using continuous data. The main results using logistic regression, described below, are presented in Table 8.

Aim:

1. *To assess whether the odds of psychosis will be greater in those who experience a neighbourhood with less safety and social capital.*

From examining the medians it suggests that cases lived in areas with more safety and social capital, compared with controls, case median (IQR): 0.25 (-1.24-2.12) vs. control median (IQR): -0.12 (-1.91-1.63). Investigating the relationship between SEAT and odds for psychosis, indicated that when unadjusted there was no association ($p=0.157$, see Table 8). However this association became significant when adjusting for *a priori* confounders, suggesting that a safer neighbourhood with higher levels of social capital was associated with a 1.71 increase in odds for psychosis, see Table 8. This result was further analysed by conducting the logistic regression with all possible combinations of confounders (gender, age, social class, and ethnicity), and it was found that the amplification in the odds for psychosis related to social class (see Table 8; Appendix 7 has analysis output for all other confounder combinations).

Table 7. Comparison between levels of SEAT and case-control status.

	Controls (n=258)	Cases (n=134)			
	n (%)	n (%)	x^2	df	p
SEAT					
Low (-8.86-0.05)	135 (52.3)	60 (44.8)	2.01	1	0.156
High (0.06-7.08)	123 (47.7)	74 (55.2)			

Note. IQR, Interquartile Range; df, Degrees of Freedom. (Percentages may not add up due to rounding)

Table 8. Association between SEAT and case-control status.

Outcome: case-control status						
	Unadjusted		Adjusted OR ^a		Adjusted OR ^b	
	OR (95% CI)	p	(95% CI)	p	(95% CI)	p
SEAT (n=392)	1.35 (0.89- 2.06)	0.157	1.40 (0.9-2.2)	0.140	1.71 (1.03- 2.85)	0.040*

Note. OR, Odds ratio; CI, Confidence Interval.

^aAdjusted for age, gender and ethnicity. ^bAdjusted for age, gender, ethnicity and social class

*Significant at p=0.05

Following this, the relationship between SEAT, social class and case-control status was further explored (using chi-square) by investigating the associations between:

- SEAT and social class (exposure and confounder).

Table 9 suggests that there was no difference in SEAT scores across social class categories.

Table 9. Associations between SEAT and social class.

	SEAT		x^2	df	p
	Low (n= 195)	High (n= 197)			
Social Class n (%)					
Salariat	68 (34.9)	76 (38.6)	1.84	4	0.765
Intermediate	53 (27.2)	51 (25.9)			
Working Class	48 (24.6)	39 (19.8)			
Long-term unemployed	5 (2.6)	6 (3.1)			
Not classifiable	21 (10.8)	25 (12.7)			

- *Case-control status and social class (outcome and confounder).*

This was assessed in the socio-demographic results section described above (see Table 2), which indicated that cases were more likely to be categorized as working class (cases 42.5% vs. controls 11.6%; $p < 0.001$), whereas controls were more likely to be classified into the professional category (cases 8.2% vs. controls 51.6%; $p < 0.001$).

- *SEAT and case-control status by social class (exposure and outcome by confounder; using mhdods command in Stata to calculate odds ratios).*

From examining the proportions of the cells in Table 10, it suggests that cases within an intermediate social class were more likely to live in a neighbourhood with more safety and social capital, whereas controls were more likely to live in areas with less safety and social capital; and there was an indication that this was statistically different ($p = 0.049$). Although not significant, a similar pattern is observed for cases in the salariat social class and controls in the working class. It was also noted that within the immediate class across lifetime, 48.8% of cases were currently unemployed (and 65.9% were either currently unemployed or economically inactive).

In summary, living in a neighbourhood with higher levels of safety and social cohesion is associated with higher odds of psychosis, primarily among individuals within an intermediate social class (when also accounting for gender, ethnicity and age).

Table 10: Association between SEAT and case-control status by social class

		Status		χ^2	df	p	OR (95% CI)
		Control (n=258)	Case (n=134)				
Salarial (n=144)							
SEAT							
	Low	64 (48.1)	4 (36.4)	0.56 ^b	1	0.453	1.62 (0.45-5.81)
	High	69 (51.9)	7 (64.6)				
Intermediate (n=104)							
SEAT							
	Low	37 (58.7)	16 (39.0)	3.85	1	0.049*	2.22 (1.00-4.97)
	High	26 (41.3)	25 (61.0)				
Working Class (n=87)							
SEAT							
	Low	18 (60.0)	30 (52.6)	0.43	1	0.511	1.35 (0.55-3.31)
	High	12 (40.0)	27 (47.4)				
Long-term Unemployed (n=11)							
SEAT							
	Low	0 (0)	5 (50)	0.92 ^b	1	0.338	- ^a
	High	1 (100)	5 (50)				
Not classifiable (n=46)							
SEAT							
	Low	16 (51.6)	5 (33.3)	1.36 ^b	1	0.243	2.13 (0.59-7.70)
	High	15 (48.4)	10 (66.7)				

Note. df, Degrees of Freedom; OR, odds ratio. (Percentages may not add up due to rounding)

*Significant at $p < 0.05$

^a Value missing as sample size too small to calculate odds ratio

^b Indicates Fishers Exact test, all other values are χ^2

Mediation

This section addresses study aim 3 assessing mediation, the results are presented in Table 11.

Aim:

3. To assess possible mediation effects of the psychological variables: Whether the association between current urban environment and psychosis is mediated

by psychological variables (anxiety, JTC bias, negative self and other beliefs, positive self and other beliefs).

Anxiety, a JTC bias, positive self beliefs, and negative self and other beliefs, did not significantly mediate the relationship between SEAT and case-control status (see Appendix 8, for table of results).

Positive other beliefs

The mediation analysis using bootstrapping indicated no direct effects of SEAT on psychosis, but a significant indirect effect of positive other beliefs when unadjusted or adjusted for *a priori* confounders (confidence interval did not cross zero; adj CI: -0.05 – -0.01; Table 11)¹. Positive other beliefs partially mediated the association between SEAT and psychosis (mediation: 22.1% of the total effect), by decreasing the odds of psychosis. A conceptual model of this mediation is illustrated in Figure 5.

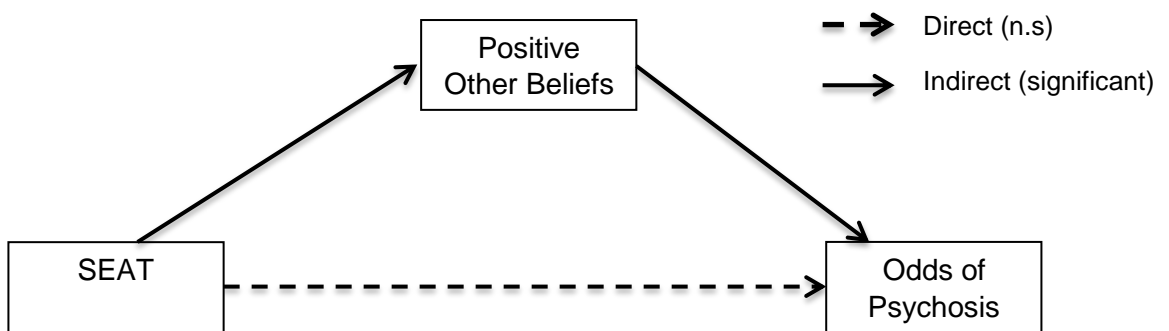


Figure 5. Conceptual mediation of positive other beliefs.

Direct effect of SEAT on odds of psychosis and an indirect effect of SEAT on psychosis via positive other beliefs. (Note. ns, non-significant; the coefficients are not presented, as STATA does not provide standardised coefficients for each path).

¹ In analysis between psychosis and safety and social capital using logistic regression, n= 392, whereas in mediation analysis, n=382 and also controls for positive other beliefs in the direct effect

Table 11. Total, direct and indirect effects of SEAT and positive other beliefs on case-control status

Outcome: case control status						
	Unadjusted			Adjusted ^a		
	Coefficient	(Bias Corrected 95% CI)	Proportion of total effect mediated	Coefficient	(Bias Corrected 95% CI)	Proportion of total effect mediated
SEAT (n=382)						
Direct Effect	0.122	(-0.01 – 0.23)		0.118	(-0.01 – 0.24)	
Indirect Effect - Positive Other	-0.026	(-0.06 – -0.01)*	27.4	-0.021	(-0.05 – -0.01)*	22.1
Total Effect	0.096	(-0.02 – 0.21)		0.097	(-0.03 – 0.22)	

Note. OR, Odds ratio; CI, Confidence Interval. The n differs from total sample size (n=392) due to missing data relating to the belief measure.

^a Adjusted for age, gender, ethnicity and social class

*Significant at p=0.05

Moderation

This section addresses study aim 4 assessing moderation, the results table are presented in Appendix 9.

Aim:

4. To assess possible moderating effects of the psychological variables: Whether current urban environment interacts with each psychological variable (anxiety, JTC bias, negative self and other beliefs) to increase the odds of psychosis; or interacts with positive self and other beliefs to reduce odds of psychosis.

There were no significant results for the interaction analysis between SEAT and the psychological variables. Anxiety (adj. $x^2(1) = 2.90$, $p = 0.088$), JTC (adj. $x^2(1) = 0.02$, $p = 0.885$), Negative self beliefs (adj. $x^2(1) = 1.25$, $p = 0.263$), Positive self beliefs (adj. $x^2(1) = 0.40$, $p = 0.527$), Negative other beliefs (adj. $x^2(1) = 0.03$, $p = 0.853$) and Positive other beliefs (adj. $x^2(1) = 0.96$, $p = 0.326$) did not modify the effect between SEAT and odds of psychosis (see Appendix 9, for table of results).

Exploratory analysis: three-way interaction

This section addresses study aim 5 assessing an exploratory three-way interaction, the results are presented in Table 12.

Aim:

5. To conduct an exploratory three-way interaction, to assess whether anxiety and neighbourhood safety and social capital interact with a presence of the JTC bias, to further increase the odds of psychosis.

This exploratory analysis indicated a significant interaction between SEAT, anxiety and JTC bias on odds of psychosis, both unadjusted (unadj. $x^2(1) = 4.4$ $p = 0.036$) and after adjusting for *a priori* confounders (adj. $x^2(1) = 5.26$ $p = 0.022$). Table 12 suggests the following results when unadjusted:

- 1) Having a JTC bias was associated with a 17.14 increase in odds of psychosis when living in an area of low safety and social capital in the context of low anxiety (compared to absent JTC, low safety and social capital and low anxiety).
- 2) Having a JTC bias was associated with a 3.27 increase in odds of psychosis in the context of high anxiety even when living in an area of high safety and social capital (compared to absent JTC, high safety and social capital and high anxiety).
- 3) Having a JTC bias was associated with a 2.88 increase in odds of psychosis in the context of high anxiety even when living in an area of high safety and social capital (compared to absent JTC, high safety and social capital and high anxiety).
- 4) There was no significant interaction found for the presence of JTC while living in an area with low safety and social capital in the context of high anxiety.

When adjusting for *a priori* confounders, the results followed the same pattern, but only the group with a JTC bias living in an area of low safety and social capital in the context of low anxiety remained significantly significant (OR: 14.98; Table 12).

In summary, in an unsafe environment with low social capital, amongst people with low anxiety, the presence of JTC is associated with a 14.98 increase in the odds of psychosis, but there are wide confidence intervals ranging between 2.6 - 85 times more likely to develop psychosis (when controlling for gender, age, ethnicity and social class). When demographic differences were not accounted for (unadjusted), the presence of JTC was also associated with an increased likelihood of psychosis in safe neighbourhoods with high social capital, in people with high anxiety (OR: 3.27) or low anxiety (OR: 2.88); but in people with high anxiety living in unsafe and non-cohesive neighbourhood, the presence of JTC does not further increase the odds of psychosis.

Table 12. Associations between the comparison groups and case-control status within the three-way interaction

	Unadjusted		Adjusted ^a	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
JTC Present*High Anxiety*High SEAT	3.27 (1.20-8.88)	0.020*	2.72 (0.80-9.32)	0.111
JTC Present*High Anxiety*Low SEAT	1.87 (0.78-4.48)	0.163	1.17 (0.42-3.25)	0.756
JTC Present*Low Anxiety*High SEAT	2.88 (1.27-6.51)	0.011*	1.8 (0.67-4.83)	0.246
JTC Present*Low Anxiety*Low SEAT	17.14 (3.67-80.03)	0.001*	14.98 (2.62-85.53)	0.002*

Note. OR, Odds ratio; CI, Confidence Interval. n= 386, and differs from total sample size (n=392) due to missing data relating to the anxiety measure.

^a Adjusted for age, gender, ethnicity and social class

*Significant at $p < 0.05$

Discussion

This large case-control study is the first to assess psychological pathways between current environment and psychosis using this design. An increased odds of psychosis was found for those who experience higher anxiety, more negative beliefs about self and others and exhibit a JTC bias. The relationship between current environment and psychosis indicated that individuals who experienced psychosis were more likely to report living in a neighbourhood with higher levels of safety and social capital, and this pattern was particularly evident within the intermediate social class. When assessing the interplay between environment and psychological variables, positive beliefs about others were shown to mediate the relationship between neighbourhood safety and social capital, and psychosis. Lastly an exploratory investigation, suggested that JTC is a particularly strong predictor of odds of psychosis in individuals with low anxiety living in a more deprived neighbourhood.

Psychological variables

As hypothesised, cases reported increased levels of anxiety, negative beliefs about self and others, and were more likely to show a JTC bias; and these variables were associated with an increased odds for psychosis. This is consistent with a large body of literature which has found that affective disturbance, a JTC bias and negative core beliefs were associated with the transition to psychosis and the persistence and severity of symptoms (Falcone et al., 2015; Dudley et al., 2013; Fisher et al., 2013; Freeman et al., 2013; Garety & Freeman, 2013; Fisher et al., 2012; Garety et al., 2007; Gracie et al., 2007; Peters & Garety, 2006). These results re-iterate the importance of affective and cognitive processes involved in psychotic disorders, providing further support for the aetiological and cognitive models of psychosis that highlight the putative effects of these factors.

Neighbourhood safety and social capital: bad for your mental health or a complex story?

Living in a safer neighbourhood with more social capital, was surprisingly found to be associated with an increased odds of psychosis. The correlation between the SEAT assessment and IMD deprivation measure validates the proposal that neighbourhood safety and cohesion was found in areas of low deprivation (although the correlation was low, $r = -0.13$). Therefore, this finding is contrary to the studies aims, as it appears that areas with higher SEAT scores, thus lower deprivation is associated case status. Furthermore, this relationship was found to be more evident in the intermediate social class. This result does lend support to the suggestion that neighbourhood characteristics may be a putative factor in psychosis, although it does not support the body of literature, which suggests that more urban adversity is associated with increased risk of psychosis. However, the SEAT does not measure direct experience of adversity but reports on neighbourhood safety and cohesion.

Additionally, some literature has found no relationship between social capital, neighbourhood and psychosis, whereas others have found non-linear associations (Kirkbride et al., 2008; Drukker, Krabbendam, Driessen & van Os, 2006). For instance, it was found that increased rates of psychosis were evident in areas with high or low social cohesion and trust (a dimension of social capital) compared to areas with intermediate levels (Kirkbride et al., 2008). One possible explanation for this current finding is that individuals in 'high safety, high social capital' areas, may have been excluded from the resources or social capital available, which subsequently increased risk for psychosis. The potentially limited access may have resulted in isolation, greater stress as an 'outsider' and less availability of resources to reduce stress. This relates to theories for varying incidence neighbourhood, such as social capital, social integration and social defeat, where experiences of marginalisation, discrimination and seclusion underlie the environmental risk on

psychosis (Allardyce & Boydell, 2006; Krabbendam & van Os, 2005). Additionally it is possible that individuals that experience psychosis in these 'high social capital, high safety' areas are more likely to come to the attention of services; as research has indicated that neighbourhoods with more informal social control (a dimension of social capital) have more in-patient service use (Drukker et al., 2006).

Social comparison and neighbourhood quality

In relation to social class, it appears that an intermediate class was associated with increased risk. Some literature have also found similar results, such as a case-control study of schizophrenia and social class at birth, which found an increased risk schizophrenia in higher social classes, with earlier treatment also indicated by younger age at presentation to services (higher social class age 24 vs. low social class age 33; Mulvany et al., 2001). However a systematic review of literature has found inconsistent evidence of a link between social class and psychosis (Kwok, 2014).

In regards to the current study, facilitated detection and the exclusion from the cohesion, trust and mutual aid within the environment, may have occurred within this intermediate class rank, which is supported by Mulvany et al., (2001). This type of area, may have been more unreceptive and marginalising of individuals who were young, male and from a minority ethnic group, which are reflected in the demographics of cases within this sample and are also factors associated with higher risk of psychosis (Kirkbride et al., 2006). In addition 'social ranking' theory could provide another possible explanation. The generation of 'social ranks' are said to arise from social comparison (including comparison of power/strength, social desirability and belonging), where an individual appraising themselves as within a subordinate rank would experience a loss of role/goal, and feel threatened, inferior and unable to move forward (Gilbert & Allan, 1998; Gilbert, Price & Allan, 1995). It is

suggested that these rank patterns and associated beliefs within the social world are also mirrored internally, therefore influencing psychotic symptomology (Birchwood et al., 2004; Birchwood, Meaden, Trower, Gilbert & Plaistow, 2000), which is also parallel to cognitive models of psychosis (e.g. Garety et al., 2007). For instance, individuals who believed they did 'not belong' and felt more subordinate to others, also felt more subordinate to and distressed by voices (Birchwood et al., 2000). It is possible that individuals in this intermediate class experienced a high degree of social comparison, when living in a safe and cohesive neighbourhood, and subsequent appraisal of relative inferiority, may have led to a vulnerability to psychosis, via biased and more threatening appraisals. These discrepancies might have been less pronounced when living in poorer (and less cohesive and safe) neighbourhoods.

Moreover the social class category was based on an individual's main occupation throughout the lifespan and the demographic data suggests that cases were actually more likely to be currently unemployed (within the immediate class, 48.8% of cases were currently unemployed and 65.9% were either currently unemployed or economically inactive). This suggests that some downward social drift occurred, potentially indicating that individuals who were in the intermediate class category, may no longer fall within this class or were not classified as this around onset. Therefore, further exclusion and social comparison due to changes in status during prodrome or this social drift prior to onset, may have further driven risk of psychosis. It would be of further interest to see if this result held, when assessing current social class category or social class at onset of psychosis.

Furthermore, this finding could also be due to a sampling issue, as the sampling within the social class categories, indicated that the intermediate group had a more even distribution compared to that of other groups (e.g. a comparison of 1 control

vs. 5 cases in the long-term unemployed category; or 69 controls vs 7 cases in the salariat category). The controls were also not recruited to be representative of the social class within the local population (only representative of area age, gender and ethnicity) and given the finding on the direction of the SEAT, future research should quota sample for social class.

Positive beliefs about others: protection against psychosis emerging from cohesive neighbourhoods

Positive other beliefs were found to be significant mediators of the impact of current environment on psychosis risk. Specifically, having positive other beliefs was a protective factor, which decreased the odds of psychosis. Theoretically, broad schematic beliefs an individual holds about the self and others are said to have an influence on psychosis through biased appraisal of anomalous experiences and via the generation of themes associated with paranoid and delusional symptomology (e.g. threat, mistrust; Garety et al., 2007; Freeman et al., 2002). Research has indicated no difference in positive beliefs in chronic psychosis samples (Fowler et al., 2006), with less known about positive beliefs in early psychosis. Most literature highlights an effect of negative self and other beliefs in psychosis (Thomas et al., 2015; Oliver et al., 2012; Garety et al., 2007; Freeman et al., 2002) and this may reflect the potency of negative beliefs in impacting the distress and disability evident in psychosis.

In the current study, evidence that neighbourhood safety and cohesion can influence beliefs about others to reduce the likelihood of becoming psychotic, relates to social support literature. Limited social support and poor perception of support is proposed as a possible risk factor in psychosis (Sundermann et al., 2014; Gayer-Anderson & Morgan, 2013; Sundermann et al., 2013) and relationships and living with someone were indicated as protective factors (Stilo et al., 2013). Both the

quantitative (size/reciprocity) and the qualitative (satisfaction, loneliness, confident availability, connectedness) features of support are said to be important, as the discrepancy between what an individual wishes to have and what they perceive to have from their social relationships may be detrimental to wellbeing and result in loneliness (Sundermann et al., 2014; Heinrich & Gullone, 2006; Peplau & Perlman, 1982). Strong social support is also thought to be protective, by increasing self-esteem and buffering against the impact of stress and trauma (Brugha, 2010). It is possible that positive other beliefs, are generated from more supportive current or past social networks/interpersonal experiences, resulting in a protective effect, whereby viewing others more positively reduces threat themes or biased appraisals implicated in psychosis, or reduces affective disturbance due to confidants available and the positive perceptions of the accessibility of resources and a wider network.

Data gathering bias: the importance of JTC in the context of neighbourhood safety and social capital

Cautiously, this exploratory analysis indicates that JTC will substantially increase the odds of psychosis in an unsafe and non-cohesive environment, even without the presence of anxiety. The interpretation of these interactions is tentative, due to large confidence intervals associated with the results. Given the correlation indicating that low safety and social capital was associated with an area of high deprivation, this analysis tentatively suggested that having a JTC bias increased odds of psychosis by 14.98 (unadj. CI: 2.62-85.53) when living in a highly deprived environment in the context of low anxiety. This is potentially in line with original ideas around low social capital and more deprivation or crime increasing risk for psychosis, where there is less opportunity to buffer social stress of urban living in these types of areas (Kirkbride et al., 2007b; Lofors & Sundquist, 2007; Allardyce & Boydell, 2006; Krabbendam & van Os, 2005; Putnam, 2001). Tentatively, JTC presence and high deprivation increase the odds of psychosis irrespective of anxiety being present,

suggesting JTC as a risk factor within its own right, given that the combination with high anxiety was not significant. Specifically, in relation to a cognitive model, seeing potentially threatening events in the environment and exposure to urban living stressors (e.g. crime, less cohesion, less resources) may interact with JTC, creating themes of threat and less likelihood of reality testing or searching for alternatives/more information, when searching for meaning of experiences, thereby increasing the risk for psychosis. Additionally, JTC did not appear to be a predictor of odds of psychosis for individuals with high anxiety living in deprived and less cohesive neighbourhoods, suggesting an alternative route to psychosis in which anxiety drives increased odds of psychosis (regardless of environment, as seen by main effects of anxiety and lack of mediation/moderation; Garety et al., 2007).

Moreover, this exploration suggested that JTC and anxiety both play a role in increasing odds of psychosis in safe and cohesive neighborhoods, but this seems to be explained by socio-economic variables. Specifically, a JTC bias significantly increased the odds of psychosis onset when individuals living in a safe and cohesive area were either highly anxious (OR 3.27) or not anxious (OR 2.88); but this was only evident in unadjusted analyses, not controlling for *a priori* confounders (age, gender, ethnicity and social class). However, it is also important to assess the magnitude of the change in odds ratios between the groups, which indicated that when adjusted for confounders a similar pattern was evident although not statistically significant. This indicates a possible affective interaction with the JTC bias in areas with more safety, social capital and less deprivation; potentially people in an anxiety state use less information to understand situations or anomalous experiences, thereby increasing the risk for psychosis. Taken together this is suggestive of JTC bias increasing vulnerability within urban environments, in its own right as a trait like cognitive variable and in combination with an affective process. Importantly these results are to be interpreted cautiously, as the odds for psychosis

were coupled with large confidence intervals, which suggest that the precision of this analysis was not very reliable. When including more variables in the model for analysis the confidence intervals were increasingly wider (due to the estimation of more parameters) and reflecting on the power analysis it suggests that the final sample size was not adequate to detect a precise effect, resulting in a more exploratory analysis. This result, however, does indicate a need for future research in this area, using much larger samples.

Strengths and limitations

The case-control design is thought of as an efficient epidemiological study design for investigating rare disorders (e.g. psychosis) and multiple exposures (Mann, 2003). This is one of the first studies using a large FEP sample to assess possible psychological pathways to psychosis, from urban living. Although several of the study findings mirror previous literature, it is not without limitations.

Methodological components

One common methodological issue with this study design is selection bias, where selection is related to the exposure or outcome under investigation rather than being representative of cases and controls in the wider population (Susser, Schwartz, Morabia & Bromet, 2006). There were inevitably missed cases for reasons such as not presenting to secondary services, not seeking help or non-attendance to appointments. This could result in some selection bias; if cases with possibly more unstable lives or environments were unable to be recruited due to missed appointments, this may have underestimated the association between safety and social capital in the environment and psychosis. Furthermore, this bias may also be reflected in the reduction in the sample completing the SEAT measure, which also could have been associated with severity of illness or instability within the

environment. A further analysis, comparing those who completed the SEAT vs. those who did not, would be able to assess this. However for cases, the study's rigorous recruitment process included various sources (inpatient and community teams, home treatment teams, early intervention and forensic services) to reflect a representative FEP sample within the catchment area and to ensure a range of presentations were recruited.

The two control recruitment routes would have possible pitfalls in oversampling of certain groups, e.g. the PAF route being more likely to consist of older, more 'adjusted' individuals (Norris, 1992; Bebbington Tennant & Hurry, 1991), which may have over-estimated the safety and cohesion available, whereas the GP lists may be more likely to recruit migrant populations compared to the PAF, which may underestimate safety and social capital, possibly indicated by research on minority status within an area (Suvisaari, Opler, Lindbohm & Sallmen, 2014 ; Kirkbride et al., 2007b; Alladyce & Boydell, 2005). In regards to controls, the dual-approach to recruitment was to minimise bias related to each individual method and the study also used quota sampling, which found that the actual control sample was broadly representative of the local population in the catchment area (in terms of age, gender and ethnicity). However given the relevance of social class indicated in this study, it may have been useful to recruit controls also representative of local population social class. An additional strength of control recruitment, was that exclusion of controls was only for history of psychosis (i.e. not other disorders), therefore differences between the groups were likely to not be overestimated due to having solely 'well controls' (Schwartz & Susser, 2011).

Moreover, self-selection biases may have occurred within this study (i.e. characteristics of individuals that make them more or less likely to participate), such as paranoia, other psychiatric symptoms (e.g. depression, anxiety), length of

assessment or the overall premise of the study (i.e. on adversity), which could have made people less inclined to participate. Although, the study did attempt to reduce this type of effect via various methods, including researchers being regularly available to enable enquiry about the study, allowing various opportunities to consider participation, being flexible in terms of appointments, compensation for participating and ensuring people felt comfortable and understood confidentiality.

In this design, there is also a query on reporting (e.g. on the SEAT) being biased by psychotic symptomology. However research has shown that individuals who experience psychosis do not necessarily over-report experiences of adversity, which has also been evidenced via the consistency of reporting across various types of study designs (Beards et al., 2013; Varese et al., 2012; Fisher et al., 2011; Wigman et al., 2011; Brown and Birley, 1968).

Causality

Case-control studies do not imply causality and the prospect of reverse causality cannot be fully ruled out (Mann, 2003). As psychosis was already present at recruitment, it was therefore possible that the illness caused the exposures to occur. In this type of social epidemiology research it is hard to always establish temporal ordering, when adversity (e.g. life events, low social capital, risk of victimisation) can occur due to illness-related behaviour. Therefore it is not fully possible to determine whether individuals were excluded from or exposed to the level of neighbourhood safety and social capital needed to influence psychosis onset. Even with the possibility of reverse causality, it is still useful to assess associations, as it provides essential information for future search, prevention and intervention. Additionally, the SEAT was validated within the preliminary checks, therefore being associated with an objective area deprivation measure, which can be assumed to have occurred irrespective of illness.

Mediating and moderating effects

This study did not find other mediating effects as indicated in previous literature or other possible moderating effects from theoretical understandings (i.e. anxiety, JTC bias, negative self and other beliefs). Previous research has assessed affective and cognitive pathways between adversity and psychosis in general population studies (Fisher et al., 2012; Freeman & Fowler, 2009) and often research with clinical populations have focused on pathways between early adversity and psychosis (Fisher et al., 2013; Bebbington et al., 2011). The Camberwell Walk studies were novel in using a cross-sectional design with psychosis patients to assess the immediate effect of urban environment compared to a control condition. It is possible that the relationship between safety and social capital in the environment and psychosis is not mediated or moderated by other psychological variables. It could also be possible that other mediating/moderating factors or confounders could account for the unexplained variance that were not measured in the study (e.g. childhood adversity, depression or hostile attribution biases; Fisher et al., 2013; Garety et al., 2007). It is also conceivable that the dichotomising of anxiety, for example, did not encompass the necessary range of affective symptomology to detect a significant pathway between urban environment and psychosis, given that anxiety is theorised as a main pathway between adversity and psychosis (Garety et al, 2007; although this dichotomisation has also been used in previous literature).

Alternatively it could be due to the measure of current environment, as this is a new measure combining two aspects associated with exposure in urban living, in terms of safety and social capital. It is possible the associations are not within a global score but within the actual individual aspects. Conversely, the SEAT may also not reflect measures used in previous literature, such as national statistics (e.g. IMD which only assesses aspects of demographic deprivation) and objective measures used as proxy for area networks and cohesion. However, although the SEAT

questionnaire is early in its validation process (with not all of the sub-domains correlating in the initial checks), it was associated with an objective measure in the hypothesised direction. Additionally, the results may be associated with the complexity of the operationalisation and impact of the concepts, crime and social capital. For instance, crime and fear of crime have been shown to impact wellbeing and schizophrenia (Bhavsar et al., 2014; Lorenc et al., 2012; Lögdberg et al., 2004), but the effect of crime may be via multiple mechanisms, such the actual impact of the level of crime in an area and crime also being a marker of general area-population characteristics (e.g. deprivation). It has been suggested that influence of crime is difficult to tease apart, is not always in the anticipated direction, and the routes are often indirect and mediated by a variety of different social factors (Lorenc et al., 2012). The concept of social capital also still requires further research in terms of the definition, measurement and relationship with psychosis (Kirkbride et al., 2007b, 2008; Drukker et al., 2006; Whitley & McKenzie, 2005; Boydell et al., 2002).

Furthermore, the cross-sectional nature of the study means the assessment of urban environment was related to current experience; and potentially varying duration of untreated psychosis suggests that present area safety and cohesion may not be necessarily linked to that at onset. However given the given the infancy of this type of research, it would be of interest to investigate more complex putative processes involved in urbanicity and risk for psychosis, by further assessing the psychological pathways between neighbourhood characteristics and their interactions.

Statistical components

Power could be a limitation within this study due to sample size (especially in terms of detecting mediating and moderating effects) as previous studies have used larger

samples for more complex analysis (average 7000 people; Fisher et al., 2012; Bebbington et al., 2011). Additionally limited power could affect results via confounders, whereby having many confounders within a model can reduce precision and miss true associations, (Susser et al., 2006). Therefore, although it is possible that other potential confounders exist, this study included the smallest number of confounders and both unadjusted and adjusted analyses were reported to assess their potential impact. The *a priori* cofounders included (age, gender, ethnicity, social class) were in line with other research conducted within this study team and was related to previous literature identifying independent associations between the exposures in the wider study (adversity) and psychosis. Additionally it was evident that some analyses resulted in wide confidence intervals (i.e. the three way interaction), indicating a possible lack of precision in the effects identified and was potentially due to lack of power. These assumptions around power are also reflected in the more stringent power analysis conducted, where approximately 364 participants between groups were indicated as necessary for a more conservative odds ratio of 1.5 to be detected, when controlling for more predictors. Therefore some of the findings are cautiously interpreted and it would be recommended to replicate the study using much larger sample sizes.

Lastly, research has indicated a relationship between a JTC bias and intellectual functioning, with some literature suggesting that this reasoning bias is explained by IQ or education (Lincoln, Ziegler, Mehl & Rief, 2010). Additional research has suggested a less clear association, with more task dependent-results, where low IQ may contribute to reasoning errors (e.g. JTC bias) in harder and more complex situations (e.g. more ambiguous information; Jolley et al, 2014). This suggests that reasoning biases may be associated with 'poorer understanding, ability or concentration' (Jolley et al, 2014). Therefore not controlling for IQ was a limitation, as for example, the main effect of the JTC bias might have been fully or partially

explained by cognitive ability. However, in limiting parameters, social class was used within this study over education and current employment, due to controlling for wider social-economic status (SES), which could possibly confound the urbanicity measure. This social class measure was a detailed assessment of an individual's occupational status (e.g. job title, managerial tasks, numbers supervised, job responsibilities), which was then used for the assignment into class categories. Consequently, it could be said to associate with educational attainment/intellectual functioning (as well as wider SES), and not just related to an occupational title. This therefore is suggestive of a strength within the study, as the measure could be a proxy for education and more suited as a control variable for the overall study aims.

Implications

Research implications

The impact of psychological variables on psychosis is supported by this study, reflecting current theoretical understanding. There was a suggestion that the environment one lives in does appear to have an influence, indicating the need for further study to elucidate this relationship. Given the exploratory three-way analysis, it indicates a need for future research to assess the possible putative interactions between these variables in a more complex model (e.g. structural equation modelling). This will further assess the theoretical pathways between the environment and psychosis, indicated in theoretical and aetiological models of psychosis. Furthermore, it would be important to assess both area level variables (e.g. IMD) and individual level factors (e.g. SEAT) in a multi-level modelling analysis. This would identify and assess interactions between putative environmental interactions at both levels, and could also further understanding on the underlying mechanisms between urban environment, safety and social capital and psychosis. For example, residential mobility and social fragmentation are associated with psychosis (Allardyce et al., 2005; Silver, Mulvey & Swanson, 2002),

and residential stability is said to be necessary for the generation of social capital (McCulloch, 2003). Longitudinal and prospective assessments of environment, safety and social capital could also further investigate this, especially as the conceptual understanding of social capital and the relation to psychosis is a developing theory (Whitley & McKenzie, 2005).

Clinical implications

This study further re-iterates the benefit of interventions around cognitive and affective process in psychosis, such as cognitive behavioural therapy and family interventions (Onwumere, Bebbington & Kuipers, 2011; Bird et al., 2010; Gaudiano, 2005; Petersen et al., 2005; Craig et al., 2004). It highlights positive other beliefs, indicating the importance of schema and the potential preventative or protective nature this could have. Evidence that neighbourhood safety and cohesion can influence beliefs about others to reduce the likelihood of becoming psychotic suggests that interventions facilitating support and engagement in wider networks could reduce risk of relapse or onset of psychosis. There is potential for programmes to be implemented in general or specialist CMHTs and early detection services, additional to current treatment to help promote recovery. For example, a study assessing assertive community outreach in FEP, indicated that this intervention improved clinical outcomes by sustaining or rebuilding relationships with significant others within their network (family, friends and acquaintances; Tempier, Balbuena, Garety & Craig, 2012). There is also a connection to the field of Community Psychology, which emphasizes material and social reasons of distress, with interventions focused on, community action to change sources of distress in society, strengthening individuals' and communities' existing resources and resilience, and supporting and empowering marginalised individuals (Orford, 2008; Rappaport & Seidman 2000). Community based work has aimed to bring 'psychology in the real world', using groups such as 'walk and talk' which facilitates

supportive social and community relationships; and connection with one's environment (Holmes, 2010). The potential benefit is also reflected in various befriending and peer support schemes implemented in both inpatient and outpatient services. This type of scheme has shown improvements in the progression and outcomes of other mental health difficulties (Mitchell & Pistrang, 2011; Harris, Brown & Robinson, 1999a, 1999b) and shown benefits for recovery in psychosis when befriending was used as a control group in a randomised control trial (Jackson et al., 2008). These types of intervention could improve or develop more positive beliefs and provide supportive interpersonal experiences, which may enable people to engage in the social capital and networks available in their environments and reduce vulnerability to psychosis.

Conclusion

Cognitive models of psychosis propose the importance of psychological factors in driving various processes and behaviours that could increase vulnerability to and maintenance of psychotic symptoms. For example, threat anticipation, the use of less information in meaning making, selective attention and hyper-vigilance to experiences confirming psychotic beliefs and safety behaviours which prevent disconfirmation of beliefs (Garety et al., 2001 2007). This study highlighted the importance of affective and cognitive processes (anxiety, schematic beliefs and JTC bias) theorised in models of psychosis and some potential implicated pathways. The results indicate the possibility that neighbourhood characteristics, such as safety and social capital, are associated with psychosis. However it appears that this is a complex and possible non-linear relationship, which may interact with various other individual (and possibly area level) variables. The protective benefit of positive-other beliefs, also draws links to a growing body of literature on the effect of social support in psychosis and the field of Community Psychology. Overall further research is needed to investigate multi-level models of the relationship between

urbanicity (safety and social capital) and psychosis; as well the complex interplay with psychological factors that may be pertinent in development and maintenance of psychosis.

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Part 3: Critical Appraisal

The critical appraisal is a reflection on the process of this current thesis, and will consider three particular themes that arose throughout the completion of the research. It will begin by discussing the scientist-practitioner model, highlighting experiences of the cyclical process between my research skills and clinical practice on placement, including personal reflections on the journey ahead as a clinician who wishes to continue a wider research career. Secondly, the move for research and literature reviews to investigate complex causal pathways, 'the how', will be discussed in relation to assessing psychological models and formulations. Subsequently, personal reflections will be outlined on the need to acknowledge the influence of wider contexts and the role of a psychologist within these areas. The appraisal will also consider how these themes interact and will inform my practice beyond qualifying.

Research and clinical practice

The scientist-practitioner model is an important feature underlying the competencies, contributions and values of clinical psychology as an applied science. It embodies a framework of training aimed to develop a discipline of being both practitioners and scientists (Shapiro, 2002). Shapiro (2002) outlines examples of core competencies based on this model, for the preparation and education of clinical psychologists. This includes:

- *'Delivering assessment and intervention procedures in accordance with protocols.*
- *Accessing and integrating scientific findings to inform healthcare decisions.*
- *Framing and testing hypotheses that inform healthcare decisions.*
- *Building and maintaining effective teamwork with other healthcare professions that supports the delivery of scientist-practitioner contributions.*

- *Research-based training and support to other health professions in the delivery of psychological care.*
- *Contributing to practice-based research and development to improve the quality and effectiveness of psychological aspects of health care.'* (Shapiro, 2002, p.234).

The importance of interweaving a research philosophy into clinical practice, is mirrored by competencies outlined by criteria from professional bodies indicating core skills of evaluation, research and audit (Cogan, 2013; British Psychological Society, 2010). This research ethos promoted evidenced-based practice, which involves clinical decision-making using research evidence, clinical expertise, and client preferences and characteristics (Spring, 2007). This is enhanced by practise-based evidence, where as a profession we evaluate the service and interventions we provide, develop new ideas and are able to assess the effectiveness of research into everyday practice (Shapiro, 2002). These skills are also especially essential when inconsistencies or a lack of evidence is available, where the practitioner is able to critically assess and use the science, in combination with clinical skills to formulate, intervene and evaluate, to enable a service that is person-centered and responsive to the needs of service-users. Therefore there is a cyclical relationship between research and clinical work, as the two arenas are fundamental to each other.

As a trainee, I feel this model has been instilled as a discipline for the work I do, most importantly via the observation of the cyclical process itself throughout training. From the teaching, use of and critical evaluation of evidence-based practice and practice-base evidence, to the use of trainees in feeding back the newest approaches, research and practice, to the services we are placed in. I have valued service-user involvement, with the process of integrating this information with

research/clinical 'knowledge' to develop groups/workshops, while automatically considering audits/reviews to evaluate the aims and outcomes of what was set out to do. This seems imperative, with the change in commissioning and the evolving role of clinical psychology in leadership, as well as a with a more creative use of 'what evaluation and outcomes are' for clinicians, services and service-users. For example, as well as using questionnaire based measures to assess outcomes, I have also used principles from Solution Focused Therapy to hear reflections from group sessions about what was taken away (which aims to facilitate action by making preferred futures more concrete; George, Iveson & Harvey, 2006); and facilitated service-user created booklets and resources on managing stigma as part of a group. Another example of creative use of evaluation derived from partnership working between an NHS service and a third sector organisation, who incorporated ideas from the therapeutic function of storytelling (e.g. Recipes of Life, Wood, 2012; Tree of Life, Ncube, 2006) into their handcraft group, where they created a blanket and a book, about their stories of reunion (Derman, 2015). Therefore, throughout training I was able to witness and participate in how research and clinical practice inform one another and this thesis highlighted the reciprocal process of idea development, integrating information and evaluation.

During this thesis, I was able to learn more about the vast national statistics available and the maneuvering of this information, beyond basic breakdowns of borough demographics. This was inevitably more complex than it initially appeared and was only possible via liaison with multiple statisticians within this area of research. What was more interesting however was that this statistics procedure seemed useful specifically for my research question, but to my surprise this new knowledge was utilized on a placement to aid the development of a more detailed commissioning report. This highlighted the importance of inter-disciplinary working and further research skills, in terms of abilities I would not necessarily of learned

within 'solely clinical psychology' training (as the statisticians were not within the clinical field), but also how these extended to more practical skills on a placement. On the opposite side, my clinical skills further enabled me to perform my research duties, such as liaison and conceptualising models/implications. Particular skills, which benefited the research process was formulation, consultation, working with organisations as clients and management of process issues. This enabled me to approach and reflect on my research duties, in relation to the different contexts involved, such as, the research departments, the past experiences of the benefits and tensions of large-scale projects and managing research relationships. Coming from a background of research and doing the clinical psychology training, I value both the research and clinical work within the profession, and the use of both in progressing etiology of mental health difficulties, psychological intervention and of service development; but I also recognise that this relationship goes beyond that to the actual process of this work and the day-to-day interweaving of fundamental skills from both.

This scientist- practitioner model was shown to viewed positively and endorsed by psychologists, but the majority of psychologists do not continue to do research after qualifying, with increased demand on clinical work and less support within services for pursuing research (Cogan, 2013; Rushton, Golding & Cohen, 2013). This mirrors some of my concerns about balancing research and clinical activity post training, as I step into a new system with different challenges, constraints and priorities.

Doctoral training has made an effort in preparing us for qualified life through both teaching and placements. There is an effort to discuss changes within the role of psychologists, policies and commissioning, encouraging leadership and service-level activities. However, even though we can envisage what post-qualification may look like, and welcome this step (with less case-reports and exams), as with all change, the reality of the transition may be a bit trickier than expected. I have a

perspective of working within the NHS witnessing advantages/potential, constraints and workload of the NHS on placements, but I also felt slightly detached from being fully immersed within the context, by the nature of being a trainee (e.g. short placements, protected case load and time, other training demands). It will be interesting to finally be at a place that may last longer than 6 months where I can develop my role as a clinician within a team; at the same time I am sure I will feel a loss in terms of protected time for teaching and learning, for both clinical and research work, and having a large cohort of peers to always bounce ideas off (as well as access to journals!). Being a trainee and having a post-qualification role within the NHS, will definitely be different and during placements I was able to identify some services that may support my interests in research and clinical work. For example, within my IAPT placement I could not see the time for a clinician to be involved in research, whereas my placement within an early intervention service (EIS) and BME Access Service, had demands in terms of clinical responsibilities but there was also more space and support for research within my areas of interest. However, I also think that this does fit into a wider context, of the team, the service, the NHS trust, the needs of service-users within borough and the wider financial climate. A last concern in balancing both interests in research and clinical practice is time constraints, between finding time for research within the priorities and demands of the service; and ensuring a better balance between work-and-life, especially after the doctoral training. Conversely the juggling of many aspects of training does prepare and instill core skills for the juggling of new demands post-qualification.

These concerns around the research-clinical balance have been reflected within the wider profession. A qualitative study Rushton et al. (2013) outlined the internal scientist-practitioner model, the 'reality check' of the demands post-qualification, available support structures (e.g. time for research, trainees and assistants, a research community), and perceived competency (e.g. statistical skills, feeling

incompetent and the aversive experience of publishing) as important factors in influencing attitudes to research in practice. This is useful as a discourse in providing possible solutions in advancing this balance within the profession. Moving forward I do aim to continue research within my clinical work, by conducting service related research and service development, I hope to work within a service with time dedicated to such research or evaluations (or foster support for this) and by staying connected with a research peer network. Although, I do wonder how I will balance time for my interest in wider research elements, such as new statistical procedures. Other recommendations outlined in literature, suggest looking for research opportunities and continuing professional development, forming relationships with research bodies and professional bodies and universities providing top-up training in research and training on applying for research grants (Hutton, Robinson & Holliday, 2013; Rushton et al., 2013). Given this is the beginning of my career and the profession is discussing this imbalance (e.g. an issue of the Clinical Psychology Forum devoted to this topic), it does seem hopeful that there will be continued possibilities to develop research alongside clinical practice.

Moving towards mechanisms and casual pathways

One of the reasons urbanicity was a topic within this thesis was an interest in social adversities as influential factors in mental health and well-being, but also due to little literature on how urbanicity may link with psychological processes known to be implicated in psychosis. Literature has suggested that although it is useful to assess individual exposures, moving beyond this is essential as no singular factor is '*necessary or sufficient to cause psychosis*' (Morgan et al., 2014). Much research has now assessed various interacting or mediating effects across various factors within psychosis (e.g. Gayer-Anderson et al., 2015; Wickham, Shryane, Lyons, Dickins & Bentall, 2014; Fisher et al., 2013; Fisher, Appiah-Kusi & Grant, 2012; Lincoln, Lange, Burau, Exner & Moritz, 2010; Cooper et al., 2008; van Os, Pedersen

& Mortensen, 2004), similar to this thesis. Literature has also used this accumulating evidence on social and environmental factors to develop models on how these variables may relate, e.g. the relationship between abuse, migration, ethnicity, adult adversity, with other biological and psychological factors (e.g. Howes & Murray, 2014; Morgan, Charalambides, Hutchinson & Murray, 2010). It has been stipulated that to advance the field in this area, we need to investigate the influence of cumulative adversity or protective factors, how these factors interact and the mechanisms with which they have an effect (Morgan et al., 2014; Hatch, 2005); therefore, beginning to assess potential complex causal pathways. For example, Morgan et al. (2014), assessed how childhood and adulthood adversity combined to influence risk of psychosis, via simultaneous mediation and interacting pathways over time (mediated synergy model). This movement is not without its limitations, in terms of critiques of statistical procedures, the need for large sample sizes, the need for more detailed measures of social exposures and an early stage, for these techniques in encompassing the complexity of a developmental pathway (Morgan et al., 2014; Zammit, Lewis, Dalman & Allebeck, 2010; Hatch, 2005). However, it was interesting to learn more about these statistical developments as it draws parallels to how we may formulate difficulties or resilience in clinical practice.

This transition to investigating 'what happens' in a more multifaceted approach has also been mirrored within literature reviews. Specifically, a recent article suggested that principles underpinning evidence synthesis methods were evolving, to integrate different types of research designs and evaluate more complicated questions, due to previous approaches not being fully suitable to review 'complex questions and interventions' (Petticrew, 2015). Historically reviews have assessed specific simple questions, e.g. around effectiveness of an intervention or whether an exposure was a risk factor, and although there is a continued role for this, progression is required to assess more '*complex, socially embedded interventions*' (Petticrew, 2015).

Asking these types of questions of complex social processes may be 'misleading, too simplistic', or lack meaning due to the limited and inconsistent evidence often accompanying complex exposures (Petticrew, 2015). Therefore more reviews should begin evaluating a variety of evidence, regarding what occurs when an intervention is conducted and how effects have transpired, as well as how risk factors exert an effect (e.g. Petticrew, 2015; Hawe, Shiell & Riley, 2009). Although the literature on how urbanicity poses a risk, as well as potential interventions to mitigate this, is within its infancy, it would potentially involve complex relationships. For instance, the finding that urbanicity risk is increased for individuals with a certain characteristic that represents a minority within their residential area (e.g. Schofield, Ashworth & Jones, 2011; Das-Munshi et al., 2012; Kirkbride et al., 2007; Allardyce & Boydell, 2006; van Os, Driessen, Gunther & Delespaul, 2000), is suggestive of a complex web of individual, community and societal factors; that a simple question of what the risk is or whether an intervention to tackle this works, may not highlight the multifaceted nature of the process involved.

Other areas that stood out to me about the development of reviews were reflections on the exclusion of 'weak studies', which may actually be assessing systemically different types of interventions to 'high-quality studies'; and more use of qualitative research to not only assess intervention acceptability but also the variety and nature of impacts of interventions (Petticrew, 2015; Thomas et al., 2004). This is important to consider potential bias and the use of all types of available evidence that could provide useful information to inform research, clinical and policy decisions. Overall there are interesting developments and discourses within research, around how to assess putative causal pathways simultaneously, as well as how to review and synthesize literature on these multi-faceted exposures and interventions.

Connecting this with the balance of research and clinical work, I do wonder how these developments may influence doctoral training in the future, in terms of research teaching on conducting these types of analysis or literature synthesis. It also makes me think about how I will balance this interest within a clinical career. I may have a solid basis in analysis such as t-tests to regression, but I am interested in developing skills in more complex statistical procedures to assess simultaneous interplay between factors and be aware of new guidelines and procedures for combining different types of research. This seems an exciting prospect, to further assess and understand theoretical models and formulations, which reflect what I will be using in clinical practice. I would hope to have a combined clinical and research post, but this also depends on limited opportunities to do so and the uncertainty of funding applications (White, 2013). It is useful to have this discourse within the profession and it will be a journey balancing expectations of post-qualification aims and interests with the context of new demands, challenges and priorities within the workplace.

Wider systems – community psychology

Whilst reading the literature on urbanicity, various factors arose such as deprivation, discrimination, minority characteristics, fragmentation and lack of community ties; and I began to reflect on the wider context these factors reside in. I noticed that these many studies assessing urbanicity also failed to comment directly on the societal framework that may be driving these variables. For example, social disadvantage tends to continue over time, cluster within individuals, families and areas and lead to poorer outcomes, creating a vicious cycle of adversity and marginalization (Pantazis, Gordon & Levitas, 2006). Morgan et al. (2014) cited this as a useful reason, as to why research should assess the effect of multiple adversity

over time, which is valid, but what about the system which is perpetuating this vicious cycle? How do we assess that within our field? How do we intervene there? My thesis also looks at how the 'urban environment' interacts with more individual psychological process, and there has been modified cognitive behavioural therapy aimed at helping individuals experiencing paranoia to enter busy social environments, by targeting anxiety process triggered by urban settings (Freeman et al., 2015). This literature is useful in terms of thinking about etiology of mental health difficulties, to understand what risk or resilience factors are, how they influence/interact with the individual. But I also wonder about the lack of direct acknowledgement and discourse, of how this links to wider structural contexts - racism, inequality, sexism, discrimination, oppression. I am curious as to whether this individual approach may also be perpetuating the structural inequalities that do exist, by focusing just on the internal processes, as I also began to forget about the wider context in the midst of the thesis.

Systemic issues in society do directly and indirectly influence mental health and wellbeing. How do we make sure we are not placing all the responsibility within the individual and further marginalizing the marginalized; by ignoring perceived and experienced injustice and by just implementing interventions where only the individual 'needs to deal' with inequality. These approaches are beneficial and necessary, but I believe that one also has to acknowledge the influence of these wider contexts, so the individual is not left feeling that the 'problem lies within them'. Formulation in clinical practice can encompass the narratives and systems people reside in, and this should also be reflected in research. Our assessment and intervention within bio-psycho-social models as essential but as we also look more at social factors we also need to embrace our role in intervening at different levels beyond the individual, towards the community and society. Undoubtedly, it appears 'easier' to intervene individually than intervene within a system, although, 'I alone

cannot change the world, I can cast a stone across the waters to create many ripples (Mother Teresa). The potential to change or influence a system may appear more daunting and may be contrary to the Eurocentric and individualistic origins of the profession; but clinical psychology does have a role to not only formulate within clinical practice but to research and intervene to facilitate change beyond the doors of its service.

Community psychology reflects these ideas, as it focuses on the context of people's lives and social causes of distress, acknowledging and influencing change surrounding disempowerment, oppression and inequality (Orford, 2008). Social justice is a core value within the field, with other core principles including empowerment (*a process where individuals, communities and organisations develop mastery over issues that concern them*; Rappaport, 1987), and liberation (concerned with the understanding and awareness of the social issues, with action towards changing these circumstances; Orford, 2008). Therefore this approach, promotes prevention, support and resilience, while acknowledging issues of power and engaging in action to tackle this (Bostock & Diamond, 2004). Interventions are motivated towards community action to change sources of distress in society, strengthening individuals' and communities' existing resources and strengths, and supporting and empowering marginalised individuals (Orford, 2008; Rappaport & Seidman, 2000).

In terms of urbanicity, how do interventions facilitate social ties and influence system structures (e.g. community, services, society). One example that comes to mind, is The Trailblazers Project (Byrne et al., 2011), aimed to improve the acceptability and accessibility of talking therapy within African and Caribbean men, using workshops on the Tree of Life (Ncube, 2006). The community connected with the idea of a piece of work where strength was central (especially due to historical

negative experiences within the NHS) and broader cultural, social and political subjects were addressed (Byrne et al., 2011). The members of Trailblazers then became very vocal in the benefits of the Tree of Life, with this narrative approach then embraced as a useful option across wards and community teams. Additional examples include, The Alchemy Project, a dance-led pilot intervention within EIS, which was highly valued by participants and the future aims are to create an integrated approach to recovery within EIS (Gavaghan, 2015); and the Bridge Project set up by Sue Holland as a prevention strategy to reduce depression in women on a London estate and to empower them to enlist change within their communities (Totton, 2006). These projects all encompass a space for connection with communities, shared learning for all those involved, the identification and utilization of strengths and the facilitation of the voice, of marginalized groups, to be heard. Therefore, there is a partnership between a variety of services, service-users and community organisations, to really listen to the needs of our communities to develop relevant beneficial initiatives.

Another important element within community psychology is linking the values of social justice, which may translate into a profession being involved in activism and having a responsibility in improving the visibility and influence of clinical psychology in wider contexts e.g. political and policy arenas. For instance, the Psychologists Against Austerity campaign, *'mobilizes psychologists to speak out on political practices whose impacts are to dehumanise, exclude and damage both vulnerable people and those made vulnerable by austerity'*

(<https://psychagainstausterity.wordpress.com/>). A final role I see for psychologists is the action research, assessing these projects or community-led programmes, sharing the research skills we have learnt throughout training, to co-develop, evaluate and support initiatives important to communities and individuals we work with. Also psychologists contributing to new approaches, e.g. a systems-perspective

to evaluate and synthesize information, which assesses the impact of interventions in a variety of settings and the 'dynamic properties' within each environment (person-time-place) that may change relationships, activities and resources (Petticrew, 2015; Hawe et al., 2009). My personal values connect with the community psychology approach, but also as a profession I believe we have a public and professional responsibility to move beyond formulating wider context within clinical services, to using our scientist-practitioner discipline to work in partnership with communities, to cultivate and evaluate interventions, give-away and develop psychological knowledge and participate in social change within wider arenas.

Conclusion

This critical appraisal outlined three themes, which arose throughout the completion of the thesis, which covered clinical practise, research, wider societal issues and my personal reflections on the post-qualification journey ahead. The process of the thesis highlighted the cyclical relationship between clinical and research practices, in both informing and progressing the field of clinical psychology, and my day-to-day practice. The complexities of operationalizing and identifying what constitutes the risk of urbanicity, as well as putative interactions, emphasised the need for the profession to continue to move towards developing procedures to assess complex social processes and causal pathways. This research also indicated the inequality and disempowerment that co-exist within this urbanicity risk, and made me reflect on not only formulating the influence of wider contexts within the clinical room but more often within research. Considering the possible message being given when not acknowledging any wider influences an individual deems important, made me think differently about how research is potentially conveyed, but also the influence of clinical psychology in various systems. The discipline of a scientist-practitioner is not only inward, to the understanding of developmental psychopathology, but also

outward, with the profession being visible within wider contexts we reside in, that may also foster vulnerability and disempowerment of individuals we work with.

This appraisal outlined the themes/benefits of working with the individual and internal processes, but also the external, effecting change within wider systems, whether that is the NHS, the communities we work in or political and societal arenas. For me, it would involve being active in community initiatives, participating in wider societal issues, but also attempting to influence change within systems closer to the workplace; for instance, fostering a strong research ethos within a clinical service and facilitating service-user voices to be heard. It has made links between my professional, personal and political ideas and the balance of values, new challenges and interests in the journey ahead as a clinical psychologist. In the spirit of Solution Focused Therapy, what I take away is:

Act as if what you do makes a difference. It does. (William James)

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Appendix

Appendix 1. Anchoring points to help with coding of the quality rating tool

Scoring method: Score '2' if the study meets all the applicable criteria (full); Score '1' if the study meets only some of the criteria (partial); Score '0' if the study does not meet any of the criteria or unable to assess presence of criteria; N/A if criteria not applicable to the study.

Quality rating criteria	Anchoring points to aid QRT scoring	Score
A. Is the study design evident and appropriate for assessing gender differences in childhood abuse and psychosis?	<ul style="list-style-type: none"> • Design can assess differences in gender in child abuse relating to psychosis populations. • Design described • Follow-up appropriate (if applicable) 	
B. Is the method of subject/comparison selection OR source of information/variables described and appropriate?	<ul style="list-style-type: none"> • Recruitment described and appropriate/reliable system for selecting a representative sample of the defined populations (or reference to another study for clear details). • Clear definition of population -exclusion and exclusion criteria defined. • Account of potential selection biases (e.g. method to account for bias or report of possible bias) • Appropriate selection of controls (if applicable)- source and method of matching or random sampling. 	
C. Is the sample size appropriate?	<ul style="list-style-type: none"> • Appropriate sample size depending on design and analysis (e.g. power calculation, reasonable size between groups) 	
D. Are the subject/ comparison group characteristics sufficiently described?	<ul style="list-style-type: none"> • Characteristics of sample described sufficiently (including number, gender and age distribution other demographics) • Statistical comparison on general group characteristics. • Drop-out/non-response described and methods to compensate (if applicable) 	
E. Are possible confounding variables controlled for (if applicable)?	<ul style="list-style-type: none"> • Possible confounders described and controlled for if applicable 	
F. Is the outcome measure used for psychosis or psychotic-like experiences, well defined and robust to measurement or misclassification bias?	<ul style="list-style-type: none"> • A specific measure of psychosis or psychotic-like experiences (i.e. excludes other related constructs or diagnosis) • Validity and Reliability: validated measure, accurate measurement with trained clinicians/staff where appropriate; reliably tested assessment, comprehensive, corroborating information used) • Include blinding where feasible 	
G. Is the exposure measure used for childhood interpersonal adversity, well defined and robust to measurement or misclassification bias? Is it a valid and reliable?	<ul style="list-style-type: none"> • Validity, Reliability and Method used accounting for any bias: abuse types well defined and as objective as possible; not too restrictive or over-inclusive; If assessment is part of another more general measure/ interview is it valid/comprehensive; reliably tested assessment, corroborating information used, trained clinicians/staff where appropriate) 	
H. Is the gender difference results described and analysed?	<ul style="list-style-type: none"> • There is a clear analysis description and report of data on childhood abuse in the psychosis/PLE population by gender. • There is a statistical analysis and report of output for gender differences in childhood abuse in the in the psychosis/PLE population (e.g. group comparison of rate of reporting, interaction or stratified analysis by gender). • Do they report information to interpret result precision (e.g. range in CI in OR, size of p-value, missing data) 	

Note. QRT, Quality Rating Tool, PLE, psychotic-like experiences

Information and Consent Form (not for data entry)

You have been asked to take part in a study being conducted in the South London and Maudsley NHS Trust. Before you decide whether to enter the study, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information and ask any questions if something is not clear or you wish to know more.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

What are the aims of the study?

In our research project we are interested in identifying what the main risk factors that predispose to psychosis are. In particular, we want to know whether there are any genes that increase the risk of developing a psychotic disorder, either alone or by interacting with environmental factors such as stress, cannabis, and infections. Part of the reason why some people become ill may lay in genetic differences between people, in the same way that we are different in the colour of our eyes, hair etc. To achieve this, we will compare the genetic make-up of people with a diagnosis of psychosis with the make-up of people with similar characteristics but no history of mental health problems.

We also aim to establish whether some genes might influence the course of the illness and response to medication. Some patients experience an improvement of their psychiatric symptoms when they are treated with medications, whereas others do not do so well and/or experience severe side-effects. Therefore we aim to look at how genes can influence individual differences in response to drug treatment so that we may be able to choose better drugs for each person. The type of genetic analysis that we carry out is only for research purposes and does not at present produce clinically relevant results.

Finally, an additional aim of the study is to understand how the social environment may contribute to the onset of illness and the illness experience.

Why are we asking for your help?

You have been invited to take part in this study because of the nature of the symptoms that you appear to have been experiencing. During the course of the study approximately 1000 people who have had symptoms like yours will be asked to take part.

Note that a patient does not have to be involved in the GAP project research and, if they decide not to take part, it will not affect their current or future medical care in any way.

What will we ask of you if you take part in the study?

For this project we will ask from you a small sample of blood, about 20 mL (a few tablespoons full) or cheek swab and saliva samples for metabolic and genetic analysis. We may also use your blood and saliva sample to:

- 1) Measure the level of hormones and proteins contained in the blood serum and in the saliva.
- 2) Look at the expression of some genes of interest in the white cells contained in the blood.

A medically trained researcher will take the blood sample using disposable sterile equipment. It will only take few minutes as for any routine blood sample. If you are unable or unwilling to give a blood sample it is also possible to perform genetic analysis from cheek

swab samples, a simple procedure that (we can show you the kit and illustrate the procedure) collects dead cells present in your saliva and in your mouth. From the cheek swab sample we cannot measure level of medication or look at expression of genes, we can only extract a small amount of DNA. Therefore we prefer to ask for a blood sample to guarantee a better quality of our results and make the most out of your generous help.

A researcher will demonstrate how to collect the saliva sample and will provide you with the tubes required. The level of some proteins contained in the saliva can give us an indication of differences in the level of stress experienced by healthy volunteers and people suffering from mental illnesses.

We will also ask for some of your time to collect clinical and socio-demographic information using standardised research instruments: diagnostic interview, symptoms rating scale, socio-demographic interview and neuropsychological tests. We may also ask you to participate in an interview asking about your own perspectives on your social environment and your health condition.

If you have already taken part in other research projects at the Institute of Psychiatry, London that involved some of the assessment we are interested in, we will not ask you to undergo them again but we request your permission to use the existing data.

Some people within the study will be invited to undergo an MRI scan of the head and of another region of the body (the adrenal gland, a small gland above the kidney). They will be presented with separate information and consent forms for this procedure.

The sample collection and the clinical assessment will require approximately 3 hours of your time. Moreover we would like to contact you again for follow up (up to 24 months) to repeat the above assessments to investigate changes over time. We will also reimburse any travel expense related to your participation into the study.

We will also ask for your consent to contact your GP, mother (or father) and a sibling. This is 1) to collect information from your GP records and mother about events that may have occurred very early in your life, such as complications during pregnancy and neonatal infections, 2) to conduct some of the same assessments with your sibling that we have conducted with you, and 3) to ask your sibling similar questions that we have asked you about the environment in which you both grew up and experiences you may have had in childhood. We will only contact your GP and/or relative(s) with your explicit consent and we will not disclose any information we have collected from you to them. If you agree for us to contact your mother (or father) and/or a sibling, we will only proceed to interview them if they provide consent.

What are the risks?

The risks involved are those of ordinary blood tests such as small pain and occasionally a small bruise around the area from where the sample has been taken. There is no risk involved in the collection of saliva.

Is Confidentiality guaranteed?

All personal information about you is regarded as strictly confidential; only researchers belonging to the study team, and not external collaborators, know which sample belongs to whom. All the information about you will be coded; you will not be identifiable in any research outcome.

- 1) The blood samples first and the DNA samples after extraction will be stored in the Institute of Psychiatry secured laboratory until reporting is complete.
- 2) The samples will be coded using bar codes (numbers and letters not referring to your name or date of birth) that will be entered on a secure computerized data base.
- 3) The clinical information collected on the sample will be securely held in the Institute of Psychiatry building.

- 4) Nothing that you have told us will be mentioned to any relative you might give us permission to contact.

The access to the samples and the related information will be restricted to the researchers involved in the study. In case of commercial collaborations only the coded data will be shared, therefore no researcher external to the study team will ever have access to personal data concerning participants.

Any future work will pursue aims related to the topic of this project and any extension of the project beyond 5 years, will be subject to review by a research ethics committee. You are free to withdraw from this study at any point without giving a reason by contacting the researcher whose details are at bottom of the consent form. Withdrawal will not affect any of the care and treatment you receive.

What are the benefits for you of taking part?

This is a research project, looking at comparing a group of healthy volunteers with people experiencing their first psychotic episode. As mentioned before, this study will not produce individual test results for any of the data collected. Therefore we cannot offer direct benefits for you. We will be able to provide all participants with a general summary of our research, when the project is complete, through a project newsletter. Our research study is also described on the Institute of Psychiatry general website (www.iop.kcl.ac.uk), under the Department of Psychosis Studies section.

Who is funding this project?

This study is funded by the The Maudsley Charitable Fund, the Department of Health, **the Wellcome Trust and the European Union**. Thank you very much for your time and once again please ask for more information on both the project and/or your illness/symptoms if it is still unclear.

Contact details for research team:

Dr Marta Di Forti

Institute of Psychiatry

Tel 020 7848 5352

e-mail: marta.diforti@kcl.ac.uk

CONSENT FORM

If you have come to the decision to enter the study after carefully considering the information provided, please read and sign this form.

TITLE OF PROJECT: GENETICS AND PSYCHIATRIC ILLNESS (GAP)

Researcher: Dr Marta Di Forti, Institute of Psychiatry

- | | | |
|--|---------------------------------|--------------------------------|
| 1) I have read the information sheet and I have been given a copy. I was given the opportunity to ask questions. I understand why the research is being done and the risks involved. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 2) I agree to give a sample of blood/cheek swab and saliva samples for research in the above project. I understand how the sample will be collected, that giving the sample is voluntary and that I am free to withdraw at any time without giving a reason, and without my medical treatment or legal rights being affected. I understand that I will be contacted in the future to repeat part of the assessment. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 3) I understand that research using the sample I give will involve genetic analysis aimed at understanding the role of genes in disease and response to drugs, that the data produced are for research rather than clinical purposes, and that these results will have no implications for me personally. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 4) I understand I will not receive any 'test' results from this study , because the assessment I will undergo, does not produce clinically relevant information but just research data. The project newsletter will describe the general importance of any research results obtained. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 5) I give permission for my previous research records to be looked at, and information from them to be analysed in strict confidence by responsible professional staff from the research team. Researchers external to the study team, collaborating in the project (including commercial collaborations) will only access my coded data. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 6) I agree that the samples I have given and the information gathered about me can be examined and stored until reporting is complete at the Institute of Psychiatry. I understand that future authorised research may be performed by researchers other than those who conducted the first project, including researchers from commercial organisations. To guarantee confidentiality, I agree that researchers external to the study team, including those from commercial collaborators, will only have access to coded data and not to personal details. Any future research will only pursue aims related to the topic of this project, and any extension of the project will be subjected to review by a research ethics committee. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 7) I consent to the input of coded data obtained from my blood sample and from the information gathered about me into a computer, to be used for statistical analysis and research. I understand I have the right to request, via the study co-ordinator, to review data concerning me, and to have such data modified if inaccurate, or deleted. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 8) I consent to participate in a digitally-recorded interview about my own perspectives on my health condition and on my social experiences. I understand that this interview would be recorded to ensure that my own views are adequately represented. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 9) I understand I will not benefit financially if this research leads to the development of a new treatment of medical test but my travel expenses will be reimbursed. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |
| 10) I give permission for my GP records to be looked at. | Yes
<input type="checkbox"/> | No
<input type="checkbox"/> |

11) I agree to my mother being approached to participate in this study.

Yes

No

Contact details:

Name

Address

.....

Phone Number

12) I agree to a sibling being approached to participate in this study.

Yes

No

Contact details:

Name

Address

.....

Phone Number

.....

Name of Subject

Date

Signature

.....

Name of Researcher

Date

Signature

Would you like to be sent further information about the project in our newsletter?

Yes

No

Contact details for research team:

Dr Marta Di Forti

Institute of Psychiatry

Tel 020 7848 5352

e-mail: marta.diforti@kcl.ac.uk

Appendix 3. Psychosis screening questionnaire

Subject number: 2EU02. __ __ __ __	Date of Birth __ __ __ __ __ __
Time interval: Lifetime	
Interviewer:	Date __ __ __ __ __ __

Code: No = 0 Unsure = 1 Yes = 2

In this survey we have to ask about a whole range of experiences. Some of these experiences are quite rare. However, I would be very much obliged if you would bear with us and answer the questions I am going to ask you now.

- Q1. Over the past year, have there been times when you felt very happy indeed without a break for days on end?
- (a) Was there an obvious reason for this?
- (b) Did your relatives or friends think it was strange or complain about it?
- Q2. Over the past year, have you ever felt that your thoughts were directly interfered with or controlled by some outside force or person?
- (a) Did this come about in a way that many people would find hard to believe, for instance through telepathy?
- Q3. Over the past year, have there been times when you felt that

...

people were against you?

(a) Have there been times when you felt that people were deliberately acting to harm you or your interests?

(b) Have there been times when you felt that a group of people was plotting to cause you serious harm or injury?

Q4. Over the past year have there been times when you felt that something strange was going on?

(a) Did you feel it was so strange that people would find it very hard to believe?

Q5. Over the past year, have there been times when you heard or saw things that other people couldn't

(a) Did you at any time hear voices saying quite a few words or sentences when there was no-one around that might account for it?

Q6. Have you ever received treatment for any psychiatric or psychological problem?

.....

Appendix 4. *Social environment assessment tool (SEAT)*

Removed due to the paper on the scoring and validation of the measure being in preparation and the public availability of this thesis prior to this paper publication.

Appendix 5. *SEAT scoring guidelines (Kirkbride, in preparation)*

Removed due to the paper on the scoring and validation of the measure being in preparation and the public availability of this thesis prior to this paper publication.

Appendix 6. Table of case-control group comparisons for the SEAT and psychological variables using continuous data

Association between psychological variables (anxiety, JTC and schematic beliefs) and case-control status for the continuous data

	Controls	Cases	t	df	p
	Mean (sd)	Mean (sd)			
SEAT (n= 392)	-0.1 (2.6)	0.2 (2.8)	-1.03	390	0.302
Positive Other (n= 382)	12.7 (4.9)	11.3 (5.6)	2.53	380	0.012*

	Controls	Cases	U	df	p
	Mean (sd)	Mean (sd)			
Anxiety (n= 386)	4.7 (4.5)	8.7 (6.8)	-5.72	-	<0.001*
JTC (n= 392)	5.6 (4.6)	3.4 (3.3)	-5.08	-	<0.001*
Negative Self (n=387)	1.2 (2.3)	3.5 (4.8)	-4.57	-	<0.001*
Positive Self (n= 379)	13.4 (5.1)	12.5 (6.7)	0.22	-	0.828
Negative Other (n= 387)	3.9 (5.3)	7.4 (6.6)	-4.82	-	<0.001*

Note. sd, standard deviation; df, degrees of freedom. The n for each variable differs due to missing data relating to those measures (total sample n=392). (Percentages may not add up due to rounding)
*Significant at p<0.05

Appendix 7. Table of associations between SEAT and case-control status, with all confounder combinations

Association between SEAT and case-control status, with varying combinations of confounders.

		Adjusted OR	95% CI	<i>p</i>
Adjusted for social class				
	SEAT	1.74	1.06-2.86	0.028*
Adjusted for gender				
	SEAT	1.36	0.89-2.07	0.157
Adjusted for age				
	SEAT	1.43	0.92-2.21	0.110
Adjusted for ethnicity				
	SEAT	1.32	0.85-2.023	0.212
Adjusted for gender & age				
	SEAT	1.41	0.09-2.18	0.128
Adjusted for gender & ethnicity				
	SEAT	1.32	0.85-2.03	0.213
Adjusted for gender & social class				
	SEAT	1.73	1.05-2.84	0.031
Adjusted for age & ethnicity				
	SEAT	1.43	0.91-2.23	0.119
Adjusted for age & social class				
	SEAT	1.77	1.07-2.94	0.026*
Adjusted for ethnicity & social class				
	SEAT	1.67	1.02-2.76	0.043*
Adjusted for gender, age & social class				
	SEAT	1.75	1.05-2.90	0.031*
Adjusted for age, ethnicity & social class				
	SEAT	1.73	1.04-2.88	0.034*
Adjusted for gender, ethnicity & social class				
	SEAT	1.66	1.00-2.74	0.048*

Note. OR, Odds ratio; CI, Confidence Interval.

*Significant at $p=0.05$

Appendix 8. Mediation results table (non-significant results)

Mediation results: total, direct and indirect effects of SEAT, anxiety, JTC and schematic beliefs on case-control status

Outcome: case control status

	Unadjusted			Adjusted ^a		
	Standardized Coefficient	(Bias Corrected 95% CI)	% of total effect mediated	Standardized Coefficient	(Bias Corrected 95% CI)	% of total effect mediated
SEAT (n=386)						
Direct Effect	0.113	(-0.00 – 0.23)		0.122	(-0.01 – 0.25)	
Indirect Effect - Anxiety	-0.025	(-0.07 – 0.01)	28.7	-0.027	(-0.06 – 0.01)	28.5
Total Effect	0.088	(-0.05 – 0.19)		0.095	(-0.04 – 0.22)	
SEAT (n=392)						
Direct Effect	0.082	(-0.03 – 0.20)		0.091	(-0.01 – 0.21)	
Indirect Effect - JTC	0.004	(-0.03 – 0.04)	4.2	-0.002	(-0.03 – 0.03)	2.8
Total Effect	0.086	(-0.01 – 0.22)		0.089	(-0.01 – 0.23)	
SEAT (n=387)						
Direct Effect	0.095	(-0.04 – 0.18)		0.098	(-0.05 – 0.19)	
Indirect Effect – Negative Self	-0.002	(-0.03 – 0.03)	2.2	-0.002	(-0.03 – 0.03)	2.4
Total Effect	0.093	(-0.40 – 0.19)		0.096	(-0.04 – 0.18)	

Appendix 8 continued

Outcome: case control status

	Unadjusted			Adjusted ^a		
	Coefficient	(Bias Corrected 95% CI)	% of total effect mediated	Coefficient	(Bias Corrected 95% CI)	% of total effect mediated
SEAT (n=379)						
Direct Effect	0.100	(-0.04 – 0.20)		0.105	(-0.02 – 0.24)	
Indirect Effect - Positive Self	-0.003	(-0.02 – 0.01)	3.6	-0.004	(-0.03 – 0.12)	3.7
Total Effect	0.097	(-0.05 – 0.20)		0.102	(-0.04 – 0.22)	
SEAT (n=387)						
Direct Effect	0.109	(-0.01 – 0.22)		0.121	(-0.01 – 0.23)	
Indirect Effect -Negative Other	-0.009	(-0.04 – 0.02)	8.7	-0.011	(-0.04 – 0.01)	10.1
Total Effect	0.100	(-0.03 – 0.21)		0.110	(-0.02 – 0.22)	

Note. OR, Odds ratio; CI, Confidence Interval. The n for each variable differs due to missing data relating to those measures (total sample n=392).

^a Adjusted for age, gender, ethnicity and social class

*Significant at p=0.05

Appendix 9. Moderation results table (non-significant results)

Likelihood ratio tests assessing models with and without interaction terms (moderation) between SEAT and each psychological variable (anxiety, JTC, schematic beliefs) on case-control status

	Unadjusted			Adjusted ^a		
	<i>x</i> ²	df	<i>p</i>	<i>x</i> ²	df	<i>p</i>
SEAT* Anxiety (n=386)	1.51	1	0.220	2.90	1	0.088
SEAT* JTC (n=392)	0.17	1	0.682	0.02	1	0.885
SEAT* Negative Self (n=387)	0.31	1	0.576	1.25	1	0.263
SEAT* Positive Self (n=379)	0.84	1	0.359	0.40	1	0.527
SEAT* Negative Other (n=387)	0.16	1	0.689	0.03	1	0.853
SEAT* Positive Other (n=382)	0.08	1	0.777	0.96	1	0.326

Note. df, degrees of freedom. The n for each variable differs due to missing data relating to those measures (total sample n=392).

^a Models were adjusted for age, gender, ethnicity and social class

*Significant at p=0.05.