

Triangulating epidemiological and data science approaches to evaluate the impact of public health interventions on the prevention of type 2 diabetes.

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Declaration

I, Vincent Nguyen, 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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Abstract

Background: The NHS has deployed the NHS Health Check (NHS HC) and the Diabetes Prevention Programme (NHSDPP) to reduce rates of preventable diseases such as type 2 diabetes (T2DM) without randomised controlled trial evidence. Previous observational investigations were limited by missing data, confounding, selection bias and more. I aimed to reduce these limitations when using observational data to evaluate the effectiveness of the programmes on the incidence of T2DM and to complement different analytical techniques to address these issues.

Methods: Using linked electronic health records, I triangulated a range of study designs to investigate the impact of the NHS HC and NHSDPP on preventing T2DM. Study designs included: systematic reviews, interrupted time series, target trial emulation, and data science approaches.

Results: Systematic reviews suggest that the NHS HC detects the same or higher rates of T2DM and is attributable to detection of undiagnosed cases in attendees. Interrupted time series failed to detect population level impacts of the NHS HC, likely attributable to limited uptake. Trial emulation found that the NHSDPP reduces individual incidence of recorded T2DM in high-risk adult with a 59% [54%-62%] risk reduction at 3 years and that the NHS HC reduced the incidence of recorded T2DM by 54% [95%CI 53% - 55%] at 10-years. Data Science approaches produced potential targetable subgroups to improve effectiveness based upon ethnicity, blood glucose measures and body mass index. Triangulation suggests that whilst the NHS HC/NHSDPP can prevent individual cases of recorded T2DM, (non-targeted) uptake of the NHS HC could lead to failures of detecting population level impacts.

Conclusion: Using multiple approaches to understand the impact of public health interventions on the incidence of recorded T2DM allowed me to triangulate, complement and synergise methods to provide a balanced

assessment of the likely impact of the NHSHC/DPP on the incidence of T2DM and reduced uncertainties in any isolated study design.

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Impact Statement

The impact of this PhD is multifaceted as it demonstrates how the careful selection of epidemiological methods can reduce biases when using observational data to estimate a randomised controlled trial to answer important clinical and public health questions.

The public health problem that my PhD investigates is the evaluation of interventions that aim to reduce the risk of developing preventable non-communicable diseases such as type 2 diabetes. If effective in preventing the incidence of type 2 diabetes, the NHS Health Check and Diabetes Prevention Programme can improve the quality of life for nearly 1 million people in England by 2030 through the prevention of further disease progressions such as retinopathy, chronic kidney disease, diabetes-related amputation, and cardiovascular complications. Financially, type 2 diabetes costs £21.8 billion yearly in England, which comprises around 10% of the NHS budget; preventing type 2 diabetes could also reduce the financial cost of further associated comorbidities, particularly cardiovascular disease, the world's number one killer.

In addition to the impact on the quality of life and finances, my PhD also helps policymakers target and adapt the NHS Health Check and NHS Diabetes Prevention Programme to be more inclusive and effective. Such information is imperative for reducing healthcare inequities, particularly in ethnic minority and deprived populations who are disproportionately experiencing non-communicable diseases such as chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes when compared to less deprived populations.

Policymakers are unlikely to fund further randomised controlled trials to investigate the preventive impact of the NHS Health Check and NHS Diabetes Prevention Programme due to the human, time and financial cost

and their existing widespread use. By using administrative primary, secondary and mortality datasets, which are shown to be representative of the English population, it is possible to emulate trials with a large number of participants with long follow-up periods. Careful study design and cross-referencing of cohort results against externally validated datasets and studies, allows policymakers to reduce the uncertainty in using observational data to evaluate public health interventions.

By undertaking the evaluations of the NHS Health Check and NHS Diabetes Prevention Programme using triangulation, this PhD identifies where “conflicting” results arise and postulates the causes (see Chapter 8 for further discussion), thereby aiding policymakers in making appropriate decisions surrounding these programmes. The analyses conducted in my thesis have already received stakeholder interest from Public Health England, the Office for Health Improvement and Disparities, the NHS and the National Institute for Health and Care Excellence, and as a result has begun to demonstrate its public health impact by providing evidence to the Diabetes lead at NHS Improvement.

Furthermore, my PhD also introduces a variety of methods to be used in epidemiological studies to strengthen their findings; some of which have already been applied by other researchers.

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Abbreviations

Abbreviation	Full explanation
95% CI	95% Confidence Interval
aHR	Adjusted Hazard Ratio
BMI	Body Mass Index
CALIBER	Cardiovascular disease research using linked bespoke studies and electronic health records
CKD	Chronic Kidney Disease
CONSORT	Consolidated Standards of Reporting Trials
Cox PH	Cox Proportional Hazards
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DiD	Difference in Difference
DPP	Diabetes Prevention Programme
eGFR	estimated Glomerular Filtration Rate
FGP	Fasting Plasma Glucose

Abbreviation	Full explanation
FERITS	Framework for Enhanced Reporting of Interrupted Time Series
GP	General Practitioner
GPRD	General Practice Research Database
HbA1c	Haemoglobin A1C
HDL	High-density lipoprotein
HES	Hospital Episode Statistics
HR	Hazard Ratio
HT	Hypertension
ICD10	International Classification of Diseases version 10
ICER	Incremental Cost-Effectiveness Ratio
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
IRR	Incidence Rate Ratio
ISAC	Independent Scientific Advisory Committee
ITS	Interrupted Time Series
ITT	Intention to Treat

Abbreviation	Full explanation
KG	Kilogramme
KNN	K's Nearest Neighbour
LDL	Low-density lipoprotein
MAR	Missing at Random
MCAR	Missing Completely at Random
MICE	Multiple Imputation using Chained Equations
MICE-RF	Multiple Imputation using Chained Equations using Random Forests
mmol/mol	millimoles per mole
MNAR	Missing not at random
NA	Not applicable/available
NHS	National Health Service
NHSDPP	National Health Service Diabetes Prevention Programme
NHSHC	National Health Service Health Check
NICE	National Institute for Health and Care Excellence
ONS	Office of National Statistics
OR	Odds Ratio

Abbreviation	Full explanation
PhD	Philosophiae Doctor
PHE	Public Health England
PICO(T)	Population, Intervention, Comparison, Outcome (Time)
QALY	Quality Adjusted Life Year
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOF	Quality Outcome Framework
RECORD	Reporting of studies Conducted using Observational Routinely collected Data
RR	Relative Risk
SBP	Systolic Blood Pressure
SMOTE	Synthetic Minority Oversampling Technique
SNOMED-CT	Systematized Nomenclature of Medicine Clinical Terminology
T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
UCL	University College, (University of) London
UK	United Kingdom of Great Britain and Northern Ireland

Abbreviation	Full explanation
USA	United States of America
UTS	Up-to-standard

Executive Summary

Launched in 2009, the NHS Health Check is a general practice-driven public health intervention aimed at identifying patients between 40 and 74 who are at a high risk of developing or have a previous undiagnosed case of: heart disease, hypertension, kidney disease, stroke, and type 2 diabetes. The NHS Health Check achieves this by assessing measures such as blood pressure, blood glucose, and cardiovascular event risk (QRisk2) as well as food, alcohol, and tobacco intake. The NHS Health Check aims to help high-risk patients reduce their risk of developing heart disease, hypertension, kidney disease, stroke, and type 2 diabetes by using preventive measures such as lifestyle advice and referrals to specialist prevention programmes such as NHS Smoking cessation services or the NHS Diabetes Prevention Programme. However, there is no definitive evaluation of the NHS Health Check's effectiveness in preventing these diseases, with studies of similar programmes suggesting a negligible impact on healthcare outcomes. Given the current lack of randomised controlled trial evidence evaluating the NHS Health Check, and the associated cost of operating the NHS Health Check, more research is needed. Whilst research has contributed information on the uptake of the NHS Health Check, such studies have not evaluated the long-term incidence of healthcare outcomes between participants and non-participants of the NHS Health Check. A similar programme, the NHS Diabetes Prevention Programme, was also introduced without a randomised controlled trial. Therefore, this PhD aims to strengthen the evidence base by analysing the NHS Health Check and NHS Diabetes Prevention Programme using robust and complementary methods using observational data designed to generate a better understanding of the effect of these programmes on preventing outcomes such as the incidence of type 2 diabetes.

The first chapter of my PhD introduces in deeper detail the public health challenges that are the burden of heart disease, hypertension, kidney

disease, stroke, and type 2 diabetes. I then introduce the interventions aimed at tackling these problems, namely the NHS Health Check and the NHS Diabetes Prevention Programme as well as the arguments for and against their effectiveness. In brief, there is limited systematic review evidence that the previous implementations of a health checks do not produce a detectable “effect on clinical events or other measures of morbidity” (Krogsbøll et al., 2012) , however, such conclusions were based upon older implementations of health checks that do not provide access to “modern” interventions such as statins or diabetes prevention programmes. Recent studies which have analysed the NHS Health Check on hard outcomes (detection of heart disease, hypertension, kidney disease, stroke, and type 2 diabetes) have struggled to disaggregate between detection of previously undiagnosed cases and the preventative effect of the NHS Health Check. Other challenges of studies that evaluated the NHS Health Check included missing data and an imbalance between baseline covariate amongst attendees and non-attendees of the NHS Health Check. In terms of the NHS Diabetes Prevention Programme, due to the recent phased deployment, whilst there is promising data on its ability to promote weight loss, there is limited evidence on its ability to prevent the development of type 2 diabetes.

The second chapter introduces a systematic review using PubMed and Embase via OVID, which aims to understand current evaluations of the NHS Health Check on measurable estimates of healthcare outcomes. I found 19 studies, primarily consisting of observational studies, with 13 analysing cardiovascular outcomes, four analysing diabetic outcomes, three analysing strokes, four analysing chronic kidney disease and six analysing hypertension. This overall evidence suggests that the NHS Health Check reduces the cardiovascular event risk score compared to no NHS Health Check. The systematic review also suggested that the NHS Health Check can identify previously undiagnosed prevalent cases of heart disease, hypertension, chronic kidney disease, stroke, and type 2 diabetes at higher

rates compared to no NHS Health Check. Whilst detecting prevalent cases of the aforementioned diseases can prevent disease progression, it biases evaluations that aim to understand the prevention of incident cases due to selection bias (often dealt with in a randomised controlled trial using an eligibility criteria). Therefore, to expand the evidence base, studies need to differentiate between inviting those who are eligible on record and then checking their eligibility with a screen that includes a strict inclusion and exclusion criteria. The analysis should then compare matched cohorts to establish the preventative effect of the NHS Health Check on the incidence of disease akin to a randomised controlled trial.

My third chapter documents an interrupted time series study design which aims to estimate the population level impact of the NHS Health Check. The aim of this analysis was to evaluate whether the introduction of the NHS Health Check has reduced national hospital admissions of heart disease, diabetes, and stroke. I chose this method as it evaluates national level interventions on outcomes in a defined population, and interrupted time series are suitable for assessing interventions introduced at a single time point with a background rate of change. I evaluated a total of 6,665,709 hospital admissions between 2003 and 2017 for heart disease, stroke and diabetes with an interruption in 2009 (the introduction of the NHS Health Check). Using Hospital Episode Statistics, there was insufficient evidence to conclude that whether the NHS Health Check had a significant population level impact is effective or not at reducing admission rates for heart disease, stroke, and diabetes. This was partially due to the poor-quality data with abrupt temporal changes likely caused by clinical coding practises modifications introduced in 2012. Low uptake and eligibility criteria may also have limited population impact.

My fourth chapter documents a systematic review to identify code lists that can be used to identify NHS Health Check and NHS Diabetes Prevention

Programme participants in primary care records and phenotyping their cardiovascular disease, hypertension, stroke, and type 2 diabetes outcomes. This work introduces methods that overcome problems in establishing clinical code lists in previous studies; they are often conducted by two individuals, a clinician and clinical coder, which can lead to variation in identifying healthcare outcomes between studies. Overcoming the limitation of having two individuals conducting the study was achieved by creating an evidence-based code list: a list of clinical codes, and a link to all the studies which reference them. This allowed me to understand which clinical codes are more prevalent in the scientific literature. This fourth chapter also enables further chapters to appropriately identify cohorts and outcomes in further chapters to conduct retrospective observational cohort studies. In total, I found 167 articles that produced 9215 READ (non-unique) codes relevant to the NHS Health Check, with 4018 codes describing heart disease, 2551 codes describing hypertension, 951 codes describing stroke, 1991 codes describing type 2 diabetes and 412 codes describing the NHS Health Check. I found 5 READ codes to identify the NHS Diabetes Prevention Programme.

My fifth chapter used the previously established clinical codes and phenotyping algorithms identified in chapter four to conduct a retrospective observational cohort study to evaluate the impact of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes using primary care datasets linked to secondary care and mortality records. As there are comparable trials worldwide evaluating similar programmes to the NHS Diabetes Prevention Programme, I conducted trial emulation using these studies as a framework for the target trial which includes strict inclusion and exclusion criteria. External datasets have also validated the NHS Diabetes Prevention Programme cohort and their socio-demographic breakdown; therefore, I compared my imputed sociodemographic and clinical covariates with the externally validated dataset to estimate the confidence in the methods used in this PhD. The primary methods in this analysis were multiple

imputation using chained equations, followed by propensity score matching and Cox proportional hazards regression. For each participant who were eligible, I calculated an estimated “entry” time; for NHS Diabetes Prevention Programme individuals, this was the earliest date of their NHS Diabetes Prevention Programme activity (including rejecting the programme), and for non-participants, I used regression analysis to estimate a plausible date when they could have been invited; this allowed individuals to have similar follow-up periods. Participants who were found to have a phenotypical recording of type 2 diabetes within 90 days of entry were excluded as this is likely a previously undiagnosed case. I identified 2,205 individuals who participated in the NHS Diabetes Prevention Programme in the Clinical Practice Research Datalink and 8820 matched controls with a similar socio-economic and clinical background. The socio-demographic background of my sample cohort was similar to that of other studies which evaluated the NHS Diabetes Prevention Programme’s population. My results indicate that NHS Diabetes Prevention Programme referrals were associated with 59% [95%CI: 56% - 59%] reduction in type 2 diabetes recorded incidence rates after adjusting for sociodemographic and clinical covariates [adjusted hazard ratio=0.41;95%CI=0.38-0.44] during the 2.5 year study period when adjusted for sociodemographic and clinical factors and are in line with randomised controlled trials evaluating similar programmes internationally which were considered by Public Health England as part of their initial investigation of diabetes prevention programmes.

My sixth chapter used the previously established clinical codes and phenotyping algorithms from chapter four to conduct a retrospective observational cohort study to evaluate the impact of the NHS Health Check on the incidence of type 2 diabetes using linked electronic health records. Without a comparable randomised controlled trial, I envisioned a target trial in a similar manner to the NHS Diabetes Prevention Programme. In this target

trial, I excluded those with a prior diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke on entry to emulate an eligibility screening process in a randomised controlled trial. For those who did not attend an NHS Health Check, I estimated their entry date using sociodemographic and geographic data and used this date to establish their eligibility. The primary methods in this analysis were multiple imputation using chained equations, followed by propensity score matching and Cox proportional hazards regression. I identified 105,382 individuals who participated in the NHS Health Check in the Clinical Practice Research Datalink and 105,382 matched controls with a similar breakdown in sociodemographic and clinical covariates. During the 10-year study period, 1.04% (95%CI: 0.98% - 1.11%) of NHS Health Check individuals developed newly recorded type 2 diabetes vs 2.06% (95%CI: 1.98% - 2.15%) of controls. My multivariable results indicate that NHS Health Check referrals were associated with a 54% [95%CI 53% to 55%] reduction in recorded type 2 diabetes incidence rates [adjusted hazard ratio= 0.46 95% CI:0.45 – 0.47] when adjusting for sociodemographic and clinical covariates.

My seventh chapter work builds on the fifth and sixth chapters by identifying weaknesses associated with using these well-established epidemiological techniques, particularly methods used in observational studies. I identified weaknesses such as the assumption of linear data, missing data, and low sample sizes. In this chapter, I aim to reduce these weaknesses by exploring complementary modern data science methods. These methods include using K-Nearest Neighbour and Random Forests for imputation missing data, Synthetic Minority Over Sampling for resampling data to avoid small sample sizes, and multivariate survival trees to better understand the sub-groups where the NHS Health Check and the NHS Diabetes Prevention Programme are a good explanatory variable on the incidence of type 2 diabetes by not assuming distributions of the data. Using K's Nearest Neighbour imputation

produced a similar result to the externally validated NHS Diabetes Prevention Programme dataset without the need for generating multiple datasets. When using the Synthetic Minority Oversampling Technique, I increased the analytical numbers of the NHS Diabetes Prevention Programme from 11,025 (2205 intervention + 8820 propensity score-matched control) to 53,575 individuals (24393 synthetically generated intervention patients + 29182 control patients). By using survival trees, I estimated that patients were less likely to have newly recorded type 2 diabetes who have a baseline HbA_{1c} higher than 44 mmol/mol or an HbA_{1c} higher than 42 mmol/mol with a BMI higher than 27.45 kg/m² if they participated in the NHS Diabetes Prevention Programme. By using survival trees, I estimated that specific subgroups of patients were more likely to benefit (i.e., less likely to have newly recorded type 2 diabetes) if they participated in the NHS Health Check. Notably, those with a baseline HbA_{1c} higher than 35 mmol/mol and a BMI higher than 25 kg/m². I also identified subgroups of patients with poorer outcomes (i.e., those most likely have newly recorded type 2 diabetes) who participated in the NHS Health Check. Notably, patients who identify as non-White (including Asian, Black or Mixed) with a baseline HbA_{1c} higher than 45 mmol/mol and BMI higher than 25 kg/m².

My eight chapter builds on all previous analyses to generate a triangulation study that aims to understand the effect of public health interventions on preventing the incidence of type 2 diabetes in English adults. In this chapter, I applied a pre-existing triangulation framework to understand any biases and the direction these biases may have on any results. Using systematic reviews (Chapter 2), I found that the NHS Health Check could underestimate the preventative impact of the NHS Health Check on the incidence of type 2 diabetes as studies did not remove detection of previously undiagnosed cases in Health Check individuals which are less likely to occur in non-Health Check individuals (that is disproportionate access to diagnosis tools). Using interrupted time series (Chapter 3), there is potential to underestimate the

impact of the NHS Health Check when compared to a randomised controlled trial due to adherence rates of the NHS Health Check and a low overall incidence rate of type 2 diabetes in “healthy” individuals. There is a risk that using propensity score matching in retrospective trial emulation studies using observational (Chapter 6) may overestimate the impact of the NHS Health Check on incidence of type 2 diabetes, however, the overestimation may not be significant when compared to an equivalent randomised controlled trial. Data science methods that build on observational data are likely to overestimate the impact of the NHS Health Check on the incidence of type 2 diabetes as they isolate the combination of patient baseline covariates where the NHS Health Check is effective in preventing type 2 diabetes. For the NHS Diabetes Prevention Programme, the use of propensity score matching could overestimate the impact on prevention of type 2 diabetes when compared to an equivalent randomised controlled trial. Using data science methods is likely to overestimate the impact of the NHS Diabetes Prevention Programme as it isolates situations where the NHS Diabetes Prevention Programme is likely to work.

My final chapter provides an overall interpretation of the PhD and future work. Overall, my results show that the NHS Health Check reduces individual risk of type 2 diabetes in those who do not have a previous chronic kidney disease, diabetes, heart disease, hypertension, or stroke at the start of follow-up. However, there is limited evidence to show that the NHS Health Check reduces rates of type 2 diabetes at the population level, perhaps due to the uptake rate of the NHS Health Check and the eligibility criteria of “healthy” individuals without recorded pre-existing non-communicable diseases. Data science methods have helped identify scenarios where the NHS Health Check is more effective and is based upon type 2 diabetes risk factors such as ethnicity, baseline blood glucose levels and body mass index. For the NHS Health Check, I suggested future work should investigate whether early detection (a part of the NHS Health Check) can reduce disease progression

(for example, diabetic foot related amputations or diabetic retinopathy), in those invited compared to those not invited. Using observational data, I have found similar short-term results for the NHS Diabetes Prevention Programme on the incidence of newly recorded type 2 diabetes when compared to randomised controlled trials from around the world and future research should concentrate on understanding whether these results are sustainable long term.

Chapter 1 - Introduction to the NHS Health Check and NHS Diabetes Prevention Programme

Abstract

Non-communicable diseases such as chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes are preventable diseases that currently have a high financial cost to the National Health Service (NHS) and often disproportionately impact deprived and ethnic minority populations.

To reduce the financial burden and close inequity gaps caused by these diseases, Public Health England and the NHS have deployed a public health intervention called the NHS Health Check in England in 2009. The NHS Health Check invites individuals between the ages of 40-74 who do not have on record a prior diagnosis of chronic kidney disease, heart disease, hypertension, stroke, or type 2 diabetes with the aim of identifying previously undiagnosed cases and to reduce the risk of developing one of the aforementioned diseases.

Currently there is limited evidence of the NHS Health Check in reducing mortality or morbidity related to chronic kidney disease, heart disease, hypertension, stroke and type 2 diabetes and previous systematic review evidence of similar programmes worldwide demonstrated limited impact on mortality and evidence of higher rates of “new detection” in morbidity when compared to no health check. Therefore, there is currently a debate on the effectiveness of the NHS Health Check in disease prevention. Despite this lack of evidence of the effectiveness of the NHS Health Check on non-communicable diseases, the NHS have also deployed the NHS Diabetes Prevention Programme which specifically aims to reduce the incidence of type 2 diabetes. Whilst similar programmes to the NHS Diabetes Prevention Programme have demonstrated promising results in the reduction in the incidence of type 2 diabetes, there is no study that specifically evaluates the

NHS Diabetes Prevention Programme on the same outcome. Therefore, the aim of my PhD is to evaluate the preventative impact of the NHS Health Check and the NHS Diabetes Prevention programme on hard morbidity outcomes such as the incidence of type 2 diabetes.

Introduction to the public health challenge

The Global Burden of Disease study has established the large disease burden attributable to high blood pressure, tobacco/alcohol consumption, poor diet and having a high body mass index (Murray and Lopez, 2013). Such attributes put individuals at a higher risk of non-communicable diseases such as cardiovascular disease (such as coronary heart disease, myocardial infarctions, stroke), chronic kidney disease, hypertension, and type 2 diabetes. The Office of National Statistics estimates that cardiovascular disease is the number one cause of death in England and Wales, with an associated financial burden of £29.1 billion to the British taxpayer (Luengo-Fernández et al., 2006). The British Heart Foundation, Britain's leading cardiovascular research charity, estimates that cardiovascular disease impacts 7.6 million people in the United Kingdom (UK), with as many as 100,000 hospital admissions each year due to heart attacks (British Heart Foundation, 2023). Type 2 diabetes impacts approximately 4.5 million people in the UK (3.5 million diagnosed, and approximately 1 million undiagnosed (NICE, 2023)), or around 7% of the UK population. It costs the British taxpayer £21.8 billion yearly (£8.8bn for direct costs and £13bn for indirect costs); this accounts for approximately 10% of the National Health Service (NHS) budget (Hex et al., 2012). Furthermore, the NHS Business Authority estimates the cost of pharmacotherapy, prescribed general practice to account for 12.5% (£1.19 billion) of the total spend on prescribe items in the 2020/2021 financial year in England (Wilson, 2021). In addition to the financial burden posed by type 2 diabetes, it is linked to a higher risk of death through heart disease as well as a reduction in quality of life, for example through complications of the eye (retinopathy) and feet (diabetic foot) which may, if untreated, even require amputation conducted in secondary care (Papatheodorou et al., 2018). Type 2 diabetes is also associated with chronic kidney disease which is estimated to impact 1.8 million people in the UK, with

an associated cost of £1.5 bn (Kerr, 2012). Therefore, these diseases represent a burden in primary care, prescription costs and secondary care.

Cardiovascular disease, high blood pressure and type 2 diabetes are associated with similar socio-demographic determinants of health such as age, deprivation, and ethnicity, representing intersecting inequities in health. A recent report by Diabetes UK, the leading Diabetes charity in the United Kingdom, estimated that those in the most deprived income bracket are twice as likely to develop type 2 diabetes when compared to the average income bracket (Diabetes UK, 2021). Type 2 diabetes disproportionately impacts patients from an ethnic minority background (that is, those who are non-white British), with South Asian and African-Caribbean men having double the risk when compared to their aged-matched White European counterparts (Goff, 2019). Similar trends were found for cardiovascular disease, where ischaemic heart disease impacts South Asian populations 1.5 times more than the average population (Chaturvedi, 2003). Coronary heart disease mortality was also found to be associated with deprivation and increases with a 1.03 odds increase (Theocharidou and Mulvey, 2018) per point on the index of multiple deprivation rank score, a rating derived from seven factors related to socioeconomic status. These figures highlight the substantial economic and human cost alongside inequalities associated with these preventable diseases and risk factors.

The prevention of cardiovascular disease, chronic kidney disease, hypertension and type 2 diabetes in the United Kingdom involves similar management approaches. The National Institute for Health and Care Excellence (NICE), the English non-departmental body that provides clinical guidelines, recommends lifestyle and behaviour change programmes that provide patients with support to increase physical activity, improve dietary intake, improved weight management and a reduction in alcohol intake for the prevention of type 2 diabetes (NICE, 2017) and cardiovascular disease

(NICE, 2014). For example, the NHS Diabetes Prevention Programme is a nine-month behaviour change programme for people identified as being at risk of diabetes, commissioned locally and delivered by a range of providers (Penn et al., 2018) (described further below). Furthermore, cardiovascular disease prevention also focuses on smoking cessation and reducing sodium intake (which also reduces the risk of hypertension (NICE, 2019)).

The proposed solution: National Health Service Health Check

As a result of the financial impact and inequitable effect of these preventable diseases, the Department of Health modelled the cost-effectiveness of vascular checks and found that they would cost approximately £2480 per quality adjusted life year (QALY) and is considered cost effective (Department of Health, 2008). Therefore, these vascular checks were implemented by the National Health Service (NHS) with the aim of postponing and preventing patients from developing chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes and is called the NHS Health Check (Forster et al., 2014). With a gradual launch starting in 2009, the NHS Health Check is a general practice (primary care) driven programme, eligible to patients between the ages of 40-74 who do not have a previous record of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes. Therefore, if successful, the NHS Health Check can reduce care provision across primary care, secondary care and prescriptions.

Eligible patients are invited to their general practice or another community setting such as a pharmacy (Corlett and Krska, 2016) to conduct the Health Check. Invites are sent every 5 years through verbal invitations or letters (Forster et al., 2014). If the patient accepts the NHS Health Check invitation, the patient has an initial NHS Health Check screening consultation where their medical history, demographic details, risk factors and clinical details such as age, weight, ethnicity, blood pressure, height, smoking history, average alcohol consumption and a family history of cardiovascular disease,

hypertension, and diabetes status are collected (See Table 1-1 for how the collected items are related to the diseases the NHS Health Check aims to prevent). Where prior blood samples are not available, a blood test maybe given to establish glycated haemoglobin (HbA1c) levels, fasting plasma glucose for signs of type 2 diabetes or serum creatinine/estimated glomerular filtration rate for signs of chronic kidney disease. See Figure 1-1 for the components of the NHS Health Check and Table 1-1 for how sociodemographic and clinical characteristics are related to diagnosis and risk of non-communicable diseases.

Figure 1-1: Components of the NHS Health Check as described by: <https://web.archive.org/web/20230208225548/https://www.healthcheck.nhs.uk/commissioners-and-providers/delivery/>

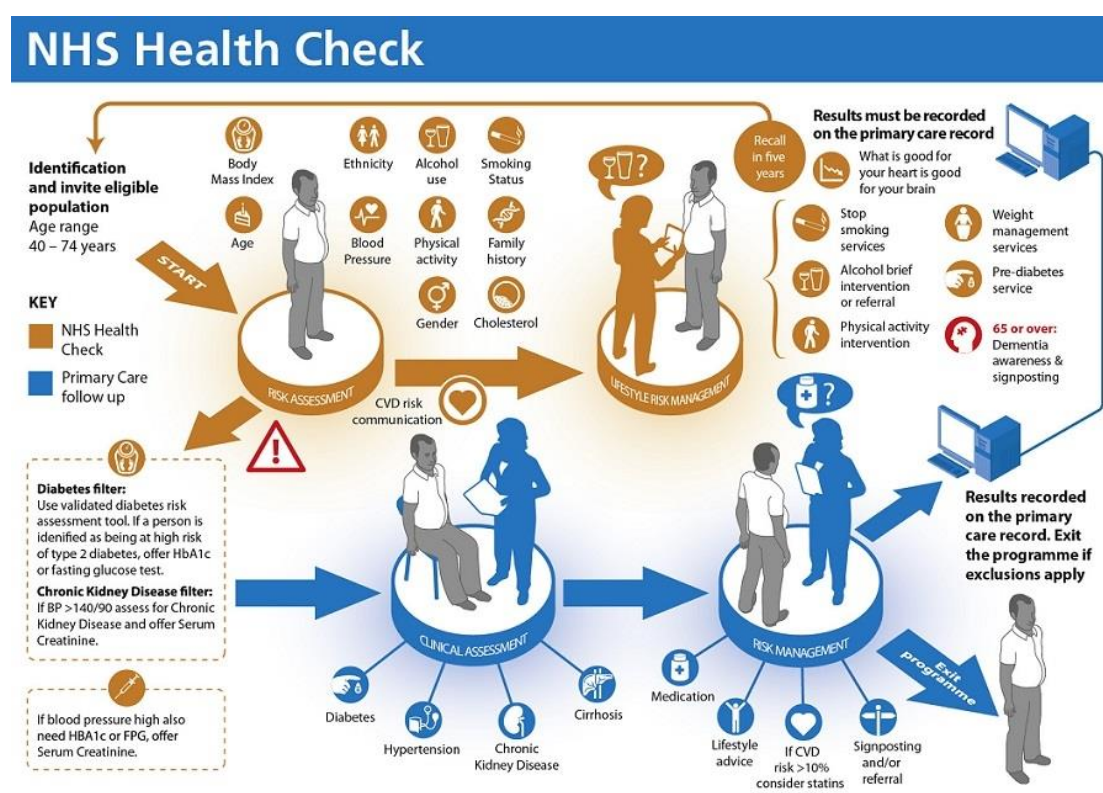


Table 1-1: Diseases that the NHS Health Check is aimed at tackling, their sociodemographic relevant characteristics and their relevant clinical characteristics.

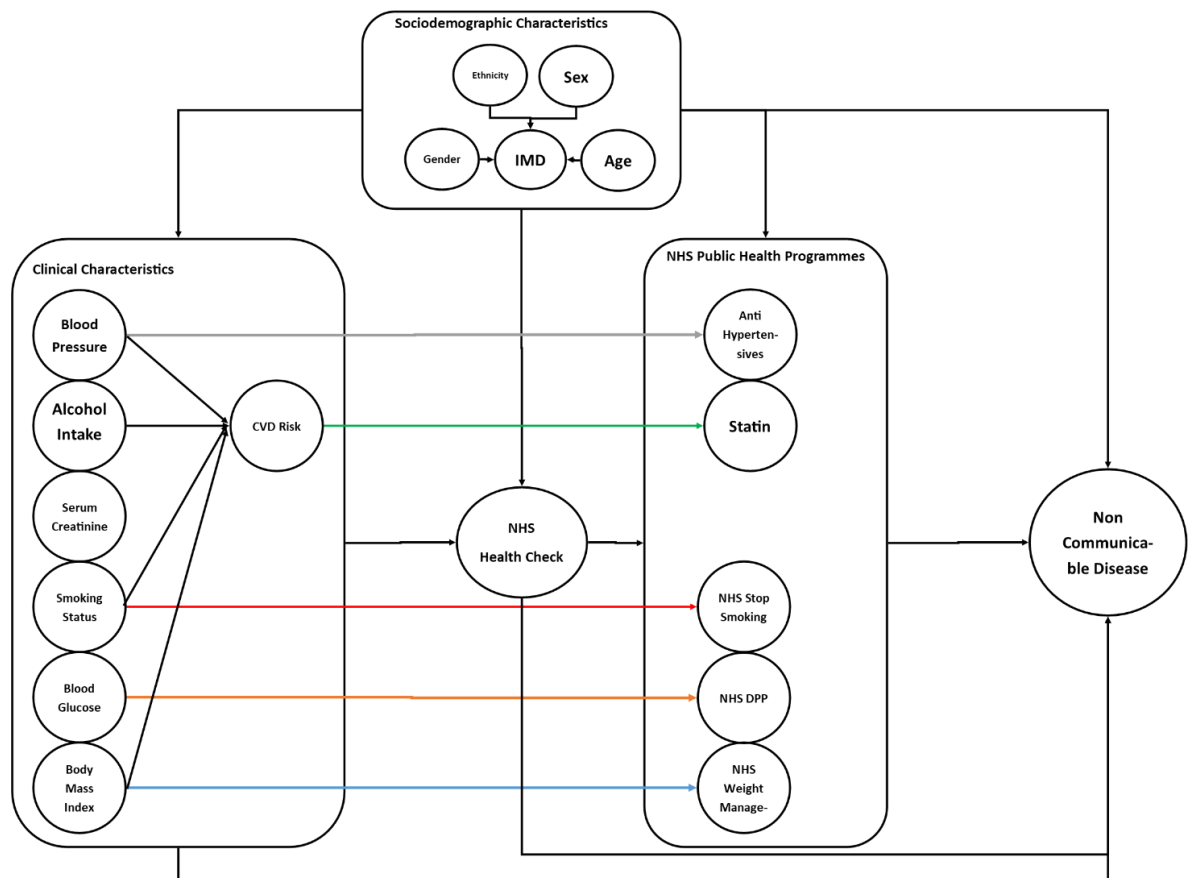
Disease Group	Sociodemographic related characteristics	Clinically relevant characteristics used for diagnosis	Clinically relevant characteristics not related to diagnosis
Type 2 Diabetes	Age Ethnicity Gender Deprivation	Measures of blood glucose including: -Haemoglobin A1C (HbA _{1c}) -Fasting Plasma Glucose (FPG)	Alcohol Consumption Smoking status Body Mass Index
Hypertension		Measures of blood pressure including: -Systolic Blood Pressure (SBP) -Diastolic Blood Pressure (DBP)	Alcohol Consumption Smoking status Body Mass Index
Chronic Kidney Disease		Measures of kidney function including: -Serum creatinine -Estimated glomerular filtration rate (eGFR)	Blood Pressure Alcohol Consumption Smoking status Body Mass Index

Disease Group	Sociodemographic related characteristics	Clinically relevant characteristics used for diagnosis	Clinically relevant characteristics not related to diagnosis
Stroke			Alcohol Consumption Smoking status Body Mass Index Cardiovascular Risk scores e.g., QRisk2, Framingham
Heart Disease			Alcohol Consumption Smoking status Body Mass Index Cardiovascular Risk scores e.g., QRisk2, Framingham High-density lipoproteins and Low-density lipoproteins

Using these details, cardiovascular disease risk factors are calculated, for example, through the QRisk2 Score, a validated score used to estimate the risk of a cardiovascular event in the next 10-years (Hippisley-Cox et al., 2008, p. 2). Other examples of risk include being pre-hypertensive (a systolic blood pressure between 120 mmHg-139 mmHg, or the diastolic reading between 80 mmHg-89 mmHg.) or non-diabetic hyperglycaemia (HbA_{1c} levels of 42-47 mmol/mol or fasting plasma glucose (FPG) levels of 5.5-6.9 mmol/L). Where the need is identified (i.e., those at risk of developing aforementioned diseases through a high QRisk2 score, being non-diabetic hyperglycaemic or having prehypertension), the patient may be prescribed a combination of

preventative treatments such as antihypertensives, statins, clinical advice or referrals to further NHS clinics as appropriate to their clinical situation. This secondary prevention aims to reduce their risk of developing chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes through alcohol/smoking cessation, improved dietary intake and weight control. For example, patients suffering from non-diabetic hyperglycaemia (previously known as pre-diabetes) may be referred to the NHS Diabetes Prevention Programme. See Figure 1-2 for how the data collected during the NHS Health Check are related to future interventions that the NHS Health Check mediates and how these could impact the risk of developing a non-communicable lifestyle related disease.

Figure 1-2: Graphic of how socio-demographics and clinically relevant characteristics are potentially related to the NHS Health Check and outcomes.



If the patient is found to have a previously unrecorded history of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes during the consultation, a referral to their general practice is made for treatment; at this stage, these patients are no longer eligible for further inclusion in the NHS Health Check. By identifying and referring patients with a previously unrecorded history of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes to their general practice, the NHS Health Check also aims to reduce disease progression in these individuals: for example, a progression of type 2 diabetes onto diabetic retinopathy or diabetes-related amputations.

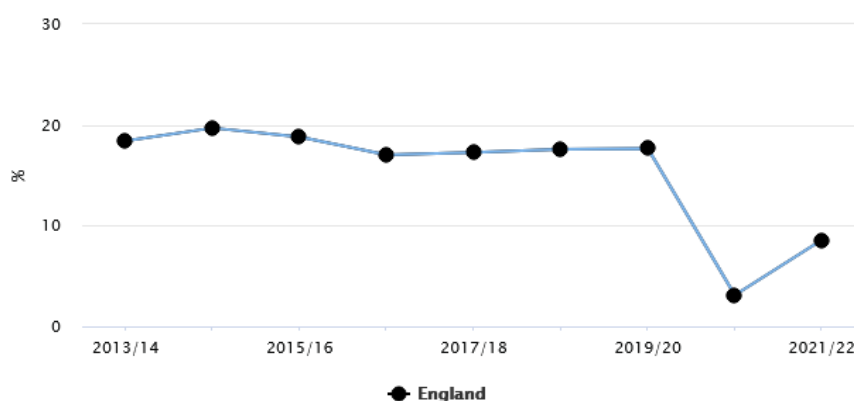
Initial economic modelling of the NHS Health Check estimated that it would cost less than £3000 per Quality-Adjusted Life Year (QALY) gained, below the National Institute of Healthcare Excellence benchmark of £20000/QALY for an intervention to be deemed cost-effective (Department of Health, 2008). The NHS Health Check was also designed to identify patients with undiagnosed cases of chronic kidney disease, cardiovascular disease, hypertension, stroke and type 2 diabetes. These diagnoses can occur at the initial consultation when the medical history and clinical details are collected. It is estimated that 1 million people have undiagnosed diabetes (Diabetes UK, 2016) and that 3.8%-20.4% of patients at general practices have undiagnosed hypertension (PHE, 2016). Detection of previously undiagnosed cases aims to prevent disease progression, which should in turn lead to a lower associated cost as compared to a late diagnosis and disease progression, provided that effective secondary prevention measures can be implemented. These epidemiological, economic, and public health data highlight the value of the NHS Health Check in relation to its potential to prevent a range of high burden conditions.

Challenges in the uptake of the NHS Health Check

Uptake of the NHS Health Check has increased since its inception, especially in those who have a higher cardiovascular disease risk; however, uptake decreased after 2013/2014 and has always remained lower than the government-set target, encompassing 20% of the eligible population (Robson et al., 2016) (Figure 1-3 for Uptake). Robson et al. (2016) investigated the uptake and found that in their sample, 1.5 million patients were eligible for the NHS Health Check between 2009 and 2013, only 200,000 took up the offer of an invitation during this period (Robson et al., 2016). The same study has estimated higher uptake rates in males, 60–75 year-olds and ethnic minorities, especially those of Bangladeshi origin. Simulation studies have estimated that a 30% increase in attendance for an NHS Health Check would reflect a net gain of 10,000 Quality-Adjusted Life Years (QALY) (Mytton et al., 2018). Qualitative studies have explored the factors which prevent higher rates of uptake amongst those who are eligible for the NHS Health Check. Usher-Smith et al., 2017 (Usher-Smith et al., 2017) synthesised 10 qualitative studies and found 4 themes that prevent uptake: 1) “Lack of awareness or knowledge”, 2) “Time constraints or competing priorities”, 3) “Misunderstanding the purpose,” and 4) “Aversion to preventive medicine”.

Figure 1-3: Uptake from the eligible population divided by year. Data provided by the Office for Health Improvement and Disparities via their Fingertips Application Programming Interface. Data prior to 2013/2014 was not available using Fingertips.

People invited for an NHS Health Check per year



To increase uptake, studies have investigated alternative invitation methods. Mcdermott *et al.*, 2017 (Mcdermott *et al.*, 2017) proposed using Question-Behaviour Effect questionnaire on top of the standard NHS Health Check invitation letter to improve attendance levels, however, this was proven to be ineffective (1.43% increase in attendance compared to normal invitations [95% CI -0.12% to 2.97%; $p = 0.070$]). Visram *et al.*, 2015 (Visram *et al.*, 2015) suggests that using lay health trainers to target hard-to-reach populations could be successful; however, this study lacked strong statistical analysis, consisting of 20 stakeholders and 181 questions as part of a questionnaire.

Challenges in establishing the effectiveness of the NHS Health Check

Results of studies investigating the effectiveness of the health checks have been mixed. As a result of these studies, there is an ongoing debate about the effectiveness of the NHS Health Check. There is currently no single study

evaluating the NHS Health Check's impact on the English population on the incidence of non-communicable diseases, with many studies evaluating the impact of the NHS Health Check either at the general practice level or the individual level with the outcome of change in risk factors. Therefore, the overall impact of the NHS Health Check on the public health issues described above remains uncertain.

Krogsbøll et al., 2012 (Krogsbøll et al., 2012) conducted a systematic review and found that programmes similar to the NHS Health Check in other countries globally were not effective with regard to reducing mortality. Krogsbøll and colleagues (Krogsbøll et al., 2012) compared programmes like the NHS Health Check to standard care (no Health Check) and found similar outcomes in terms of all-cause mortality (RR: 0.99, 95% CI: +/- 0.04), cardiovascular mortality (RR: 1.03, 95% CI: +/- 0.14) and cancer mortality (RR: 1.01, 95% CI: +/- 0.09). A limitation of Krogsbøll et al., (2012)'s review is that its conclusions were synthesised from studies prior to the introduction of modern interventions such as statins in routine preventative care. This is an important consideration as statins have been demonstrated to lower cardiovascular disease related mortality (RR, 0.69 [95% CI, 0.54 to 0.88]; I² = 54%) (Chou et al., 2016) and health checks could increase the number of individuals receiving statins for primary prevention of cardiovascular disease. In addition to mortality outcomes, Krogsbøll et al., 2012 (Krogsbøll et al., 2012) concluded that there was limited understanding on reduction of morbidity; with a 20% reporting of higher "new diagnoses" of chronic conditions when compared to a control group but there is little evidence on disease prevention. In terms of morbidity, the studies featured in Krogsbøll et al., 2012 (Krogsbøll et al., 2012) were also before the introduction of recently introduced diabetes prevention programmes which have been shown to reduce the incidence of type 2 diabetes (Diabetes Prevention Programme Group, 2015, 2002; Ilanne-Parikka et al., 2013).

Since Krogsbøll et al., 2012 (Krogsbøll et al., 2012), some studies have supported the effectiveness of the NHS Health Check by demonstrating its ability to significantly reduce mean cardiovascular disease risk score at the individual level (JBS2 reduction of 28.2%; 95% CI = 27.3% – 29.1%) when comparing baseline cardiovascular risks to short term follow-up cardiovascular risks (Artac et al., 2013). This is a proxy outcome measure rather than a hard disease or mortality outcome measure, the latter of which are often evaluated over the longer term, where there is mixed evidence (Byrne et al., 2019). The Artac et al. study (Artac et al., 2013) analysed the data using a per-protocol analysis without a control group and therefore the impact of non-adherence and usual-care could not be established respectively; such per-protocol analyses introduce bias (as compared to intention-to-treat analyses) as they analyse the intervention course taken as opposed to the course of intervention assigned, therefore disregarding any non-adherence issues (Ranganathan et al., 2016). Chang et al. (Chang et al., 2015) established that the NHS Health Check improves QRisk2 Cardiovascular Risk (Difference in Difference = -0.21%, 95% confidence interval [CI] -0.24% to -0.19%) when compared to usual care, that is the reduction of a 10-year cardiovascular event, however, their observational study design was limited by high levels of missing data (32.8% for ethnicity and 21.1% for deprivation measures) and coding errors (due to late publication of universal clinical codes for the NHS Health Check) in their observational data. Prospective controlled studies have established the NHS Health Check's ability to reduce cardiovascular disease risk (Cochrane et al., 2012) from 32.9% 10-year Framingham risk to 29.4% 10-year Framingham risk, however, this study was comparing the NHS Health Check to a variation of the NHS Health Check which included additional lifestyle support groups (that provides access to lifestyle coaches who aim to reduce weight/BMI) instead of comparing the NHS Health check vs usual care. Prospective controlled studies have demonstrated that general practices which offer the

NHS Health Check have similar prevalence levels for diabetes, hypertension, coronary heart disease, chronic kidney disease, and atrial fibrillation compared to practices that do not offer an NHS Health Check (Caley et al., 2014). However, one major challenge that Caley *et al.*, 2014 (Caley et al., 2014.) found that comparison groups at the general practice level had baseline differences, with practices that offered the NHS Health Check often being more deprived; this difference is an important confounding factor as deprived populations often have a higher burden of the diseases that the NHS Health Check was designed to tackle when compared to less deprived populations. It is also challenging to accurately estimate the effect of the NHS Health Check on incident cases (of the diseases it is targeting) as the NHS Health Check also identifies undiagnosed cases during the screening process; therefore, an increase in prevalence amongst NHS Health Check invitation acceptors may be associated with new diagnoses of previously undiagnosed cases as opposed to the impact of the intervention.

Since Krogsbøll et al., 2012 (Krogsbøll et al., 2012), there has been limited systematic review evidence that evaluates the NHS Health Check and the studies above are a small summary of literature on the NHS Health Check; therefore to understand the research surrounding the NHS Health Check thoroughly, including their outcomes, estimates, strengths and limitations, a comprehensive literature review is a component of this PhD to update the literature on the effectiveness of the NHS Health Check (See Chapter 2).

Rationale for an Observational Study Evaluating the NHS Health Check

Currently, the literature about the NHS Health Check evaluates proxy measures such as reduction in cardiovascular risk (Chang et al., 2015), and prevalence of diabetes, hypertension, coronary heart disease, chronic kidney disease, and atrial fibrillation (Caley et al., 2014). Whilst such outcomes are

proxies for health status, they are not measures of the incidence of diabetes, hypertension, coronary heart disease, chronic kidney disease and stroke.

As the NHS Health Check is nationally mandated, a further randomised controlled trial to evaluate whether the NHS Health Check can reduce the incidence of diabetes, hypertension, coronary heart disease, chronic kidney disease and stroke with a control group with no NHS Health Check conducted is no longer feasible. Therefore, in lieu of randomised controlled trials, alternative methods have been proposed to analyse large scale routine data using observational study designs to reduce some of the biases and weaknesses in such studies. Methods of trial emulation using observational data developed by Hernán and Robins, 2016 (Hernán and Robins, 2016) could be used to mitigate weaknesses in observational studies by, for example, analysing all-new “incident” users of the NHS Health Check using an intention-to-treat analysis as compared to analysing all existing “prevalent” users using a per-protocol analysis.

The ‘target trial’ design overcomes the limitation of a per-protocol analysis that could exaggerate the effectiveness of the intervention (Ranganathan et al., 2016), whilst analysing prevalent users of an intervention would generate an unequal baseline reading compared to the control group. Studies have also estimated that the NHS Health Check data has up to 27.4% missing deprivation data, whilst 41.8% of NHS Health Check participants had missing ethnicity data (Chang et al., 2016). Furthermore, Chang et al., 2016 (Chang et al., 2016) and Artac et al., 2013 (Artac et al., 2013) have stated that identifying NHS Health Check patients using primary care data can be difficult as some methods may under-identify NHS Health Check participants when using clinical codes alone.

Therefore, by using carefully designed observational study methodology, uncertainties in associations could be reduced by implementing methods that 1) identify the NHS Health Check population with improved certainty, 2)

account for missing data within this population and 3) techniques that reduce biases when selecting a control group.

In addition to understanding the impact of the NHS Health Check on the individual level, it is also important to understand the impact of the NHS Health Check on a population level. This is due to the fact that the diseases targeted by the NHS Health Check are considered a financial burden for the NHS, for example the cost of £21.8 billion yearly attributed to diabetes as mentioned above (Hex et al., 2012). Such a study that evaluates population level effects would also allow us to understand background rates and to obtain high-level estimates of the impact of the NHS Health Check.

[The proposed targeted solution: NHS Diabetes Prevention Programme](#)

In addition to the NHS Health Check, a disease specific public health intervention was introduced called the NHS Diabetes Prevention Programme (DPP). The NHS Diabetes Prevention Programme was piloted in England in June 2016 in 44 areas with the specific goal of preventing or postponing type 2 diabetes in England (Barron et al., 2018). The NHS DPP aims to prevent type 2 diabetes by providing 16 hours of face-to-face interactions over 13 sessions for nine months to high-risk individuals. Each session concentrates on the patient's dietary behaviour and weight management, see Figure 1-4 for an example of the patient information sheet for the NHS DPP. This includes providing personal lifestyle advice by giving each patient information on nutrition, physical activity as well as motivation techniques to sustain such behaviours in the long term. This aims to improve on the NICE guideline on preventing type 2 diabetes which only requires a single yearly review of diabetic risk without follow-up until the next annual review (NICE, 2017). The NHS Diabetes Prevention Programme aims to be an improvement from usual care by providing consistent and steady involvement from a healthcare provider.

Individuals are eligible if they are at least 18 years old and at risk of developing type 2 diabetes. Being at risk of developing type 2 diabetes is defined using either glycated haemoglobin (HbA_{1c}) levels between 42-47 mmol/mol or fasting plasma glucose (FPG) levels between 5.5-6.9 mmol/L within one year before the referral to the NHS DPP. Patients of the NHS DPP are often referred by their general practitioner and is an option for patients to be referred from the NHS Health Check in a similar manner to other NHS programmes such as the NHS Stop smoking service.

Figure 1-4: Patient information sheet for the Diabetes Prevention Programme.
Taken from:

<https://web.archive.org/web/20230605010418/https://acaciumgroup.fra1.digitallceanspaces.com/preventingdiabetes-staging/wp-content/uploads/2023/04/p7940-xyla-hw-patient-info-sheet-v4-devon.pdf>

HEALTHIER YOU
NHS DIABETES PREVENTION PROGRAMME

NHS

Patient information sheet

You have taken an important first step and found out you are at high risk of Type 2 diabetes. The NHS Diabetes Prevention Programme will help you take control of your health, supporting you to make changes to your diet, weight and the amount of physical activity you do. Taking action now is very important as it can stop you developing Type 2 diabetes.

What does the Healthier You NHS Diabetes Prevention Programme support with?

- Moving More**
Understand how physical activity is crucially beneficial to prevent type 2 diabetes and will support you to become more physically active
- Eating Well**
Support you to eat nourishing foods and achieve a healthy weight
- Taking Charge**
Understand ways to feel more in control of your health now and for the future

How to join
If you have been told that you are at high risk of developing Type 2 diabetes and haven't already been referred to our service, please ask your GP practice if you are eligible for referral to your local Healthier You programme. For further information, please contact us at:
info@preventing-diabetes.co.uk
0333 577 3010
preventing-diabetes.co.uk
scwcu.devon-ndpp@nhs.net

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What is known about the NHS Diabetes Prevention Programme (DPP) and what needs to be investigated?

Due to the recent phased deployment of the NHS DPP in 2016, there is limited research on its comparative effectiveness with most studies analysing

patient uptake (Valabhji et al., 2020) and a qualitative evaluation of the NHS DPP (Penn et al., 2018). Barron *et al.*, 2018 (Barron *et al.*, 2018) found that attending at least one session of the NHS DPP between June 2016 and March 2017 was associated with a mean weight loss of 2.3kg (95%CI: 2.2, 2.3 kilograms) and a mean HbA_{1c} reduction of 1.26 mmol/mol (95%CI: 1.20-1.31 mmol/mol); however, there was no comparison group to compare these results against. By analysing the impact of attending at least one session of the NHS DPP, Barron et al., 2018, introduces bias as this analysis selected individuals who adhered to treatment (i.e., a per-protocol analysis, instead of an intention-to-treat analysis). Therefore, it is unknown whether the impact of the NHS Diabetes Prevention Programme is due to health-seeking bias.

Similar preventative interventions worldwide demonstrate a positive impact on the incidence of type 2 diabetes using gold-standard randomised controlled trials (Diabetes Prevention Programme Group, 2015, 2002; Ilanne-Parikka et al., 2013). However, there is no study explicitly evaluating the NHS DPP's effect on preventing the incidence of type 2 diabetes in high-risk individuals compared with a similarly high-risk control group who are receiving routine care for preventing the incidence of type 2 diabetes.

Rationale and challenges for an Observational Study Evaluating the NHS Diabetes Prevention Programme

Similarly to the NHS Health Check, a randomised controlled trial evaluating the NHS Diabetes Prevention Programme (DPP) is not likely to be feasible due to its current national rollout. Therefore, studies that account for biases when using observational data to establish the effectiveness of the NHS DPP on the incidence of type 2 diabetes are required. These studies need to address the biases introduced when comparing to a control selected in non-randomised treatment assignments. Since studies that have evaluated the NHS DPP have used a proprietary dataset (Valabhji et al., 2020, Barron *et al.*, 2018) for capturing performance data (such as invitations, attendance and clinically relevant measures such as blood glucose, height and weight), the datasets do not include non-participants who could have been used as a control group. Therefore, general purpose primary care datasets such as the Clinical Practice Research Datalink (CPRD) could be used to select control groups. However, due to the recent deployment of the NHS DPP, rates of missingness and the quality of data in CPRD dataset surrounding the NHS DPP have not been investigated. Similarly to the NHS Health Check, there is also a lack of literature in identifying NHS Diabetes Prevention Programme participants and their healthcare outcomes in primary care datasets.

What this thesis aims to add to the current literature and research surrounding the NHS Health Check and NHS Diabetes Prevention Programme

My PhD research sits at the interface between data science for healthcare research and pragmatic public health research to investigate the effect of public health interventions on outcomes of cardiovascular disease and type 2 diabetes which have a high burden both financially (10% of the NHS budget) and on the quality of life (due to disease progression e.g., diabetic retinopathy, chronic kidney disease and amputation due to diabetic foot).

As a high proportion of incident cardiovascular disease and diabetes have the potential to be prevented, the National Health Service has introduced services including the NHS Health Check and NHS Diabetes Prevention Programme to tackle the growing rates of type 2 diabetes. However, as these programmes were introduced without being evaluated in randomised controlled trials, there is currently a debate on the comparative effectiveness of these public health programmes.

To better understand and account for biases in observational studies that evaluate the NHS Health Check and NHS Diabetes Prevention Programme, including (but not limited to) missing data, confounders and selection bias, my PhD contributes to research evaluating public health interventions by conducting study triangulation through a series of different of study designs where each approach has different key sources of potential bias that are unrelated to each other and can be integrated and compared. To achieve this, my PhD applies the triangulation framework developed by Lawlor et al., 2017 (Lawlor et al., 2017), which strengthens research by combining the strength of various heterogeneous study designs whilst acknowledging the biases that each method introduces. My PhD uses the following evidence synthesis methods and observational study designs as part of the triangulation study using Lawlor et al., (2017)'s framework to reduce a variety of challenges in

each study design and to integrate evidence across these diverse approaches:

- Systematic reviews to understand gaps in the respective research area(s),
- An interrupted time series study to understand these interventions' impact at the population level.
- Retrospective observational studies to emulate randomised controlled trials on an individual level.
- Data science methods to help mitigate issues with observational data.

Table 1-2 describes the seven key research gaps, Objectives, and research methods that this thesis will address.

Table 1-2: Research Gap Table

#	Research Gap	PhD Objective	Method	Chapter
1	Lack of a recent comprehensive overview of the studies which evaluate the NHS Health Check in terms of their population (inclusion/exclusion criteria), control groups, and healthcare outcomes (and how these outcomes are measured)	To update the existing evidence-based on the effectiveness of NHS Health Check, which mediates the widespread use of statins and intensive diabetes prevention programmes on healthcare outcomes by undertaking a systematic review to identify existing evaluations.	A systematic review to identify and summarise evidence on NHS Health Check evaluations with a focus on describing the populations, comparison groups and healthcare outcome measures.	Chapter 2
2	Lack of evidence about the national impact of the NHS Health Check on rates of cardiovascular disease, diabetes, and chronic kidney disease at the population level in England.	To conduct a quasi-experimental interrupted time series analysis using aggregated populational level datasets to estimate the association between NHS Health Check and changes in rates of cardiovascular disease, diabetes, and chronic kidney disease since its introduction.	Quasi-experimental interrupted time series to understand whether the introduction of the NHS Health Check was associated with national rates of cardiovascular disease, diabetes, and chronic kidney disease since its introduction.	Chapter 3 Research Paper 1
3	Lack of evidence-based clinical code list for phenotyping the NHS Health Check population and cardiovascular, diabetic, and chronic kidney disease-based outcomes in primary care datasets. Lack of consensus on the inclusion/exclusion criteria when evaluating the NHS Health Check as a preventative programme.	To improve primary and secondary care electronic health record code lists by undertaking a systematic review to generate evidence-based code lists that can be used to identify patients that have had an NHS Health Check or have participated in the NHS Diabetes Prevention Programme and their subsequent health outcomes. To introduce a method that overcomes biases when identifying clinical codes used to extract data from administrative observational healthcare datasets. To use to improve the lack of consensus on the inclusion and exclusion criteria when evaluating the NHS Health check as a preventative intervention.	Systematic review to identify health record code lists used in studies that evaluated diabetes and cardiovascular disease using primary care datasets including, but not limited to the Clinical Practice Research Datalink, The Health Improvement Network and QResearch datasets.	Chapter 4
4	Lack of observational studies emulating randomised controlled trials to evaluate the preventative effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes	To conduct a trial-emulating population-based cohort study using matched primary and secondary care health records to understand the preventative effect of the NHS Health Check and NHS Diabetes Prevention Programme on the incidence of type 2 diabetes.	A target trial emulation study using retrospective observational data was conducted. Inclusion and exclusion criteria were strictly applied upon entry for each patient. Group assignment emulated an intention-to-treat	Chapter 5 Presentation 1

#	Research Gap	PhD Objective	Method	Chapter
5	Lack of observational studies emulating randomised controlled trial to evaluate the preventative effect of the NHS Health Check on preventing type 2 diabetes		analysis to account for challenges in adherence with public health interventions.	Chapter 6
6	Lack of analyses comparing different methods and data with different forms of bias used to examine the challenges in traditional epidemiological studies in the evaluation of the NHS Diabetes Prevention Programme and NHS Health Check.	To compare data science methods used for multiple imputation, resampling and multivariable time-to-event analyses to established epidemiology methods in order to examine the effect of these modern methods on bias within the study designs of the evaluations of the NHS Health Check and the NHS Diabetes Programme.	Separate evaluations of the NHS Health Check and the NHS Diabetes Programme were undertaken using modern methods such as K's Nearest Neighbours, Random Forests and Survival Trees.	Chapter 7
7	Lack of triangulated analyses comparing studies using different datasets and methods - each with different biases - in order to examine the impact of these biases on the estimates of the effectiveness of the NHS Diabetes Prevention Programme and NHS Health Check on reducing the incidence of type 2 diabetes	To triangulate the results from all evaluations undertaken in the thesis in order to evaluate the biases and challenges introduced by each study method and investigate the overall effect of the NHS Diabetes Prevention Programme and NHS Health Check on type 2 diabetes.	The triangulation framework was applied to the studies with the direction of bias being in reference to a comparable randomised controlled trial	Chapter 8

Chapter 2 - Systematic review of the studies which evaluate the NHS Health Checks on cardiovascular disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes.

Abstract

Introduction and research gap: Prior to my PhD research, the last systematic review examining the evidence of the effectiveness of the general health checks in adults was conducted in 2012, with results covering health checks implemented up until 1999. This is before the widespread use of modern interventions such as statins and intensive diabetes prevention programmes and before the NHS Health Check itself. Therefore, there is a lack of a recent comprehensive overview of the studies which evaluate the NHS Health Check in terms of their population (inclusion/exclusion criteria), control groups, and healthcare outcomes (and how these outcomes are measured). This chapter aims to systematically review the literature specifically on the NHS Health Checks to update previous systematic review of health checks to inform the latter chapters of this PhD. The objective of this chapter is to evaluate whether and how the NHS Health Check impacts rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes or changes in measurable cardiovascular risk and health-style related outcomes such as QRisk-2 cardiovascular score and body mass index.

Method: I conducted systematic search on PubMed and Embase via Ovid for studies examining the NHS Health Check to establish its impact on cardiovascular events, diabetes, hypertension, stroke, and chronic kidney disease on 28th October 2018. My Population of interest was NHS Health Check eligible patients and practices with the Intervention consisted of the

NHS Health Check. Comparisons were made before/after the NHS Health Check and between eligible invitees and eligible non-invitees. The Outcomes included cardiovascular disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes. My inclusion criteria were English language studies that specifically examined the impact of the NHS Health Check on the above healthcare outcomes. Studies that evaluated uptake of the NHS Health Check, or other health checks were excluded (such as those outside of England). Studies before the introduction of the NHS Health Check (2009) were not included. Qualitative studies, comments, editorials, or responses were excluded. Included studies were appraised using the Centre of Evidence-based Medicine guidelines. Studies were stratified by disease and design (systematic review, randomised controlled trial and observational). Observational studies were stratified by whether included a control group for comparison. Meta-analyses were conducted where possible.

Results: Nineteen studies were included from, a total of 6,759 articles. Thirteen studies with cardiovascular outcomes were included, four with diabetic healthcare outcomes, three for stroke-based outcomes, four analysed chronic kidney disease and six analysed hypertension. Due to heterogeneous outcome measures, a meta-analysis was not possible. When compared with both pre-NHS Health Check and a control group, the NHS Health Check decreases individual risk factors for cardiovascular disease (e.g., body mass index). New diagnoses of cardiovascular disease are higher amongst NHS Health Check invitees when compared to non-invitees. Newly unrecorded diagnoses of diabetes, stroke and chronic kidney disease was the same or higher in NHS Health Check invitees compared to non-invitees, however, this may be related to baseline socio-demographic and clinical differences in the active participants of the NHS Health Check leading to detection of previously undiagnosed cases.

Discussion and Conclusion: The literature surrounding the NHS Health Check does not explain whether attending an NHS Health Check can reduce the risk of developing diabetes, heart disease, hypertension, stroke, or chronic kidney disease in individuals who have not experienced these diseases prior to follow-up. Further studies should disaggregate the difference between detecting undiagnosed cases on entry and incident cases of diabetes, heart disease, hypertension, stroke, or chronic kidney disease after receiving the interventions.

Next Steps: Further studies are required to understand the causal effect of the NHS Health Check on preventing cardiovascular disease, chronic kidney disease, hypertension, type 2 diabetes and stroke.

Notes: Due to the recent deployment of the NHS Diabetes Prevention Programme at the time of conducting this PhD, a systematic review was not conducted for the NHS Diabetes Prevention Programme.

After resuming my PhD from COVID-19 essential work, a scoping review has been published about the NHS Diabetes Prevention Programme which stated that most studies have concentrated on uptake, retention and outcomes such as weight loss and changes in blood glucose (Whelan and Bell, 2022). A further study found that there is evidence to support that the NHS Diabetes Prevention has prevented cases of type 2 diabetes on a population level in terms of the incidence of type 2 diabetes and stated more research is required at the individual level (McManus et al., 2022).

Complementary Reading Material: To aid readers in this chapter, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist has been provided in Appendix 2.1.

Introduction

As stated in Chapter One, the evidence evaluating the effect of the NHS Health Check to prevent incident cases of heart disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes is variable and rapidly evolving. This chapter attempts to estimate the effect of the NHS Health Check on the incidence, prevalence and risk reduction of these diseases using a systematic review (Guyatt et al., 1995). A systematic review was used as it combines the results from various studies with the aim of reducing biases localised to each study.

Current debate surrounding the effectiveness of the NHS Health Check is primarily based on evidence produced in 2012 by Krogsbøll et al., 2012 (Krogsbøll et al., 2012) which is a systematic review consisting of 16 studies evaluating “general health checks” between 1963 and 1999. Krogsbøll et al., 2012 concluded that they could not find “an effect on clinical events or other measures of morbidity”. However, none of these studies specifically analysed the NHS Health Check (as this was introduced in 2009) and none of these studies included modern, current interventions; a weakness which was stated by Krogsbøll et al., 2012 themselves. Examples of “modern” interventions include the introduction of statins to routine care for primary prevention of cardiovascular events and multiple successful diabetes prevention programmes. Statins are often quoted as “first choice” agents due to their ability to reduce the risk of cardiovascular events, particularly in those without a previous cardiovascular event (Chou et al., 2016; Taylor et al., 2011). Various studies have also shown the effectiveness of diabetes prevention programmes on preventing the incidence of type 2 diabetes using various diabetes prevention groups worldwide (Diabetes Prevention Programme Group, 2015, 2002). Both of these examples of “modern” interventions are important as they are vital components of the NHS Health Check that were not evaluated in (Krogsbøll et al., 2012). Therefore, there is a need to update

the literature on the impact of general health checks on adults and in particular, the NHS Health Check.

Aims and Objectives

The aim of this systematic review was to summarise the impact of the NHS Health Check on health outcomes and the quality of the evidence evaluating the NHS Health Check. This systematic review achieves this by analysing the effect of the NHS Health Checks on:

- Rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes at both a patient and practice level
- Changes in cardiovascular risk at a patient and population level
- Changes in other health-style related outcomes such as a change in weight and body mass index

Methods

To conduct the literature search, my Population, Intervention, Comparison, and Outcome (PICO) dimensions of interest were defined. My Population of interest was NHS Health Check eligible patients (those aged 40-74 without prior episode (recording or knowledge) of heart disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes). My Intervention consisted of the NHS Health Check (including those trialling additional lifestyle support). To understand the variety of studies designs, the Comparison groups consisted of 1) before and after studies, and 2) studies which had a control group consisting of those who were eligible for the NHS Health Check but were not invited and an intervention group which consisted of eligible invitees and 3) if there were no comparison groups, the study must have provided incidence/estimates in the NHS Health Check participants. My primary Outcome measure was the impact of the NHS Health Check on measurable estimates of the modelled risk of cardiovascular disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes as these were the non-communicable diseases the NHS Health Check was designed to deal with. This includes, (changes in) incidence and prevalence (new diagnoses in previously undiagnosed individuals). Secondary outcomes included the impact of the NHS Health Check of healthcare covariates including cardiovascular disease risk score (Framingham, QRisk2, JBS2), glycated haemoglobin levels (HbA_{1c}), and serum creatinine levels.

Information Sources and Search strategy:

My search strategy was conducted using PubMed and Embase (via Ovid) on the 28th of October 2018. The references of each paper found on PubMed and Embase were reviewed for additional sources as recommended by the Centre for Evidence-Based Medicine (CEBM). MESH terms used to conduct the search included the following terms: “NHS”, “National Health* Service”, “Health Check” (See Appendix 2.2 for detailed search strings). Duplicates were eliminated by using Microsoft Excel 2010 through title and author fields.

Selection Process

I had conducted the search alone; however, soon after completing this chapter, a similar systematic review that evaluated the NHS Health Check was published with similar studies (Martin et al., 2018). From Martin et al., 2018, I had added any further studies that were not found in my search; furthermore, as Martin et al., 2018 was investigating the same research request as this chapter, I also included their interpretation as external validation.

My inclusion criteria consisted of studies that were randomised controlled trials, observational, and simulation studies that were written in English. These studies had to compare the impact of the NHS Health Check on incidence, prevalence or change-in-risk for cardiovascular disease, type 2 diabetes, chronic kidney disease, hypertension or stroke.

As the NHS Health Check is specific to England, I excluded studies that were set outside of England; this excluded other general health checks from around the world. Since the NHS Health Check was introduced in 2009, studies before the 1st of January 2009 were not included. Qualitative studies, comments, editorials, or responses were excluded. Studies that quantitatively analysed the uptake of the NHS Health Check and invitation methods were also excluded as they did not evaluate the effectiveness of the NHS Health Check on health outcomes.

Data Collection and Data Items

I had independently conducted the data collection of the data items. Each study that met the inclusion criteria had the following data items manually extracted into a matrix using Microsoft Excel 2010:

- Study Design: Systematic Review, Controlled Study, Observational Study, Simulation Study
- Healthcare Outcome: Chronic Kidney Disease, Cardiovascular Disease, Hypertension, Stroke, Type 2 diabetes or Other

- Measure: Changes in Prevalence, Changes in Incidence, Changes in risk
- Analytical Unit: Individual level, General Practice Level
- Comparison Group: True or False

Study risk of bias assessment, Reporting bias assessment and Certainty assessment

I assessed the risk of methodological and reporting using the centre of evidence-based medicine's (CEBM) appraisal tool. Using the CEBM appraisal tool, I extracted the following data items in addition to those in the Data Collection and Data Item section:

- Was the assignment of the patients to treatment randomised?
- Were the groups similar at the start of the trial?
- Aside from the allocation of treatment, were groups treated equally?
- Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?
- Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?
- How large was the treatment effect?
- How precise was the estimate of the treatment effect?
- Will the results help me in caring for my patients (External Validity)

Effect Measures

As the goal of my systematic review is to understand the impact of the NHS Health Check on improved healthcare outcomes, I considered all effect measures. A-priori, this included: odds ratios, hazard ratios, incident rate ratios, means-difference, difference-in-difference measures. Other effect measures were used if found.

Synthesis methods

Descriptive tables were used to categorise studies by the study design (systematic review, controlled trial, observational studies, simulation studies), the healthcare outcome(s), measures (prevalence, incidence, other), analytical unit (individual, general practice) and whether the study used a control group.

Synthesis was stratified by disease group (Chronic Kidney Disease, Cardiovascular Disease, Hypertension, Stroke, Type 2 diabetes or Other). (Micro-)Simulation studies were not used as part of the quantitative synthesis as they did not reflect real-world results. Outcomes considered for the meta-analysis included odds ratios, hazard ratios, quality-adjusted life years, and mean differences for each health outcome. For studies evaluating binary outcomes such as incidence, I used a confusion matrix to convert values to odds ratios for the meta-analysis. For secondary outcomes evaluating differences in distributions, the effect size was calculated using Cohen's D (differences in means divided by pooled standard deviation) to establish the mean difference. Studies were weighted based upon the inverse of their variability and to calculate heterogeneity, the I^2 score was used. Further subgroup analyses were conducted where possible, through age, index of multiple deprivation and gender.

Simulation Studies

I conducted a separate analysis for simulation studies as these did not use real world patient data and their population level effects were estimated by using results found in pre-existing studies applied to a hypothetical but realistic population. Consequently, the research questions of (micro) simulation studies analyse the causal contrast of the simulated population allocated to one treatment (e.g. no NHS Health Check) versus the same population allocated to an alternative treatment course (e.g. NHS Health

Check). Therefore, where possible results were presented in reference to no NHS Health Check. I also discussed results where the current implementation of the NHS Health Check is the reference group to understand the contextualised effectiveness of the current implementation of the NHS Health Check and how this could be improved; such results are important for public health policies and supports external validation for further chapters of my PhD.

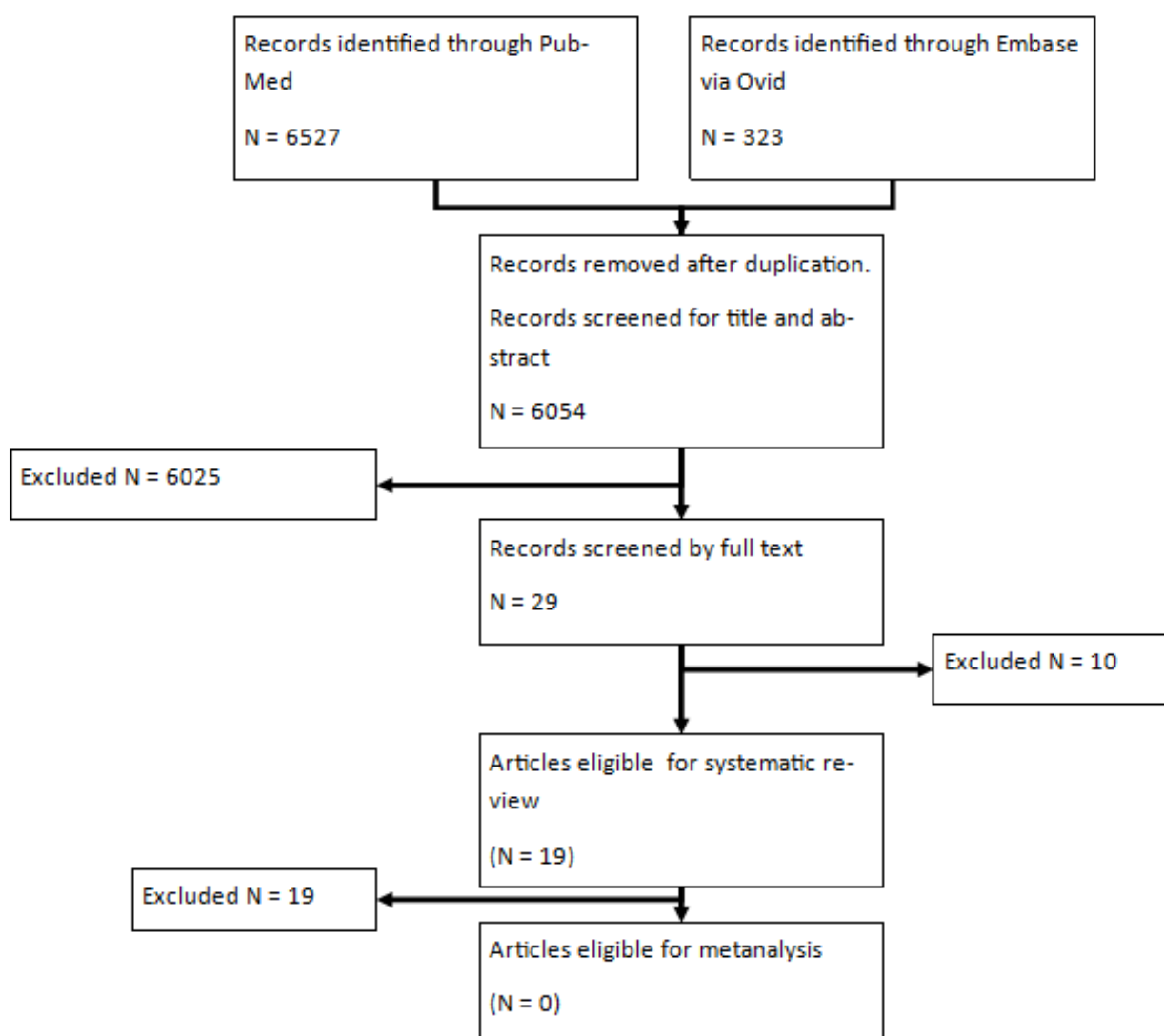
To guide the synthesis and appraisal of simulation studies, I used the guidelines created by Zhang et al., 2020 which was based upon reports and recommendations from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)-Society for Medical Decision Making (SMDM) Modelling Good Research Practices Task Force. Zhang et al.,2020 intended the checklist to be used to guide the write up (descriptive characteristics) and appraisal of simulation studies. Full details of the guidelines can be found in Zhang et al., 2020.

Results

Study selection

Nineteen articles met my inclusion criteria from an original 6,850 papers identified. After removing duplicates, 6,054 articles were eligible to be screened by title. 120 articles were left after a title screen; 5934 articles were removed as they included either chronic kidney disease, cardiovascular disease, hypertension, stroke, or type 2 diabetes in the title but did not mention a “health check”. 29 titles were left after an abstract screen; 91 studies were primarily excluded because they were either commentaries, editorials or studies evaluating the uptake of the NHS Health Check, after a full screen, 19 studies met the inclusion criteria. See Figure 2-1 for a graphical presentation of the PRISMA filter diagram.

Figure 2-1: Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram for studies analysing the NHS Health Check



Study characteristics

See Chapter 2 Table 1 for a summary representation of the included studies.

Study Design

Of the 19 studies included, there was one systematic review that was Martin et al. 2018 and three prospective controlled studies were included 1) Cochrane et al. 2012; 2) Caley et al. 2014; 3) Greaves et al. 2015.

Furthermore, eleven of the studies using observational data including: 1) Hinde et al. 2016; 2) Robson et al. 2017; 3) Chang et al. 2016; 4) Forster et al. 2016; 5) Forster et al. 2015; 6) Butterworth et al. 2015; 7) Artac et al. 2013; 8) Robson et al. 2016; 9) Lambert 2016; 10) Carter et al. 2016 and 11) Syed et al. 2012.

Four studies used synthetic data based upon observational data and were modelled using microsimulations designs. These included: 1) Kypridemos et al. 2018; 2) Mytton et al. 2018; 3) Collins et al. 2017 and 4) Kypridemos et al. 2016.

Health outcomes

Seven studies analysed results related to chronic kidney disease, including: 1) Martin et al., 2018; 2) Caley et al. 2014; 3) Robson et al. 2017; 4) Chang et al. 2016; 5) Robson et al. 2016; 6) Carter et al. 2016 and 7) Kypridemos et al. 2018.

Eight studies analysed heart disease related outcomes, including: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Caley et al. 2014; 4) Chang et al. 2016; 5) Syed et al. 2012; 6) Mytton et al. 2018; 7) Collins et al. 2017 and 8) Kypridemos et al. 2016.

Nine studies analysed results related to hypertension: 1) Martin et al. 2018; 2) Caley et al. 2014; 3) Robson et al. 2017; 4) Chang et al. 2016; 5) Forster

et al. 2016; 6) Forster et al. 2015; 7) Robson et al. 2016; 8) Lambert 2016 and 9) Carter et al. 2016.

Four studies analysed outcomes related to stroke, including: 1) Martin et al. 2018; 2) Syed et al. 2012; 3) Mytton et al. 2018 and 4) Collins et al. 2017.

Six studies analysed outcomes related to type 2 diabetes, including: 1) Martin et al. 2018; 2) Caley et al. 2014; 3) Robson et al. 2017; 4) Chang et al. 2016; 5) Robson et al. 2016 and 6) Carter et al. 2016.

Measure

Five studies analysed results that measured prevalence and newly recorded diagnoses, including: 1) Martin et al. 2018; 2) Caley et al. 2014; 4) Chang et al. 2016 and 5) Carter et al. 2016.

Four studies analysed results that measured previously unrecorded diagnoses, including: 1) Martin et al. 2018; 2) Robson et al. 2017; 3) Robson et al. 2016 and 4) Lambert 2016.

Thirteen studies analysed other forms of measures such as change in risk. These studies included: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Greaves et al. 2015; 4) Hinde et al. 2016; 5) Chang et al. 2016; 7) Forster et al. 2016; 8) Forster et al. 2015; 8) Butterworth et al. 2015; 9) Artac et al. 2013; 10) Kypridemos et al. 2018; 11) Mytton et al. 2018; 12) Collins et al., 2017) and 13) Kypridemos et al. 2016.

Analytical Unit

Sixteen studies analysed the individual as the analytical unit of analysis, including: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Greaves et al. 2015; 4) Hinde et al. 2016; 5) Robson et al. 2017; 6) Chang et al. 2016; 7) Forster et al. 2016; 8) Forster et al. 2015; 9) Butterworth et al. 2015; 10) Artac et al. 2013; 10) Robson et al. 2016; 11) Carter et al. 2016; 12) Syed et al. 2012; 13) Kypridemos et al. 2018; 14) Mytton et al. 2018); 15) Collins et al. 2017 and 16) Kypridemos et al. 2016.

Five studies included results derived from using the general practice as the analytical unit of analysis: 1) Martin et al. 2018; 2) Caley et al. 2014; 4) Forster et al. 2016 and 5) Lambert 2016.

Comparison Group

Seven studies included had a comparison group, these studies were: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Caley et al. 2014; 4) Greaves et al. 2015; 5) Hinde et al. 2016; 6) Robson et al. 2017 and 7) Chang et al., 2016.

Four following studies used a counterfactual framework for analysis; that is estimating the outcomes for the same individual under different treatment groups (including none). Therefore, individuals were their own comparisons for the following studies: 1) Kypridemos et al. 2018; 2) Mytton et al. 2018; 3) Collins et al. 2017 and 4) Kypridemos et al. 2016.

Seven studies did not include a comparison group: 1) Forster et al. 2016; 2) Forster et al. 2015; 3) Butterworth et al. 2015; 4) Artac et al. 2013; 4) Robson et al. 2016; 5) Lambert 2016; 6) Carter et al. 2016 and 7) Syed et al. 2012.

Risk of Bias in Studies, Reporting Biases, and Certainty of Evidence

There were no double blinded randomised controlled studies analysing the NHS Health Check; this is primarily due to the NHS Health Check's active participation nature. See Table 2-2 for a summary of the risk of bias, reporting bias and certainty of evidence.

Randomised Assignment

Only two studies out of 19 randomly assign treatment of the NHS Health Check due to their prospective nature, with Greaves *et al.* 2015 assigning on a patient level whilst Cochrane *et al.* 2012 assigned treatment on a general practice level.

To emulate the impact of randomisation such as equal baselines, four following observational studies applied matching methods, including: 1) Robson et al 2017; 2) Chang et al 2016 and 3) Forster et al. 2015,2016.

All simulation studies used a counterfactual outcomes framework where potential outcomes were estimated for the same cohort under different treatment groups; therefore, each individual was assigned to all treatments.

Assessment for Similar Baseline between intervention and control groups in studies

From prospective studies, Greaves *et al.* 2015 which randomised treatment on a patient level found similar baselines whilst Cochrane *et al.* 2012 found no significant differences at baseline except for weight, BMI, and pulse rate. Caley et al. 2014 found that general practices 's offering the NHS Health check were comparable in terms of size, average patient age, gender split when compared to general practices not providing the NHS Health Check; however, practices offering the NHS Health Check were more deprived.

For observational studies, Robson *et al.*, 2017 found that attendees were older than non-attendees, and more likely to be from more deprived quintiles or from South Asian ethnic groups. Chang *et al.*, 2016 found that Health Check attendees were older (mean age 53.5 v. 50.1), more likely to be women (52.6% v. 50.0%) and more likely to be from a white ethnic minority. (Forster *et al.*, 2016) and (Forster *et al.*, 2015) which used the same dataset found that baselines were similar amongst attendees and non-attendees.

As Kypridemos et al. 2018; Mytton et al. 2018; Collins et al. 2017; and Kypridemos et al. 2016 used a counterfactual framework, individuals were compared against themselves, therefore baselines were similar for these studies.

Treatment Equality

Measuring treatment equality for the NHS Health Check is difficult; this is because the NHS Health Check helps mediate a variety of treatments for attendees. For those who are found to have a previously undocumented diagnosis of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes, the NHS Health Check makes referrals to the patient's general practitioner for usual care for these diseases. For patients at risk of developing at least one of aforementioned diseases, patients are then referred to preventative programmes such as the NHS Diabetes Prevention Programme.

Missing Data or Loss to Follow-up

Reporting of loss to follow-up was dependent on study design, and of the studies identified, loss to follow-up was reported in studies which used a before and after or difference-in-difference design. This is likely because these methodologies follow-up individuals at multiple timepoints.

Three studies reported loss to follow-up: Forster et al., 2016 and Forster et al., 2015 reported loss to follow up at 8%, and Greaves et al., 2015 reported loss to follow-up at less than 20%.

Missing data was reported by two studies: Chang et al., 2016 with 20% of attendees having missing ethnicity data, whilst 40% of non-attendees had missing ethnicity data; Cochrane et al., 2012 reporting that 19% of patients had missing data.

Blinding

Due to the active participation required to 1) to provide the NHS Health Check, 2) (being) invite(d) to the NHS Health Check, 3) attending the NHS Health Check, and 4) potentially, being referred to either usual care or a prevention clinic, blinding is not applicable with the NHS Health Check.

Table 2-1: Comparison table used to determine Meta-analysis eligibility. Only studies that have the same healthcare outcomes, measures and population sizes could be used as part of a meta-analysis. CKD = Chronic Kidney disease, CVD = Cardiovascular disease, HT = Hypertension, T2DM = Type 2 diabetes, GP = General Practice

#	Study	Study Design				Healthcare Outcome						Measure			Analytical unit		Comparison Group
		Systematic Review	Controlled Study	Observational	Simulation	CKD	CVD	HT	Stroke	T2DM	Other	Prevalence	New Diagnoses	Other	Individual	GP	
1	Martin et al., 2018	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Cochrane et al., 2012		✓				✓							✓	✓		✓
3	Caley et al., 2014		✓			✓	✓	✓		✓		✓				✓	✓
4	Greaves et al., 2015		✓								✓			✓	✓		✓
5	Hinde et al., 2016			✓							✓			✓	✓		✓
6	Robson et al., 2017			✓		✓		✓		✓	✓		✓		✓		✓
7	Chang et al., 2016			✓		✓	✓	✓		✓	✓	✓		✓	✓		✓
8	Forster et al., 2016			✓				✓			✓			✓	✓	✓	
9	Forster et al., 2015			✓				✓			✓			✓	✓		
10	Butterworth et al., 2015			✓							✓			✓	✓		
11	Artac et al., 2013			✓							✓			✓	✓		
12	Robson et al., 2016			✓		✓		✓		✓			✓		✓		
13	Lambert, 2016			✓				✓			✓		✓			✓	
14	Carter et al., 2016			✓		✓		✓		✓	✓	✓			✓		
15	Syed et al., 2012			✓			✓		✓						✓		
16	Kypridemos et al., 2018				✓	✓								✓	✓		✓
17	Mytton et al., 2018				✓		✓		✓		✓			✓	✓		✓
18	Collins et al., 2017				✓		✓		✓		✓			✓	✓		✓
19	Kypridemos et al., 2016				✓		✓							✓	✓		✓

Table 2-2: Centre of Evidence Based Medicine breakdown to understand bias of the studies. Simulation studies are not included in this breakdown and were included Table 2-3 instead.

#	Study	Randomised Assignment	Similar Baseline	Equal Treatment	Loss of follow up / Missing Data	Blinding	Outcome	Effect Precision	External Validity
1	Martin et al., 2018	NA, study is systematic review	NA, study is systematic review	NA, study is systematic review	NA, study is systematic review	NA, study is systematic review	NA, study is systematic review	NA, study is systematic review	NA, study is systematic review
2	Cochrane et al., 2012	Randomization was conducted on a practice level	There were no significant differences between the groups on any of the measures. However, both groups showed significant and clinically valuable changes in CVD risk, systolic and diastolic blood pressure, total cholesterol, total/HDL cholesterol ratio and waist circumference. Weight, BMI and HDL were effectively unchanged.	No, differences were implemented on a GP level instead of per patient	Baseline inclusion required non-missing data “About 20% of data were missing at follow-up.”	Blinding was provided to researcher only due to the nature of the active participation of the NHS Health Check	Changes in CVD Risk measured using a Difference-in-Difference, reduction within group analysis	Average population CVD risk decreased from 32.9% to 29.4% (p <0.001) in the NHS Health Check only group and from 31.9% to 29.2% (p <0.001)	Study conducted in Stoke on Trent;
3	Caley et al., 2014	“A non-randomised controlled study in a mixed rural and urban county in England.”	“The intervention and control groups were reasonably well matched with no significant difference between them in terms of their list size, mean number of patients eligible for a health check, the mean age of registered patients, the proportion of registered patients that were male, and practice deprivation scores. Practices in the intervention group had significantly higher deprivation scores (that is,	No, different GP's instead of per patient	NA, the analytical unit was the general practice.	NA due to the active participation required	Diabetes, Hypertension, Atrial Fibrillation, Chronic Kidney Disease and Coronary Heart Disease prevalence evaluated using t-tests and logistic regression	P-values were < 0.001 for significant findings	Study conducted in Warwickshire

#	Study	Randomised Assignment	Similar Baseline	Equal Treatment	Loss of follow up / Missing Data	Blinding	Outcome	Effect Precision	External Validity
			more deprived) than practices in the control group”						
4	Greaves et al., 2015	Yes, patients were randomised	There were no significant differences between the intervention and control group regarding BMI, pre-diabetes status, gender, or most other baseline variables. However, the intervention group were significantly older than controls, by a mean 2.9 years, had significantly lower diastolic blood pressure by 4.5 mmHg and spent significantly more time being sedentary (42 minutes /day).	Yes	Loss of follow-up was less than 20%	Patients were not blinded due to the active participation. Statistician was blinded	Change in weight (kg) over 12 months. evaluated using Mean difference	95%CI close to null. Mean Diff 2.6Kg. 95%CI: -4.8 to -0.3, p = 0.025	The population only includes overweight patients. This is only a subset of the inclusion criteria for the NHS Health Check Study was conducted in Bath and North and East Somerset
5	Hinde et al., 2016	No, study used observational data	NA	Yes, due to simulation methodology	No due to simulation methodology	Not applicable due to simulation methodology	CVD risk and mortality Measured using. 1) £/quality-adjusted life year and Reduction in 2) Mean BMI per group	95% confidence interval was provided for the Reduction in Mean BMI. The CI was small at +/- 0.07 kg/m2	Study values from previous studies which used the CPRD

#	Study	Randomised Assignment	Similar Baseline	Equal Treatment	Loss of follow up / Missing Data	Blinding	Outcome	Effect Precision	External Validity
6	Robson et al., 2017	No, study used observational data	Attendees were older than non-attendees and more likely to be from more deprived quintiles or from South Asian ethnic groups.	Cohorts were matched for CCG, NHS Health Check year, age, sex, and ethnic group to reduce bias	Follow Up not applicable to odds ratio design	Not applicable due to observational study and intervention requiring active participation	Odds Ratios used to evaluate previously undiagnosed Chronic Kidney Disease, Hypertension and Type II Diabetes	95% CI were small for all outcomes at +/- 0.09	Study conducted in East London
7	Chang et al., 2016	No, study used observational data	Health Check attendees were older (mean age 53.5 v. 50.1), more likely to be women (52.6% v. 50.0%) and more likely to be from a white ethnic minority Differences between attendees and non-attendees were nonsignificant ($p > 0.05$) after matching, which indicates that the propensity score method substantially eliminated between-group differences in observed characteristic.	Patients were matched for cardiovascular risk	Twenty percent of attendees had missing ethnicity data, whilst 40% of non-attendees had missing ethnicity data.	Not applicable due to observational study and intervention requiring active participation	CVD Risk measured using Absolute reduction between groups was used through a difference-in-difference matching analysis	95% confidence levels were small e.g. (-0.21%, 95% confidence interval [CI] -0.24% to -0.19%)	Yes, study used CPRD, a dataset which has been shown to be representative of England
8	Forster et al., 2016	No, study used observational data	Baselines were similar terms of gender, age, and deprivation	Patients were matched based on general practice, gender, and age	8% had loss of follow-up in the NHS HC Group	Not applicable due to observational study and intervention requiring active participation	Hypertension and for Statin prescriptions measured using Hazard Ratios	Relatively small confidence intervals. E.g. hazard ratio 1.58, 95% confidence interval 1.53–1.63, $P, 0.001$	Yes, study used CPRD, a dataset which heavily presents England

#	Study	Randomised Assignment	Similar Baseline	Equal Treatment	Loss of follow up / Missing Data	Blinding	Outcome	Effect Precision	External Validity
9	Forster et al., 2015	No, study used observational data	Baselines were similar terms of gender, age, and deprivation	Patients were matched based on general practice, gender, and age	8% had loss of follow-up in the NHS HC Group	Not applicable due to observational study and intervention requiring active participation	Hypertension and for Statin prescriptions measured using Hazard Ratios	Relatively small confidence intervals. E.g. hazard ratio 1.58, 95% confidence interval 1.53–1.63, P, 0.001	Yes, study used CPRD, a dataset which heavily presents England
10	Butterworth et al., 2015	NA – study did not have control group	NA – study did not have control group	NA- study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group
11	Artac et al., 2013	NA – study did not have control group	NA – study did not have control group	Not applicable – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group
12	Robson et al., 2016	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group
13	Lambert, 2016	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group
14	Carter et al., 2016	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group
15	Syed et al., 2012	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group	NA – study did not have control group

Outcome

Five studies provided prevalence/incidence rates for the diseases of interest with a comparison group: 1) Caley et al. 2014, 2) Chang et al.2016, 3) Cochrane et al. 2012, 4) Forster et al.2016 and 5) Robson et al. 2017 .

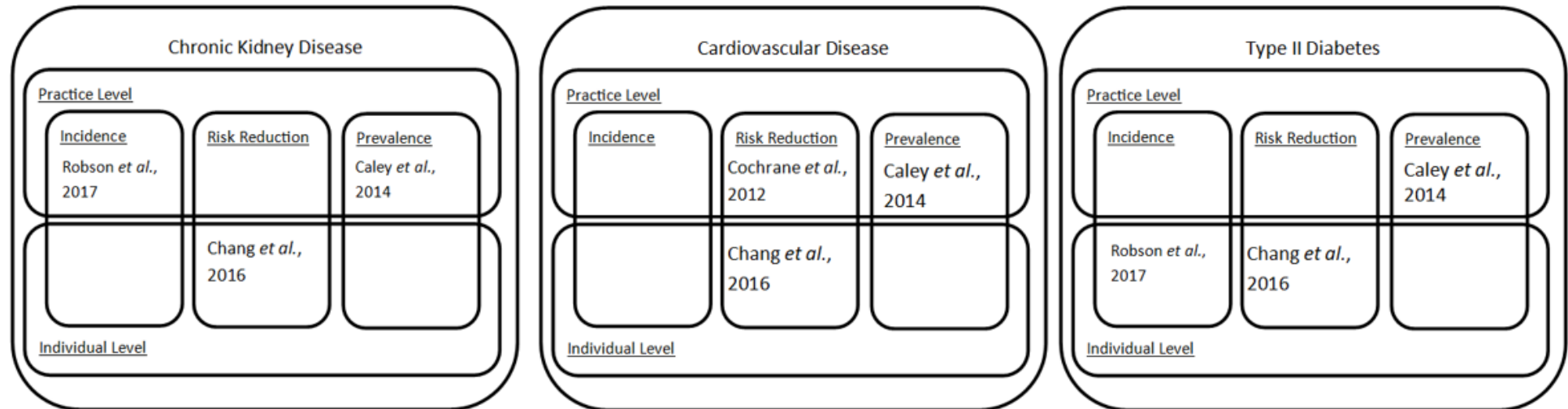
Robson et al., 2017 was a five-year observational study evaluating the incidence of chronic kidney disease, hypertension, and type 2 diabetes at a patient level from 143 general practices.

Chang et al., 2016 was a four-year retrospective observational study conducted using the CPRD and evaluated QRisk2 risk-reduction between matched cohorts from 138,788 patient records using a difference-in-difference analysis.

Forster et al., 2016 also used the CPRD to establish a net increase of a 5% prevalence for hypertension amongst 91,618 eligible participants between 2010 and 2013.

Caley et al.,2014 was a prospective controlled study analysing changes in the prevalence of heart disease, chronic kidney disease and type 2 diabetes between 38 practices providing the NHS Health Check and 41 practices that did not during a three-year period. See Figure 2-2 for a visual breakdown of different measures.

Figure 2-2: Outcomes of the studies illustrating outcome measure and whether they were presented at the individual or practice level



Heart Disease related outcomes

Thirteen studies analysed heart disease-based outcomes with one randomised controlled trial analysing the impact of the NHS Health Check against a modified version of the NHS Health Check (See Table 2-1). Of the three studies evaluating heart disease which involved a control group (see Table 2-1) all were comparing different outcomes or populations, with Cochrane et al., 2012 evaluating NHS Health Check against a modified version of the NHS Health Check, Caley et al., 2014 evaluated CVD risk between GP's offering the NHS Health Check and those GPs who did not, and Chang et al., 2016 evaluating cardiovascular disease risk between attendees and non-attendees from across a selection of general practices. Therefore, due to the differences in comparison groups and health outcomes, a meta-analysis was deemed inappropriate to evaluate the NHS Health Check 's effectiveness on heart disease.

Martin et al. 2018, (systematic review) found through their evidence synthesis, that NHS Health Check attendance provided "small increases in disease detection above routine care" with a "small decrease in modelled CVD risk". No point estimate was provided as the studies were not meta-analysable.

Cochrane et al., 2012 and Chang et al., 2016 concur that the NHS Health Check reduced cardiovascular disease risk using both the 10-year-Framingham Score and the QRisk2 Score by 3.5% (p-value < 0.001) and 0.21% (95% CI: -0.24%, -0.19%) respectively amongst attendees. Caley et al., 2014 established that GPs who provided the NHS Health Check and those that did not both were associated with a 0.1% reduction in the prevalence of heart disease (p-value = 0.639).

Syed et al., 2012 estimated that the NHS Health Check prevents 63 chronic heart disease diagnoses, 90 myocardial infarctions over a period of 5 years in but did not include a comparison group.

Type 2 Diabetes related outcomes

Six studies analysed diabetic healthcare outcomes (see Table 2-1). The studies involving a control group (see Table 2-1) could not be combined into a meta-analysis as Caley *et al.*, 2014 evaluated diabetes prevalence on a practice level, Robson *et al.*, 2017 evaluated new diabetes diagnoses on a patient level, and Chang *et al.*, 2016 presented their results using a difference-in-difference analysis.

Martin *et al.*, 2018 (systematic review) found that the rates of diagnoses of type 2 diabetes were either the same on a general practice level or higher on an individual level. No point estimate was provided as the studies were not meta-analysable.

Three observational studies demonstrated the same or higher rates of the diagnoses of diabetes in NHS Health Check GP attendees using different methods. Caley *et al.*, 2014 showed no significant difference in the prevalence of type 2 diabetes in practices that undertook a health check (0.4% reduction after NHS Health Check) compared to those that did not (0.37% reduction after NHS Health Check) with a p-value of 0.74. Chang *et al.*, 2016 demonstrated a 31% increase in the prevalence of diagnosed diabetes in those who attended health checks compared to those who did not (Difference in difference = 1.31, 95% CI = 1.17 to 1.45). Robson *et al.*, 2017 also demonstrated a 30% increase in the incidence of diagnosed diabetes in those who attended the health checks compared to those who did not (OR = 1.30, 95%CI = 1.21 to 1.39, p-value <0.001).

Robson *et al.*, 2016 found that out of 1000 NHS Health checks, there would be 9 new diagnoses of type 2 diabetes; there was no control group to compare against. Carter *et al.*, 2016 found that over a period of 5 years, 6% of attendees had a new diagnosis of type 2 diabetes; no control group was provided.

Stroke related outcomes

Two studies analysed stroke (see Table 2-1) with one study including a comparison group.

Martin et al., 2018 synthesised that rates of stroke were lower in the NHS Health Check group but did not provide a point estimate as the studies were not meta-analysable.

Chang *et al.*, 2016 demonstrated limited evidence using observational data when comparing the NHS Health Check 's impact on the incidence of stroke after comparing attendees against non-attendees (Difference-in-difference = -0.03, 95% CI = -0.05 to -0.01, $p > 0.05$).

Chronic Kidney Disease

Six studies analysed chronic kidney disease (see Table 2-1). The studies which involved a comparison group could not be meta-analysed as Caley et al., 2014 evaluated chronic kidney disease prevalence on a practice level, Chang et al., 2016 analysed individual prevalence, whilst Robson et al., 2017 evaluated chronic kidney disease new diagnoses at a patient level.

Martin et al., 2018 (systematic review) found that the rates of diagnoses of chronic kidney disease were the same higher among NHS Health Check attendees compared to non-attendees but did not provide a point estimate as the studies were not meta-analysable.

Caley et al., 2014, estimated that the NHS Health Check has no impact on the prevalence of chronic kidney disease on a practice level with a reduction of 0.60% in NHS Health Check practices and 0.38% reduction in non-NHS Health Check practices (p -value = 0.54). On a patient level, Robson et al., 2017 established that the first diagnosis of chronic kidney disease was higher in the matched group which had an NHS Health Check compared to those who did not (OR = 1.83, 95% CI = 1.52 to 2.21). Chang et al., 2016 demonstrated that the NHS Health Check participants had a higher

prevalence of chronic kidney disease with 0.17% (95% CI 0.11% to 0.23%, $p < 0.05$) higher prevalence compared to those who did not attend a health check.

Robson *et al.*, 2016 estimated that 4 out of 1000 NHS Health Checks would result in a new diagnosis of chronic kidney disease; no comparison groups were provided. Carter *et al.*, 2016 estimated that 1.64% of health checks would result in a diagnosis of chronic kidney disease in Leicester.

Hypertensive Related Outcomes

Nine studies analysed Hypertension with three studies including a control group (see Table 2-1). As Caley *et al.*, 2014 analysed the NHS Health Check on a general practice level, Forster *et al.*, 2016 analysed the NHS Health Check on a patient level and Chang *et al.*, 2016 presented their results prior to matching, a meta-analysis was deemed inappropriate due to the different comparison groups.

Martin *et al.*, 2018 (systematic review) found that the rates of diagnoses of hypertension were the same or higher among NHS Health Check attendees at the individual level but not at the general practice level but did not provide a point estimate as studies could not be meta-analysed.

Caley *et al.*, 2014 suggests there is no difference in hypertension prevalence on a practice level as practices that implemented the NHS Health Check saw an increase of 0.46%, whilst those that did not saw an increase of 0.30% with a p-value of 0.54. Forster *et al.*, 2016 demonstrated a statistically significant higher diagnosis rate of hypertension in men only when comparing on a patient-level (5%+, $p < 0.001$) to those who did not partake in an NHS Health Check. Robson *et al.*, 2017 found that those attending an NHS Health Check were more likely to be diagnosed with hypertension in a matched analysis: hypertension with an odds ratio of 1.50 (95% CI = 1.43 to 1.57).

Chang *et al.*, 2016 demonstrated that participants of the NHS Health Check were more likely to have a recording of hypertension at 4.08% compared to 0.76% for those who did not participate; this generated a difference-in-difference estimator of 2.99% (2.77 to 3.21). Forster *et al.*, 2016 found that in a matched analysis, men who received the NHS Health Check were 5% more likely to be diagnosed with hypertension compared to men who did not receive the NHS Health Check ($p < 0.001$)

Forster *et al.*, 2015 estimated (without a control group) that for every 1000 males assessed, 355 (95%CI: 340 - 369) would be newly diagnosed with hypertension and 668 (95% CI: 646 - 689) for women. Robson *et al.*, 2016 estimated that for every 27 health checks, 1 would result in a new recorded diagnosis of hypertension; no control group was provided. Lambert, 2016 estimated that new identifications of hypertension occur in one in every 10 NHS Health Checks; no control group was provided for comparison. Carter *et al.*, 2016 estimated that 19% of those who have a health check would have a new diagnosis of hypertension over a 5-year period; no control group was provided for comparison.

Other healthcare-related outcomes

Four studies met the secondary outcomes criteria (see Table 2-1). One systematic review was identified, Martin *et al.*, 2018. Martin *et al.*, 2018 evaluated the NHS Health Check in terms of coverage, uptake, and any health-related impact. In terms of health-related impact, Martin *et al.*, 2018 concluded that the NHS Health Check was associated with short term small increases of disease detection for cardiovascular disease, and higher rates of antihypertensive and statin prescriptions compared to no-NHS Health Check. Greaves *et al.*, 2015 propose that a variation of the NHS Health Check, known as 'Waste the Waist' estimated an average weight loss of 2.6Kg (95%CI: -4.8 to -0.3, $p = 0.025$) at a participant level. Hinde *et al.*, 2017 suggests that the NHS Health Check was associated with a reduction in

mean BMI of 0.27kg/m² (95% CI: 0.20 to 0.34) compared to no check. Syed, Talbot-Smith & Gemmell, 2012 has also estimated the NHS Health Check 's ability to prevent one case of lung cancer over a 5-year period.

Micro-simulation studies

I identified four micro-simulation studies; that is those that used synthetic patient data and used results from prior studies to understand how changing the parameters of the NHS Health Check would have on population level outcomes.

Table 2-3 shows the appraisal framework consisting of the 18 items developed by Zhang et al., 2020 for conducting and appraisal simulation studies. As all the studies pre-date the publication of the check list, items such as "Is predictive validation performed or attempted?" were not reported in any study whilst items such as "Is the focused health-related decision problem clarified?", "Is the model structure described?" were reported in all studies. See Table 2-3 for full details of the studies such as the healthcare related problem, the model structure, the time horizon, population, and simulated scenarios as well as the appraisal of simulation studies.

Kypridemos et al., 2018 evaluated whether the NHS Health Check's current strategy would be cost-effective using alternative recruitment strategies using the distribution of characteristics in Liverpool; they found that the current implementation of the NHS Health Check (that is inviting healthy individuals) is not likely to be cost-effective or equitable with an estimated cumulative incremental cost-effect ratio (ICER) of 11,000 (95%CI -270,000 to 320,000) and a targeted approach should be used based upon clinical need and deprivation would improve the cost effectiveness and equity of the NHS Health Check with ICER estimates of -5000 (95%CI -7400 to -3100).

Mytton et al., 2018 evaluated the effectiveness and equity of the NHS Health Check in reference to no NHS Health Check for 200,000 synthetic patients'

representative of England. They estimated that the NHS Health Check prevents 390 (95% CI: 290 - 500) premature deaths before age 80 and predicts that 1,370 (95% CI 1,100 - 1,690) individuals without the burden of disease (ischaemic heart disease, stroke, dementia, and lung cancer) at age 80 years per million people when compared to no NHS Health Check. Additionally, Mytton et al., 2018 estimated that changes to the eligibility criteria of the NHS Health Check (for example, by not excluding those with Hypertension and extending the age criteria to 80 years old), would produce an estimated three-fold decrease in mortality (1360 vs 390 premature deaths).

Collins et al., 2017 estimated the impact of four alternative treatments for the Liverpool population; 1) no NHS Health Check, 2) the current implementation of the NHS Health Check, 3) an NHS Health Check with increased uptake, prescribing and lifestyle advice and 4) targeted recruitment based upon deprivation. Collins et al., 2017 found that the current implementation of the NHS increases health inequities; that is primarily driven by participation of least deprived individuals and currently costs £17 600 per quality adjusted life year; targeted recruitment of the NHS Health Check to those who were more deprived would change this to £3000 per quality adjusted life year in terms of stroke and coronary heart disease prevalence and mortality.

Kypridemos et al., 2016 estimated the impact of the NHS Health Check in the English population. They estimated five scenarios, with the reference scenario being the current NHS Health Check trends. Kypridemos et al., 2016 estimated that an NHS Health check could be improved by combining population-wide interventions and concentrated screening and would prevent 82,000 (73,000 – 93,000) cases of cardiovascular disease and 9,000 (6,000-13,000) deaths by 2030 in a population of 400,000 people.

Table 2-3: Appraisal of micro-simulation studies based upon checklist by Zhang et al., 2020 which is based upon reports from the International Society for Pharmacoeconomics and Outcomes Research Society for Medical Decision Making Modelling's Good Research Practices Task Force

Item No	Item Description	Study			
		Kypridemos et al., 2018	Mytton et al., 2018	Collins et al., 2017	Kypridemos et al., 2016
1	Is the focused health-related decision problem clarified?	Yes, investigates whether the NHSHC is cost-effective and equitable in a city with high levels of deprivation and CVD	Yes, investigates health benefits of NHSHC and effects on inequity and whether changes to the NHSHC can change this	Yes, investigates whether the NHSHC is cost-effective and equitable in a city with high levels of deprivation and CVD	Yes, investigates whether universal screening in NHSHC reduces CVD burden
2	Is the modelled healthcare setting/health condition clarified?	Yes, general practices	Yes, general practices	Yes, general practices	Yes, general practices
3	Is the model structure described?	Yes, IMPACT _{NCD}	Yes, as a two-module model consisting of modelling baseline risk and an intervention model	Yes, IMPACT _{NCD}	Yes, IMPACT _{NCD}
4	Is the time horizon given?	Yes, 2017 to 2024	Not found	Not found	Yes, 2016 to 2030
5	Are all simulated strategies/scenarios specified?	Yes, five scenarios were described	Yes, four scenarios were described	Yes, four scenarios were described	Yes, five scenarios were described
6	Is the target population described?	Yes, 200 million adults aged 30 to 84 based upon Liverpool's demographics	Yes, 200,000 individuals aged 40-45 representative of the English population	Yes, 258,000 individuals aged 30-84 based upon Liverpool's demographics	Yes, 400,000 individuals based upon the health survey for England
7	Are data sources informing parameter estimations provided?	Yes, included in Table 1 and Appendix A	Yes, included in Table 1 and Appendix A	Not found	Yes, in Supplementary Table S1
8	Are the parameters used to populate model frameworks specified?	Yes, included in Table 1 and Appendix A	Yes, included in Table 1 and Appendix A	Yes, found on GitHub repository	Yes, in Supplementary Table S1
9	Are model uncertainties discussed?	Yes, uncertainty and sensitivity analysis section	Yes, uncertainty analyses section	Yes, found on GitHub repository	Yes, in uncertainty and sensitivity analysis
10	Are sensitivity analyses performed and reported?	Yes, uncertainty and sensitivity analysis section	Yes, sensitivity analysis section	Yes, found on GitHub repository	Yes, in uncertainty and sensitivity analysis
11	Is face validity evaluated and reported?	Not found	Yes, model validation section	Not found	Not found
12	Is cross validation performed and reported	Not found	Not found	Not found	Not found
13	Is external validation performed and reported?	Not found	Yes, "Comparison to other work" section	Not found	Not found
14	Is predictive validation performed or attempted?	Not found	Not found	Not found	Yes, in Validation section
15	Is the model generalizability issue discussed?	Yes, in Limitations	Yes, in Limitations	Not found	Not found
16	Are decision makers or other stakeholders involved in modelling?	Not found	Yes, acknowledged staff at Public Health England	Not found	Not found
17	Is the source of funding stated?	Yes, including Liverpool City Council	Yes, Public Health England	Yes, including Liverpool City Council	Yes
18	Are model limitations discussed?	Yes, in Limitations	Yes, in Limitations	Not found	Yes, in Limitations

Discussion

My updated review aimed to summarise the impact of the NHS Health Check on health outcomes and the quality of the evidence evaluating the NHS Health Check. Interventions in the included studies from 2009 and up to 2018 and found 19 studies that met the inclusion criteria. The majority of included studies examined heart disease or diabetic outcomes. Studies examining cardiovascular disease outcomes found evidence that health check interventions reduced cardiovascular disease risk measured using 10-year-Framingham Score. Studies examining diabetic disease outcomes found evidence that health check interventions increased the diagnosis of prevalence or new type 2 diabetes cases. The evidence also suggests that general practices which provide the NHS Health Check detect at least the same, and at sometimes, higher rates of previously unrecorded diagnoses of heart disease, chronic kidney disease and hypertension compared to practices that do not offer the NHS Health Check. However, it is likely that findings are a result of the NHS Health Check screening process identifying previously undiagnosed prevalent cases. Therefore, there is evidence suggesting that NHS Health Check achieves one of its goals of detecting previously undiagnosed cases of heart disease, chronic kidney disease, hypertension, and type 2 diabetes that could reduce or delay disease progression. Such results are similar to Martin et al., 2018.

Existing studies were limited as they primarily evaluated the rates of detecting disease and not specifically whether the NHS Health Check reduces the incidence of chronic kidney disease, diabetes, heart disease, hypertension, or stroke in “healthy” individuals without a prior disease burden. As a result of these limitations, there remains uncertainty about the strength of the evidence for the NHS Health Check to prevent cases of disease and reduce the incidence of diseases in patients without existing chronic kidney disease, diabetes, heart disease, hypertension, or stroke.

Evidence appraisal of the studies analysing NHS Health Check also suggests that general practices and patients who took up the NHS Health Check were often more deprived and less healthy at the start of follow-up (Robson et al., 2017; Caley et al., 2014); this could be an ascertainment bias due to the fact that those practices undertaking NHS Health Check are more proactively diagnosing these conditions compared practices that are not undertaken NHS Health Checks.

Simulation studies estimate that the current implementation of the NHS Health Check is not cost-effective; however, the simulation studies also demonstrate the NHS Health Check's ability to become cost-effective with higher rates of adherence to the lifestyle and pharmacotherapy interventions introduced by the NHS Health Check. Due to the in-silico nature of these studies, this study design can quickly generate estimates given a set of parameters and distributions. The simulation studies have provided access to their source code, allowing other researchers to conduct their own simulation studies. Unlike studies which use electronic health records (which require ethics approvals), the simulations have a special nature as they use publicly available distributions as part of their calculations, for example, Kypridemos et al., 2018 used data localised to Liverpool whilst Mytton et al., 2018 used data from the Health Survey for England. Consequently, may result in suggesting different implementations of the NHS Health Check to reflect regional differences. Furthermore, as these studies used a counterfactual analysis, treatment assignment is not related to baseline characteristics, therefore the results could be less impacted by confounding by indication.

A strength of my systematic review is that it provides a comprehensive up to date search looking at specific outcomes of the NHS Health Check during a time period when statins were widely prescribed. Unlike prior reviews, this study's analysis specifically evaluates the NHS's implementation of the Health

Check; that is, prior systematic reviews have analysed multiple implementations of a health check worldwide not designed by a single body.

One major challenge is that this study used a single reviewer for article inclusion and data extraction. Despite this, this study identified the same studies as Martin *et al.*, 2018. Similar to Martin *et al.*, 2018, no meta-analysis was conducted due to the lack of suitability of the extracted data for a meta-analysis. Secondly, though studies that apply the per-protocol analysis, it is established that the NHS Health Check can have a positive impact on patients. Therefore, increased uptake should reflect better outcomes and further work should be undertaken to investigate further the evidence for effectiveness of the NHS Health Check to prevent the development of cardiovascular and diabetic disease. Another limitation, specifically when appraising simulation studies, is that the checklist for appraisal was created after the studies had been published. This is due to the relatively new uptake of simulation studies to estimate the effectiveness of population level interventions. However, due to the opensource nature of simulation studies in terms of data generation and analysis, researchers should be able to conduct sections missing in the analysis such as “predictive validation”.

Chapter 3 – Evaluating the population level impact of the NHS Health Check: a quasi-experimental interrupted time series analysis.

Abstract

Introduction and research gap: The NHS Health Check may be considered as a population level public health intervention which identifies and introduces high risk patients to other public health interventions; for example, statin prescriptions for individuals with high cardiovascular risk (10% QRisk), advice on weight management for overweight patients, smoking/drinking cessation assistance or a referral to the NHS Diabetes Prevention Programme for patients at high risk of developing type 2 diabetes. There is currently a lack of understanding of the NHS Health Checks influence on population level health outcomes; therefore, this chapter aims to investigate the evidence for the NHS Health Check on changes in population rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes.

Methods: I conducted a quasi-experimental interrupted time series analysis using the secondary care administrative data collected between June 2003 to March 2017 (latest HES build) with an interruption in 2009, when the NHS Health check was introduced. Monthly admission rates (adjusted for population size) for chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes were estimated using Hospital Episode Statistics. To mirror the inclusion criteria of the NHS Health Check, I included individuals between the ages of 40-74 on admission. Rates of change in admission proportions were compared before and after the introduction of the NHS Health Check in 2009.

Results: Between 2003 and the introduction of the NHS Health Check (2009), I found there was a month-to-month decrease of 1.82 admissions per

month per 100,000 people [95% CI: -2.14 admissions/100,000 to -1.51 admissions/100,000] for cardiovascular disease, diabetes and stroke combined. After the introduction of the NHS Health Check in 2009 until the end of the study (2017), I found a month-to-month decrease of 0.13 admissions per month per 100,000 people [95% CI: -0.29 admissions/100,000 to 0.03 admissions/100,000]. Investigating changes in chronic kidney disease and hypertension was challenging due to varying temporal changes for these diseases during the study period.

Discussion and Conclusion

Using interrupted time series, I did not detect a superior change in rates of hospital admissions for cardiovascular disease, diabetes, and stroke after the introduction of the NHS Health Check when compared to pre-NHS Health Check. Such detections could be attributable to low NHS Health Check uptake introduced in Chapter 1. There were also difficulties in analysing hypertension and chronic kidney disease due to temporal variability in clinical coding for these diseases in secondary care.

Next Steps: A study comparing rates of healthcare outcomes in invitees of public health interventions with a comparable control group akin to a randomised control trial evaluating the preventative effect of public health interventions on healthcare outcomes.

Notes: At the time of conducting this PhD, I did not apply this method to the NHS Diabetes Prevention Programme due to limitations with sample sizes (month-to-month data points) since the NHS Diabetes Prevention Programme was a recent deployment. Upon returning from COVID-19 leave, I found a study that conducted an national level analysis of the NHS Diabetes Prevention Programme on rates of type 2 diabetes; they found that since the introduction of the NHS Diabetes Prevention Programme, there was a reduction in type 2 diabetes (IRR = 0.938 [95% CI 0.905 to 0.972]) (McManus et al., 2022) when comparing general practices who introduced the NHS

Diabetes Prevention Programme early to those who introduce the NHS Diabetes Prevention Programme at a later time point.

Complementary Reading Material: To aid readers in this chapter, the Framework for Enhanced Reporting of Interrupted TimeSeries (FERITS) checklist has been provided in Appendix 3.1.

Publications related to this chapter:

Rockenschaub, P., Nguyen, V., Aldridge, R.W., Acosta, D., García-Gómez, J.M. and Sáez, C. (2020). Data-driven discovery of changes in clinical code usage over time: a case-study on changes in cardiovascular disease recording in two English electronic health records databases (2001–2015). *BMJ Open*, [online] 10(2), p.e034396. doi:10.1136/bmjopen-2019-034396.

Introduction

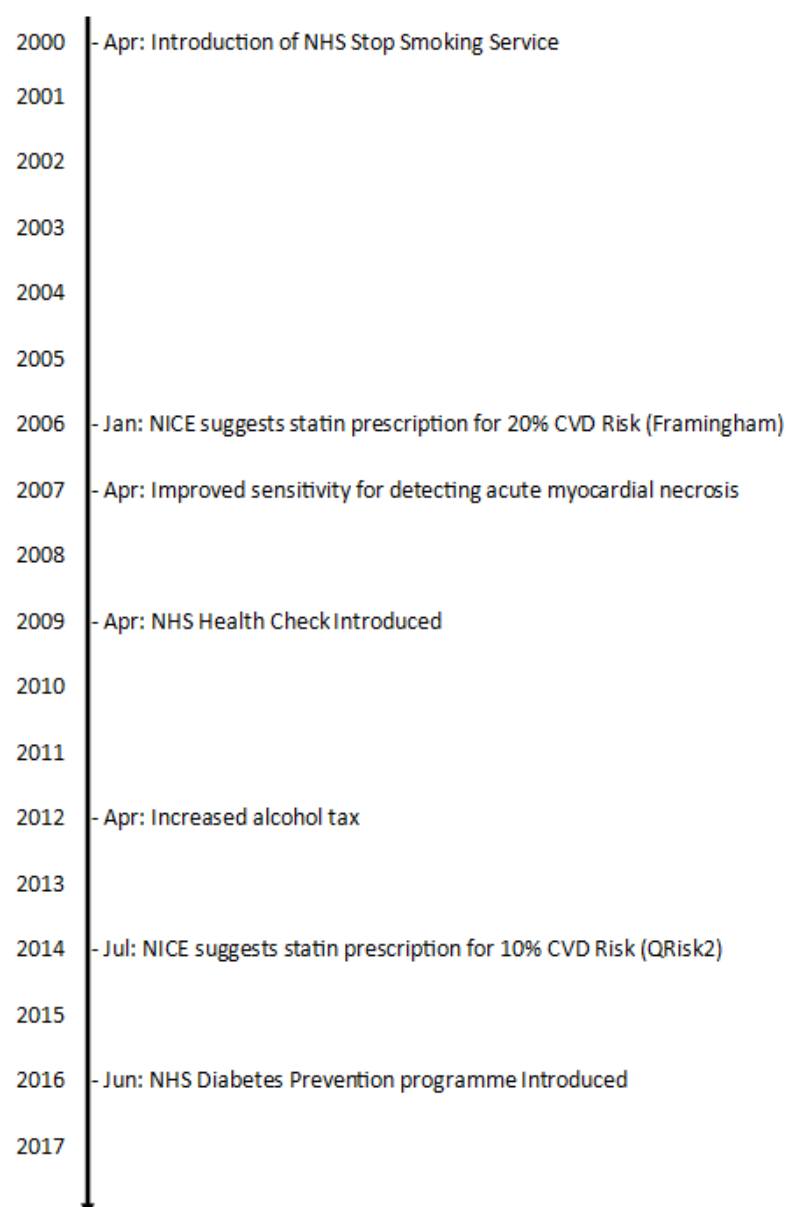
In the previous chapter, there was evidence to suggest that the NHS Health Check detected prevalent cases of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes. However, there was a lack of evidence around whether the NHS Health Check was able to reduce and prevent the development of these conditions. In this chapter, I evaluated whether there is evidence of the NHS Health Checks having an impact on national rates of cardiovascular disease, chronic kidney disease and type 2 diabetes at population level after its introduction.

The NHS Health Check is delivered at a patient level as general practitioners actively find patients between the ages of 40 to 74 who do not have a previous record of heart disease, hypertension, chronic kidney disease, stroke, or type 2 diabetes. By uncovering those who had not previously developed one of the aforementioned diseases, the NHS Health Check aims to prevent or postpone of cardiovascular disease onset through prescriptions of antihypertensives, statins and lifestyle interventions, a process that is often achieved by facilitating the referral of patients to other NHS provided public health interventions. Examples of lifestyle interventions to which patients could be referred to by the NHS Health Check include the NHS Stop Smoking Service, the NHS Diabetes Prevention programme, and several different weight management schemes. In addition to prevention, the NHS Health Check also aims to reduce disease progression in those who already have a previously unrecorded diagnosis (at the time of being invited) through early identification.

The designers of the NHS Health Check aimed for the NHS Health Check to reduce yearly growth and long-term financial burden of non-communicable diseases and their long-term consequences, specifically targeting coronary heart disease, hypertension, chronic kidney disease, stroke, and type 2

diabetes. See Figure 3-1 for an example of the events that the NHS Health Check can refer patients to.

Figure 3-1: A timeline of policies aimed at reducing cardiovascular events. For events whose exact introduction day could not be established, I used the first day of the fiscal year (1st April) for the year in which I knew the policy was introduced.



Currently there is limited research on the effects of the NHS Health Check on healthcare outcomes, particularly rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes. A great deal of existing research on the NHS Health Check has concentrated on attendance, uptake and prescribing rates (of statins and antihypertensives), with fewer studies conducted examining research on the population level health outcomes (Martin et al., 2018).

Whilst statins and antihypertensive have been proven to be clinically significant in improving cardiovascular health, the lifestyle components of the NHS Health Check are questioned due to the potential for low adherence for interventions of this nature (Cook et al., 2016; Dalton et al., 2011; Forster et al., 2014). Systematic reviews evaluating similar programmes worldwide demonstrated no difference compared to no health checks for the prevention of morbidity related to cardiovascular disease (Krogsbøll et al., 2012). Studies have attempted to establish an evidence base by establishing the effect of the NHS Health Check on healthcare outcomes by using retrospective cohort studies (Caley et al., 2014; Chang et al., 2016; Robson et al., 2017).

However, these sets of studies suffer from a variety of biases, specifically their lack of generalisability to the whole English population. For example, some studies were also limited as they conducted research on the NHS Health Check in specific geographical areas which may not be representative of the UK as a whole (Caley et al., 2014; Robson et al., 2016); this is because Caley et al, 2014 was conducted in one region Warwickshire whilst Robson et al., was conducted in East London; both of these regions have been shown to have a higher proportion of deprived individuals compared to the rest of England. Therefore, even if the NHS Health Check is effective under sub-populations, it may not reduce cases of coronary heart disease, hypertension, chronic kidney disease, stroke, or diabetes at the population level.

Aims and objectives.

The aim of this chapter is to evaluate the effects of the NHS Health Check nationally in England. This study uses national electronic record data and a quasi-experimental interrupted time series analysis to investigate whether there were changes in yearly growth of non-communicable disease (cardiovascular disease, hypertension, type 2 diabetes, chronic kidney disease) before and after the introduction of the NHS Health Check in England. To achieve this aim, my objectives for this chapter include:

- Estimating monthly national hospital admissions trends per 100,000 people in the English population for non-communicable diseases before the introduction of the NHS Health Check
- Estimating monthly national hospital admission trends per 100,000 people in the English population for non-communicable diseases after the introduction of the NHS Health Check
- Comparing the change in direction and magnitude of monthly trends of non-communicable diseases trends prior to the introduction of the NHS Health Check and after the introduction of the NHS Health Check

In addition to the specific scientific objectives outlined above, this study was also conducted as I was able to rapidly access comprehensive coverage data in England whilst waiting for other (individual level) data required in later chapters. Conducting this study also enables me to gain a comprehensive understanding of the population outcomes that are examined in detail in the later chapters. Due to the recent deployment of the NHS Diabetes Prevention Programme (2016) and the latest HES data build (March 2017), an interrupted time series analysis was deemed inappropriate for the NHS

Diabetes Prevention Programme due to low sample sizes; therefore, this chapter only examines the NHS Health Check.

Methods

Study Design

The study design was a quasi-experimental interrupted time series. This design was chosen as such methods are suitable to evaluate the impact of national public health interventions and policies (Bernal et al., 2017). In this study, the Population includes the English population between the ages of 40-74, with an Intervention of the NHS Health Check, Comparisons are done pre-and post NHS Health Check and an Outcome of change in hospitalisation rates.

Data Resource

To analyse the NHS Health Check's impact in England, I examined admitted patient care hospital records across England using the Hospital Episode Statistics (HES) dataset. HES records are recorded and coded after each admission and are collected from 451 NHS hospitals providers in England on a monthly basis since 1987 to the Secondary User Service. These data are then made available for researchers to use. I used HES records for this analysis because of its high coverage of hospital admissions compared to primary care data (Denaxas et al., 2012). To generate admission rates, population size data for England were used as denominators. My population denominators were produced by the Office of National Statistics (ONS).

Intervention

See Chapter 1 for a detailed description of the NHS Health Check. The prevention of incidence cases and disease detection of cardiovascular disease, leading to better management should result in a reduction in admissions to secondary care over longer time periods, which this study has been designed to investigate.

Uptake

Initial deployment of the NHS Health Check was phased; however, since the Health and Social Care Act 2012, all local authorities were mandated to provide the NHS Health Checks. Models of the NHS Health Check were generated in 2008, with an estimated 70% attendance rate. However, studies have demonstrated uptake of the NHS Health Check is only at around 20% of the eligible population (Robson et al., 2016). See [Chapter 1](#) for more details.

Study Population

As the NHS Health Check was only offered in England, I restricted the geographical population to the English population only. Since the NHS Health Check was only offered to those between the ages of 40-74, I also applied this restriction for each admission. Due to this age restriction, and the fact that I am analysing the cardiovascular trends over time, a rolling/changing cohort was used. To account for changes in admission rates which may be caused by a change in population size, yearly population data was used as denominator data to calculate admission rates. The year population data was also a rolling number and was also restricted to those between the ages of 40 – 74 for each year between 2003 to 2017. As my dataset has “universal coverage” (Herbert et al., 2017) of NHS hospital providers in England, biases due to under-sampling were not considered to be of substantial concern.

Comparator Populations

I made comparisons pre- and post-intervention using a segmented linear regression model and not between participants.

Study Period

My interrupted time series study used data between June 2003 and March 2017. I was limited to this period because there was inconsistent use of ICD10 codes prior to 2003 (see discussion) and population data was only available until 2017. I analysed data on a month-to-month basis; I used monthly aggregated data because yearly data would not have provided

enough data points whilst choosing daily samples would mean using insufficient numbers of admissions. I defined the pre-intervention period between June 2003 to December 2008; the intervention introduction period as January 2009, and the post-intervention period from February 2009 to March 2017. To account for the time between the introduction of the NHS Health Check and it being nationally mandated; I conducted sensitivity analyses using a 3-year lag which allowed for a transition period during the introduction of the NHS Health Check from January 2009 to January 2012.

Sample Size

Studies have demonstrated that the empirical power for interrupted time series requires a combination of total time points and the number of samples in each time point (Hawley et al., 2019). By choosing monthly aggregates between June 2003 and March 2017, 168 individual data points were analysed, more than the 24 data points recommended to reduce the impact of seasonality, and more than the 100 data points recommended for an interrupted time series (Hawley et al., 2019). As HES comprehensively captures the English population's admissions (Herbert et al., 2017), the number of samples for each time point was sufficient for empirical power. Therefore, the number of samples for each time point and the total number of timepoints would not be problematic towards empirical power.

Outcomes

My outcome of interest was monthly hospital admission rates of the diseases the NHS Health Check was designed to tackle, including heart disease, diabetes, and stroke. Therefore, in this analysis, I evaluated the chance of prevalence of heart disease, diabetes, and stroke through time. To calculate the monthly admission rates, raw numbers of admissions for a specific month were divided by the population size for the corresponding year (see analysis section). My data extraction of the outcomes was conducted by Public Health England. See Table 3-1 for ICD10 case definitions.

*Table 3-1: Case Definitions for cardiovascular disease, diabetes, and stroke. * Represents descendant codes*

Disease	Code
Cardiovascular Disease – Heart Failure	I50.*
Diabetes	E1*
Stroke/Cerebrovascular disease	I6*

Due to historical changes in clinical definitions of cardiovascular disease, I could not analyse specific cardiovascular conditions in isolation as temporal changes in admission rates were detected. For example, studies have found that changes in clinical definitions in 2007 and ICD10 changes in 2012 caused temporal changes in admission rates for myocardial infarction and stroke (Rockenschaub et al., 2020). The temporal changes also occurred for type 2 diabetes (Figure 3-2). chronic kidney disease (Figure 3-3) and hypertension (Figure 3-4). For example, for type 2 diabetes, I found a consistent rise of admission rates between 2001 until 2012, with a sudden drop in admission in 2012; see Figure 3-2 for a graphical representation of this. Such temporal variability was independently confirmed by two other teams in University College London.

To tackle these issues with temporal changes, I evaluated non-specific diseases (Rockenschaub et al., 2020); the groups I evaluated included heart disease (ICD10 – Codes I50.*, where *represents any subsequent code), diabetes mellitus (E1*) and I6* for cerebrovascular disease. I could not find a solution for generating consistent chronic kidney disease and hypertension admission rates; for example, by defining chronic kidney disease and hypertension using consistently used ICD10 subcodes had reduced the numbers evaluated. Therefore, I decided to not include these outcomes

using an interrupted time series design with Hospital Episode Statistics for this chapter.

After extracting admissions data for heart disease, diabetes, and cerebrovascular disease, I found consistent ICD10 usage for heart disease and diabetes between June 2003 and March 2017. For cerebrovascular disease, I found consistent ICD10 usage for between March 2006 and March 2017 (see results section)

Figure 3-2: Interrupted Time Series for Type 2 diabetes alone (ICD10: E11). In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates adjusted for yearly population size.*

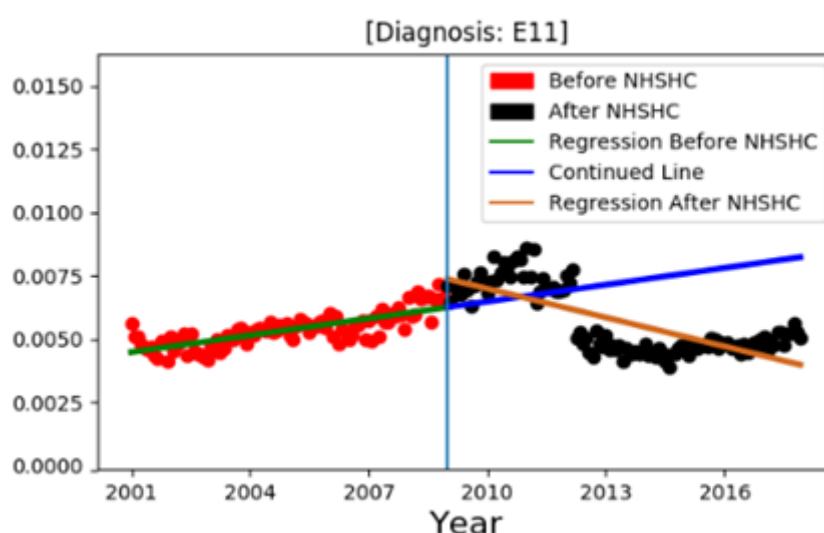


Figure 3-3: Interrupted Time Series for Chronic Kidney Disease. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for chronic kidney disease adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero.

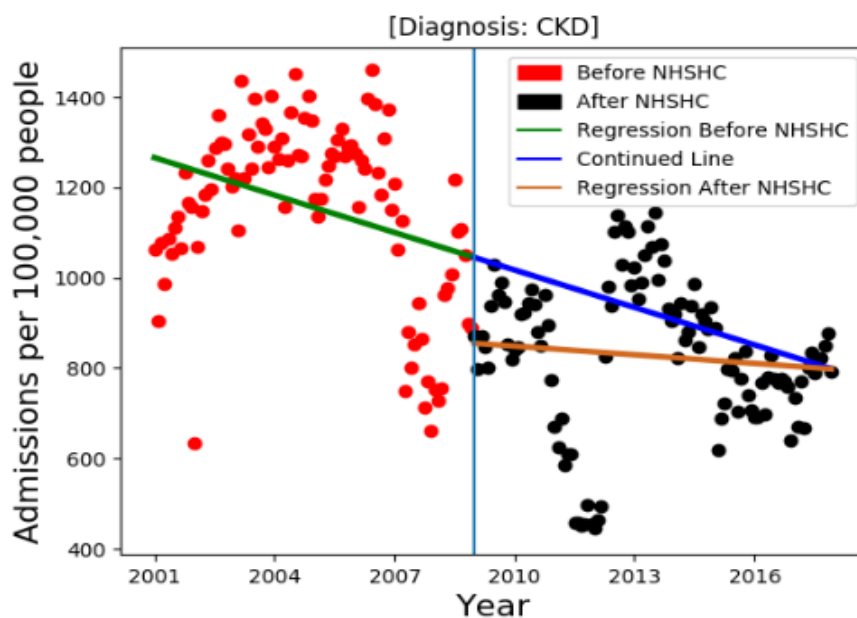
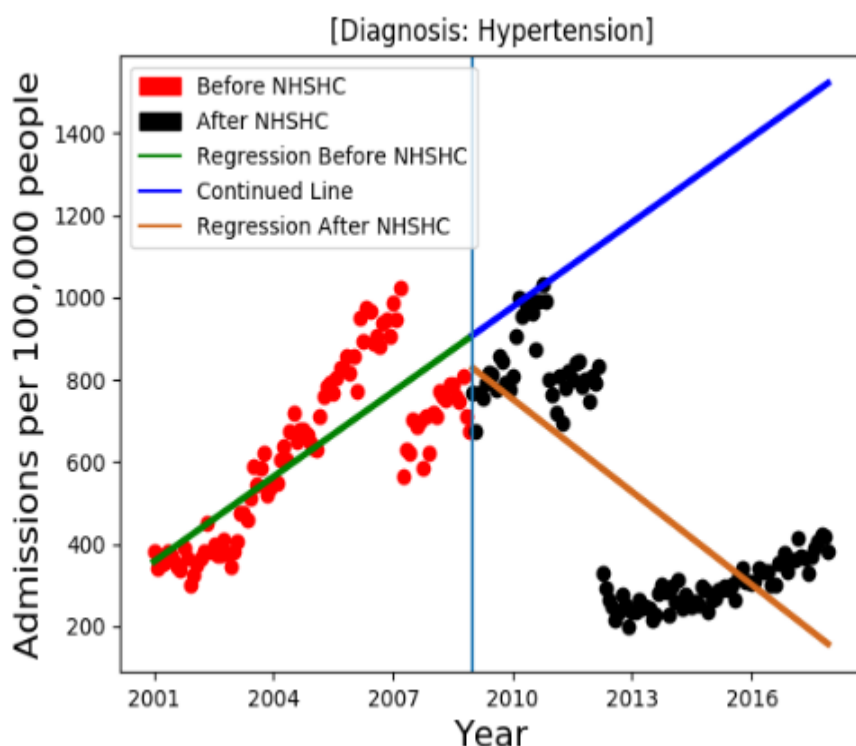


Figure 3-4: Interrupted Time Series for Hypertension. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for hypertension adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero.



Analysis

My primary method of analysis was a segmented linear regression consisting of two models with the first regression model conducted using data points from June 2003 to December 2008 and the second regression model conducted using data points from January 2009 until June 2017. I used linear regression (straight line regression) as I assumed the relationship between time and admission rates could be modelled using a linear relationship; alternative distributions could include quadratic, cubic or further models. Modelling alternative distributions such as quadratic, cubic and higher degree terms may make the interpretation difficult to interpret with time due to the fluctuation in direction of admission rates. As my analysis aims to understand whether introduction of the NHS Health Check impacts hospital admission rates either by increase, decreasing or did not impact admission rates,

straight line regression was used to help the interpretation. If the main goal of my analysis was to predict admission rates, then I would have considered other methods such as quadratic and cubic models.

My primary unit of analysis was monthly admission rates for all hospital admissions across all hospitals in England, which provided data for that specific month. To generate monthly admission rates, I conducted the following steps in order:

1. Using ICD10 codes (see Outcomes section), admissions records were extracted for the period between June 2003 until June 2017; since HES records up to 15-causes for admission, I used all instances to avoid under-recording; therefore, one admission may contribute to multiple diseases. I used multiple admissions to avoid an under-recording of admissions for each disease.
2. Aggregation occurred monthly as a count of the number of unique admissions.
3. Admission rates were then calculated by dividing the total of monthly admissions for a given month by the total population size for the corresponding year. For example, to calculate the monthly admission rate for June 2010 was calculated by dividing total admissions for June 2010 by the total population in 2010.

To establish the appropriateness of the model, the coefficient of determination was used (R^2) for data points prior to the introduction of the NHS Health Check. As the NHS Health Check was gradually introduced, I expected the a priori impact model would be reflected in a gradual slope change as opposed to an immediate step change. To model the NHS Health Check 's gradual mandated provision, I used a 3-year lag as a part of sensitivity analysis as an alternative to the a priori impact model; a year 3-year period was chosen 2012 was when the NHS Health Check was mandated, after the 2009

introduction. To identify the impact of seasonality and autocorrelation, that is prior trends are a good predictor of future trends, a visual analysis of an autocorrelation plot was achieved using 24-months (datapoints) worth of data as suggested to identify seasonality (Hawley et al., 2019). It is important to understand seasonality and autocorrelation as predictors of monthly rates of disease as the goal of the NHS Health Check is to change such trends. As my primary goal was to compare trend before and after the introduction of the NHS Health Check; specifically, to evaluate if the NHS Health Check decreased (or accelerated a decrease) in monthly admission rates, autocorrelation would not be problematic if the NHS Health Check significantly reduces admission rates as it would have changed the trendline instead of continuing it.

I also conducted two sensitivity analyses. The first sensitivity analysis evaluated the effect of the gradual introduction of the NHS Health Check with a 3-year lag by changing the interruption to 2012 instead of 2009. The second sensitivity analysis evaluated the effect of resampling time points to improve the consistent use of ICD10 codes.

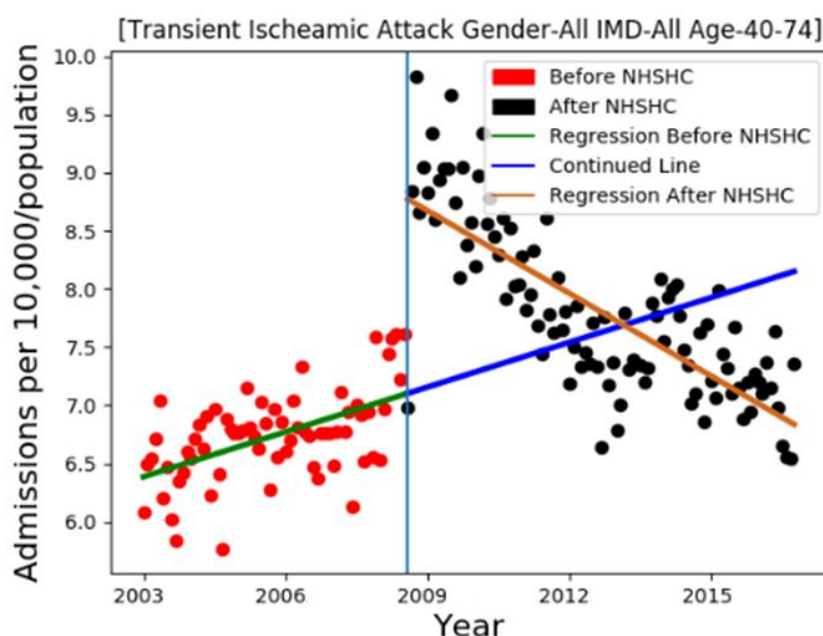
I conducted analyses for this chapter using a combination of R version 3.6 for statistical analysis, and Python 2.7 to generate visual representations of the time-series data.

Covariates

Whilst multivariate analysis was not conducted, I conducted stratification by disease (cerebrovascular disease, coronary heart disease, diabetes), age group (40 – 44, 45 – 49, 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74), gender (male and female) and index of multiple deprivation (1 most deprived – 5 least deprived). Admission rates for each stratum were calculated later using stratum specific denominators for the corresponding subgroups in the population. For example, when calculating admission rates for females for a specific month, only counts of female raw admissions were used, which were

then divided by the number of females in the population. I also aimed to stratify by ICD10 code. However, specific ICD10 codes were not consistently used, see Figure 3-5 for an example of inconsistent ICD10 code usage. Therefore, I only stratified for disease, age group, gender, and index of multiple deprivation only.

Figure 3-5: ITS for Transient Ischemic Attack (ICD10: G45). In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for transient ischemic attacks adjusted for population size for the given year. Warning: graph's Y-axis does not start at 0



Ethnics and Approval

For analysis of hospital episode statistics, I only had access to the aggregated data which was provided by Public Health England (now the UK Health Security Agency, Office of Health Inequities and Disparities). For the office of national statistics data, I only had access to the aggregated data freely available online. Therefore, no ethical approval was required.

Information governance

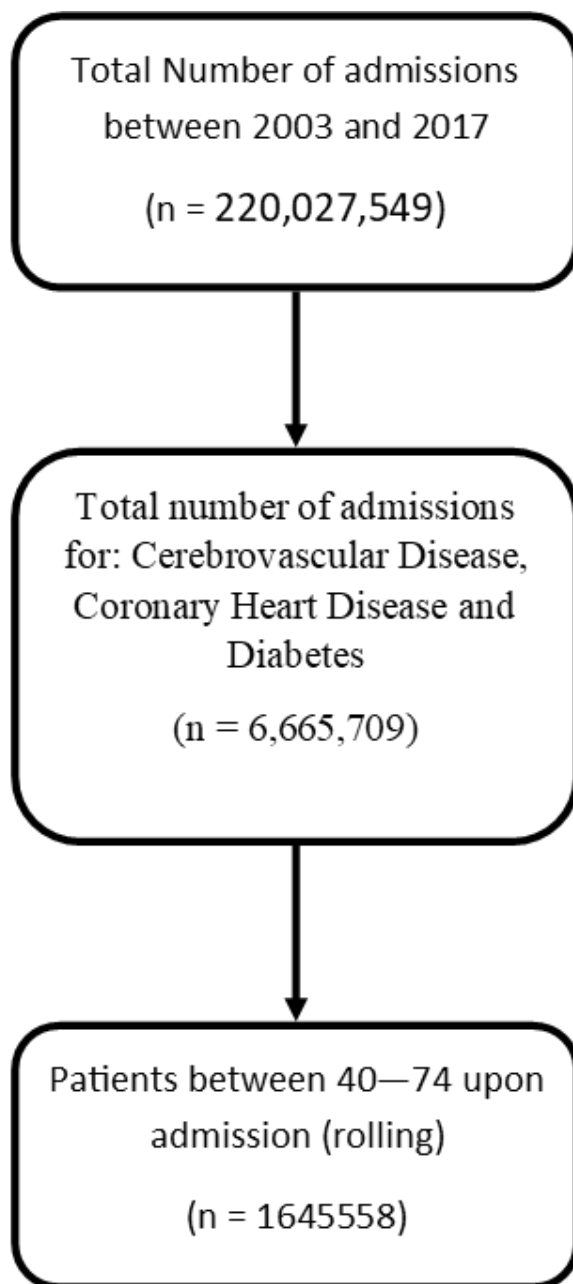
All analyses were completed on the UCL data safe haven. The aggregated dataset will be securely destroyed after 20 years in line with UCL's record retention policy. In line with policies developed for electronic healthcare research, I did not report any data with a cell containing <5 events and where necessary, I protected these counts with secondary suppression.

Results

Numbers Analysed

Between 2003 and 2017, I found 220,027,549 hospital admissions. Of these 220,027,549 admissions, 6,665,709 were either due to cerebrovascular events, coronary heart disease or diabetes. Of these 6,665,709 admissions, 1,645,558 patients were between the ages of 40 to 74 upon each respective admission. Of the patients between the ages of 40 to 74, 86 did not have a gender reported, and there was no missing data on index of multiple deprivation. See Figure 3-6 for the study population derivation.

Figure 3-6: Filter diagram of admissions data and how they were filtered.



Population and Characteristics

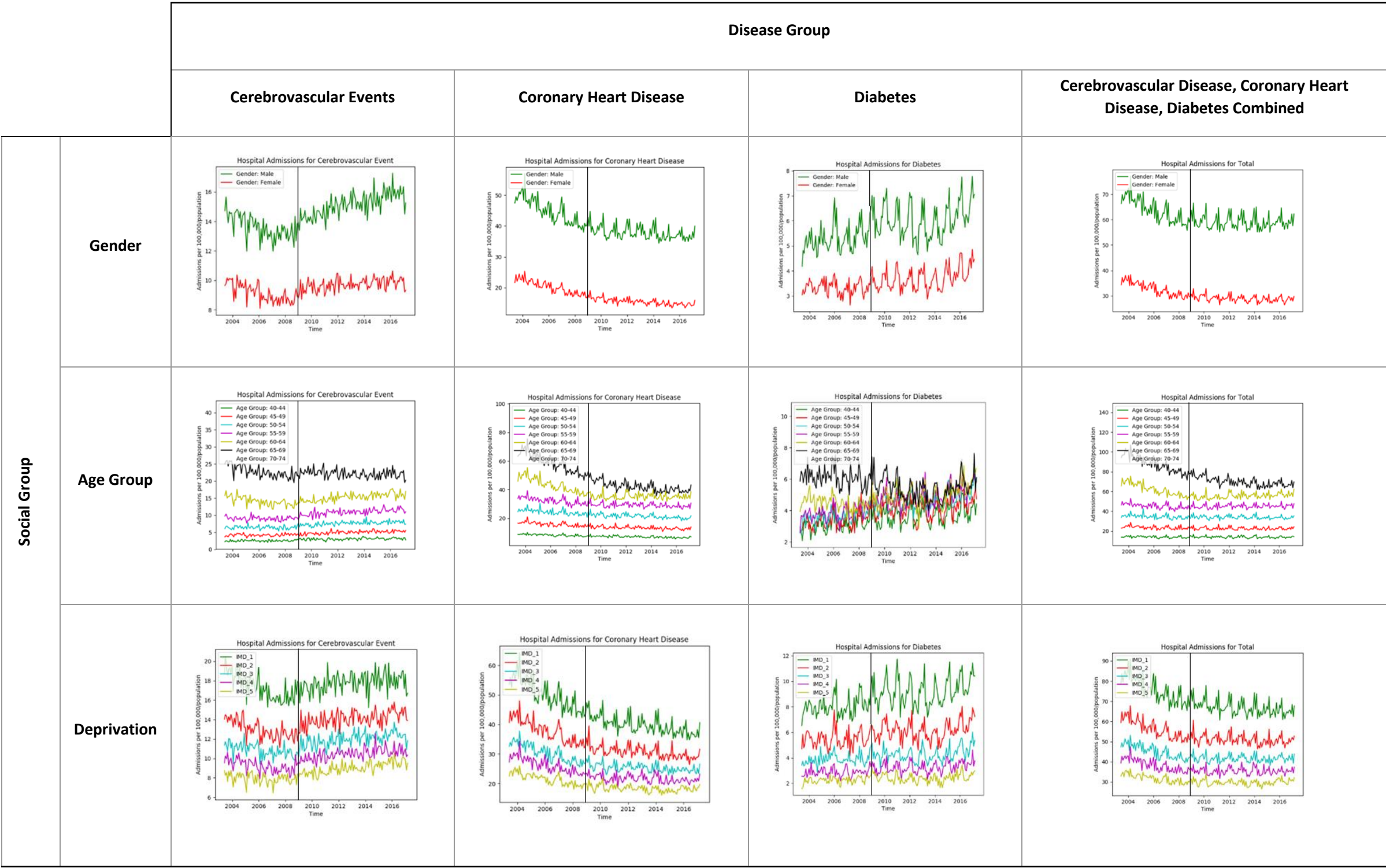
I evaluated a total of 1,645,558 admissions between 2003 and 2017, consisting of 1,042,281 admissions for coronary heart disease, 435,095 admissions for cerebrovascular events and 168,182 admissions for diabetes. See Table 3-2 for a demographic breakdown of the sample. For all diseases, males had a higher proportion of admissions rates. For all diseases, except for diabetes, older groups had higher admissions rates. For all diseases, higher deprivation levels had higher admission rates. See Figure 3-7 for a visual breakdown of admission rates by disease, gender, age group and deprivation.

Table 3-2: Demographic breakdown of admissions between June 2003 and March 2017. Note: numbers may not equal total due to missing demographics data. For example, while a patient's IMD group may be known, their gender may not be known.

Covariate Groups		Disease			
		Heart Disease	Cerebrovascular Disease	Diabetes Mellitus	Total
Gender	Male	722,455 (70%)	259,458 (60%)	102,434 (60%)	1,084,347 (66%)
	Female	319,774 (30%)	175,607 (40%)	65,744 (40%)	561,125 (34%)
	Total	1,042,229	435,065	168,178	1,645,472
	Gender	(100%)	(10%)	(100%)	(100%)
Age Group	40 – 44	48,462 (5%)	18,004 (4%)	21,978 (13%)	88,444 (5%)
	45 – 49	88,923 (9%)	29,030 (7%)	23,814 (14%)	141,767 (9%)
	50 – 54	128,109 (11%)	40,827 (9%)	24,431 (15%)	193,367 (12%)

		Disease			
Covariate Groups		Heart Disease	Cerebrovascular Disease	Diabetes Mellitus	Total
	55 – 59	161,844 (16%)	53,891 (12%)	23,895 (14%)	239,630 (15%)
	60 – 64	186,397 (18%)	72,021 (17%)	23,329 (14%)	281,747 (16%)
	65 – 69	205,928 (20%)	95,841 (22%)	24,331 (14%)	326,100 (20%)
	70 – 74	222,618 (21%)	125,481 (29%)	26,404 (16%)	374,500 (23%)
	Total Age	1,042,281 (100%)	435,095 (100%)	168,182 (100%)	1,645,558 (100%)
IMD	1 (Most deprived)	271,234 (25%)	109,215 (25%)	54,246 (32%)	434,695 (26%)
	2	225,652 (22%)	92,314 (21%)	39,690 (24%)	357,656 (22%)
	3	204,284 (20%)	86,381 (20%)	30,922 (18%)	321,587 (20%)
	4	183,674 (18%)	78,110 (18%)	24,363 (14%)	286,147 (17%)
	5 (Least Deprived)	157,437 (15%)	69,075 (16%)	18,961 (11%)	245,473 (15%)
	Total IMD	1,042,281 (100%)	435,095 (100%)	168,182 (100%)	1,645,558 (100%)

Figure 3-7: Graphs depicting the admission rates per 100,000 people in the population, broken down by disease (columns represent cerebrovascular events, coronary heart disease, diabetes and combined) and social determinants of health (rows representing gender, age and index of multiple deprivation). For all graphs, the vertical line represents the introduction of the NHS Health Check. Warning: y-axis does not start at zero. See Appendixes for larger versions.



Outcomes and Estimations

Combined admissions for cerebrovascular, diabetes and heart disease

For the combined causes of cerebrovascular disease, diabetes, and heart disease, I evaluated a total of 1,645,558 admissions between 2003 and 2017. At the beginning of the study (2003), there was an average of 50.03 admissions per 100,000 people for the year 2003. At the introduction of the NHS Health Check (2009), I found an average of 46.99 admissions per 100,000 people for the year 2009. At the end of the study (2017), I found an average of 45.74 admissions per 100,000 people for the year 2017. Figure 3-8 suggests autocorrelation of data points over a rolling 14-month period; this suggests that any given data point is predictable using the previous 14 data points and may suggest that since the introduction of the NHS Health check trends did not drastically change.

Figure 3-8: Autocorrelation plot for cerebrovascular, coronary heart disease and diabetes combined. In this graph, the x-axis represents the lag measured in months, whilst the y-axis represents the correlation. The shaded area represents a 95% CI; points outside this are statistically significant. The last point outside the shaded area is at 14 months on the x-axis. Therefore, this graph suggests that datapoints in Figure 3-9 are predictable using the previous 14 data points.

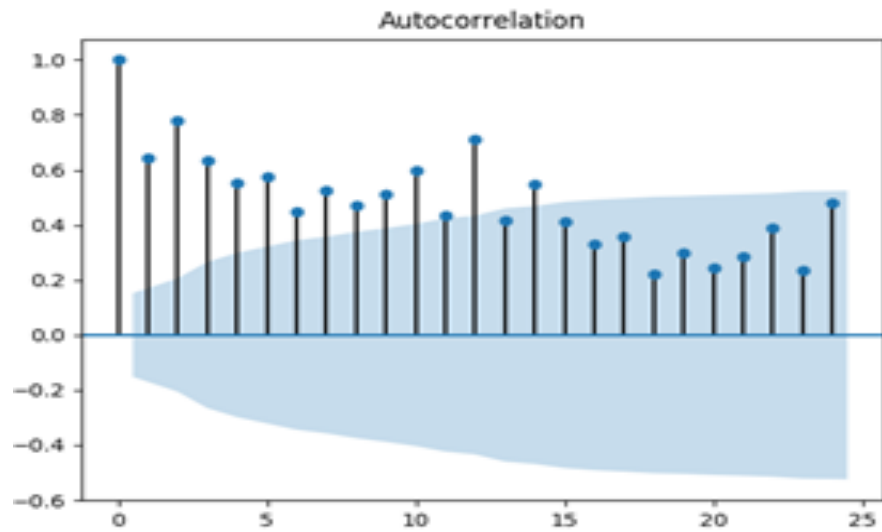
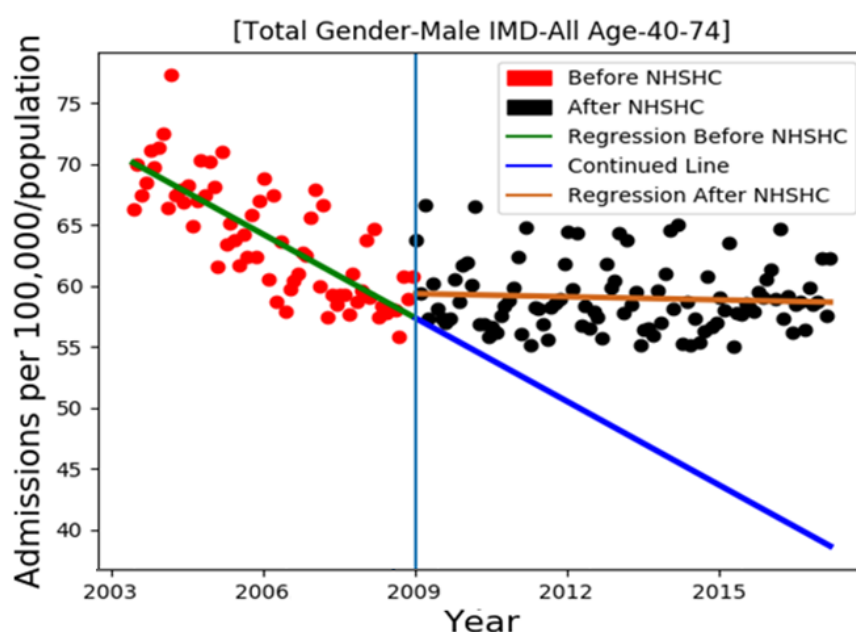


Figure 3-9: Interrupted Time Series graph for cerebrovascular, coronary heart disease and diabetes combined. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for cerebrovascular, coronary heart disease and diabetes combined when adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero



Between the start of the study (2003) and the introduction of the NHS Health Check (2009), there was a month-to-month decrease of 1.82 admissions per month per 100,000 people [95% CI: -2.14 admissions/100,000 to -1.51 admissions/100,000). Therefore, prior to the introduction of the NHS Health Check, there was already a month-to-month decrease in admission rates. Thus, to show an improvement, the post-NHS Health Check trend requires a faster rate of month-to-month decreases.

After the introduction of the NHS Health Check until the end of the study (i.e., from 2009 to 2017), there was a month-to-month decrease of 0.13 admissions per month per 100,000 people [95% CI: -0.29

admissions/100,000 to 0.03 admissions/100,000]. As the confidence intervals were not overlapping, after the NHS Health Check, trends were considered different before the NHS Health Check. See Figure 3-9 for a visual representation of the interrupted time series for the combined admissions of cerebrovascular disease, diabetes, and heart disease.

When stratifying for gender for combined causes, before the introduction of the NHS Health Check, male admission rates were decreasing at a rate of 2.28 monthly admission per 100,000/people [95% CI: -2.72 to -1.84] whilst female admission rates were decreasing at 1.39 monthly admission per 100,000/people [95% CI: -1.62 to -1.17]. After the introduction of the NHS Health Check, male admission rates were decreasing at 0.09 [95% CI: -0.32 to 0.14] admissions per 100,000 people whilst female admission rates were decreasing at 0.16 [95% CI: -0.26 to 0.06]. Both genders saw a slower monthly decrease in admissions post health check compared to pre-health check, i.e. their point estimates were lower in magnitude than their pre-health check counterparts. When stratifying for age for all-cause admissions, higher age is correlated with higher rates of monthly admission decreases prior to the introduction of the NHS Health Check; for 40–44-year-olds the rate was 0.15 admissions per 100,000 people [95%CI: -0.29 to -0.01], whilst for 70–74-year-olds this increased to 5.65 admissions per 100,000 [95%CI: -6.46 to -4.85]. For all age groups, the rates of monthly decrease were slower post introduction of the NHS Health Check. When stratifying for the index of multiple deprivation, higher deprivation (e.g., individuals living in areas with higher poverty) was correlated with faster rates of monthly decreases in admissions prior to the introduction of the NHS Health Check; for the most deprived the rate was -2.96 [95%CI: -3.56 to -2.37] whilst for the least deprived the rate was -0.95 [95%CI: -1.12 to -0.73]. Higher deprivation was also correlated with faster rates of monthly reduction of admissions after the introduction of the NHS Health Check. For all IMD groups, post-NHS Health

Check, there were lower rates of monthly decrease compared to prior to the NHS Health Check. See Table 3-3 for a full breakdown of month-to-month admission rates for all causes when broken down by gender, age group and IMD quintile.

Table 3-3: Breakdown of interrupted time series trends for all causes by gender, age group and index of multiple deprivation. Note: a Negative value denotes a monthly decrease. Mean difference represents After- Before; therefore, negative numbers represent an increased rate after the introduction of the NHS Health Check

	Covariate	Trend Before	Trend After	Mean Difference *
Gender	Male	-2.28 [95% CI: -2.72 to -1.84]	-0.09 [95% CI: -0.32 to 0.14]	-2.19
	Female	-1.39 [95% CI: -1.62 to -1.17]	-0.16 [95% CI: -0.26 to 0.06]	-1.23
Age Group	40 – 44	-0.15 [95%CI: -0.29 to -0.01]	-0.04 [95%CI: -0.01 to 0.03]	-0.11
	45 – 49	-0.37 [95%CI: -0.60 to -0.14]	-0.35 [95%CI: -0.16 to 0.09]	-0.02
	50 – 54	-0.51 [95%CI: -0.82 to -0.21]	-0.12 [95%CI: -0.27 to 0.02]	-0.39
	55 – 59	-0.87 [95%CI: -1.26 to -0.51]	0.12 [95%CI: -0.05 to 0.29]	-0.99
	60 - 64	-3.29 [95%CI: -3.74 to -2.85]	0.41 [95%CI: 0.18 to 0.65]	-3.7
	65 – 69	-4.33 [95%CI: -4.94 to -3.70]	-1.21 [95%CI: -1.52 to -0.90]	-3.12

	Covariate	Trend Before	Trend After	Mean Difference *
	70 – 74	-5.65 [95%CI: -6.46 to -4.85]	-2.84 [95%CI -3.2 to -2.46]	-2.81
IMD Quintile	1 (Most Deprived)	-2.96 [95%CI: -3.56 to -2.37]	-0.59 [95%CI: -0.88 to -0.30]	-2.37
	2	-2.34 [95%CI: -2.74 to -1.93]	-0.25 [95%CI: -0.46 to -0.04]	-2.09
	3	-1.67 [95%CI: -1.99 to -1.35]	-0.03 [95%CI: -0.19 to 0.12]	-1.64
	4	-1.44 [95%CI: -1.73 to -1.14]	-0.02 [95%CI: -0.17 to 0.13]	-1.42
	5 (Least Deprived)	-0.95 [95%CI: -1.12 to -0.73]	0.37 [95%CI: -0.84 to 0.16]	-1.32

For cerebrovascular disease, I evaluated a total of 435,095 admissions between 2003 and 2017. At the beginning of the study (2003), there was an average of 12.13 admissions per 100,000 people in 2003. At the introduction of the NHS Health Check (2009), there was an average of 11.32 admissions per 100,000 people in 2009. At the end of the study (2017), there was an average of 12.24 admissions per 100,000 people in 2017. Figure 3-10 suggests that autocorrelation of datapoints exists over a 14 month rolling period; this suggests that any given data point is predictable using the previous 14 data points and may suggest that since the introduction of the NHS Health check trends did not drastically change.

Between the start of the study and the introduction of the NHS Health Check, there was a month-to-month decrease of 0.27 admissions per month per 100,000 people [95% CI: -0.35 admissions/100,000 to -0.20 admissions/100,000). Therefore, prior to the introduction of the NHS Health Check, there was already a month-to-month decrease in admission rates. Thus, to show an improvement, the post-NHS Health Check trend requires a faster rate of month-to-month decline. After the introduction of the NHS Health Check until the end of the study, there was a month-to-month increase of 0.14 admissions per month per 100,000 people [95% CI: 0.11 admissions/100,000 to 0.18 admissions/100,000]. The month-to-month changes between 2009 and 2017 were produced with an R^2 score of 0.42. As the confidence intervals were not overlapping, after the NHS Health Check, trends were considered different prior to the NHS Health Check. See Figure 3-11 for a graphical representation of the interrupted time series for cerebrovascular events.

Figure 3-10: Autocorrelation graph for cerebrovascular disease. In this graph, the x-axis represents the lag measured in months, whilst the y-axis represents the correlation. The shaded area represents a 95% CI; points outside this are statistically significant. The last point of statistically significant was at 14-months. Therefore, this graph suggests that datapoints in Figure 3-11 are predictable using the previous 14 data points.

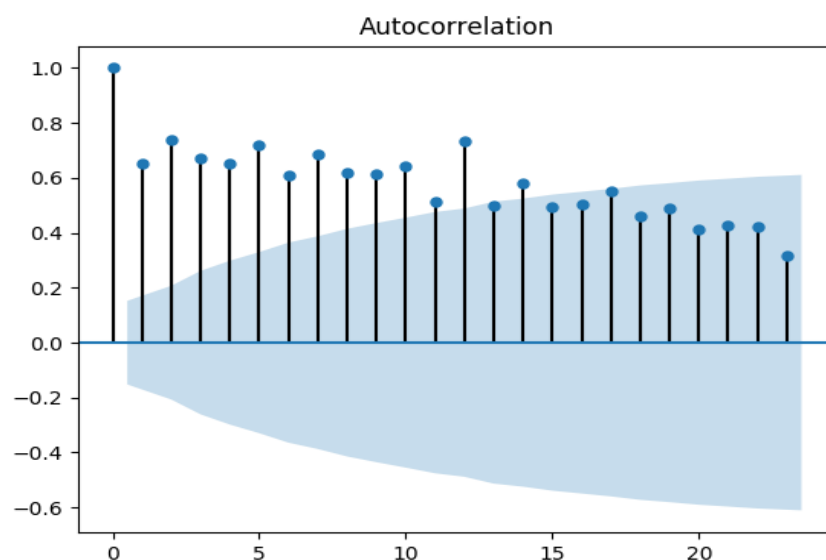
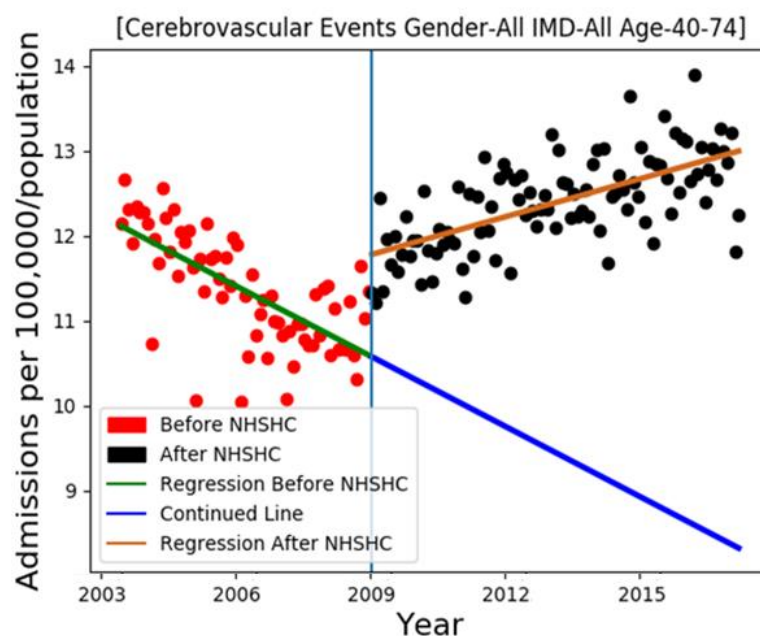


Figure 3-11: Interrupted Time Series graph for cerebrovascular disease. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for cerebrovascular disease adjusted for population size for the given year.



When stratifying cerebrovascular events for gender, there was no difference between male and female rates of admissions before the NHS Health Check (overlapping 95% Confidence intervals). After the introduction of the NHS Health Check, males' rates of admissions were increasing at a faster rate compared to their female counterparts at 0.23 additional monthly admissions/100,000 [95%CI: 0.18 to 0.28] compared to 0.06 additional monthly admissions/100,000 [95% CI: 0.03 to 0.10]. When stratifying cerebrovascular events for age groups, prior to the introduction of the NHS Health Check, older age groups were correlated with higher rates of monthly declines in hospital admissions. Post the introduction of the NHS Health Check, changes in monthly admission rates were higher compared to their pre-NHS Health Check counterparts. When stratifying cerebrovascular events for the index of multiple deprivation, prior to the introduction of the NHS Health Check, higher deprivation was correlated with faster rates in monthly

decline in hospital admissions. After the introduction of the NHS Health Check, all strata experienced an increase in monthly admission rates. See Table 3-4 for a breakdown of trends pre and post NHS Health Check for cerebrovascular events stratified by gender, age group and IMD quintile.

Table 3-4: Interrupted time series trends for cerebrovascular events broken down by gender, age group and IMD quintile. Negative values denote a monthly decrease in admissions.

	Covariate	Trend Before	Trend After	Mean Difference
Gender	Male	-0.30 [95%CI: -0.40 to -0.20]	0.23 [95%CI: 0.18 to 0.28]	-0.53
	Female	-0.25 [95%CI: -0.32 to -0.18]	0.06 [95%CI: 0.03 to 0.10]	-0.31
Age Group	40 – 44	0.02 [95%CI: -0.01 to 0.06]	0.04 [95%CI: 0.01 to 0.06]	-0.02
	45 – 49	0.03 [95%CI: -0.01 to 0.09]	0.12 [95%CI: 0.08 to 0.15]	-0.09
	50 – 54	-0.01 [95%CI: -0.09 to 0.05]	0.12 [95%CI: 0.08 to 0.16]	-0.13
	55 – 59	-0.03 [95%CI: -0.12 to 0.05]	0.21 [95%CI: 0.15 to 0.27]	-0.24
	60 – 64	-0.51 [95%CI: -0.66 to -0.36]	0.30 [95%CI: 0.23 to 0.38]	-0.81
	65 – 69	-0.72 [95%CI: -0.91 to -0.52]	-0.11 [95%CI: -0.22 to -0.02]	-0.61
	70 – 74	-1.17 [95%CI: -1.44 to -0.89]	-0.46 [95%CI: -0.61 to -0.31]	-0.71
IMD Quintile	1 (Most Deprived)	-0.57 [95%CI: -0.72 to -0.43]	0.11 [95%CI: 0.04 to 0.19]	-0.68
	2	-0.38 [95%CI: -0.48 to -0.27]	0.14 [95%CI: 0.08 to 0.21]	-0.52

	Covariate	Trend Before	Trend After	Mean Difference
	3	-0.19 [95%CI: -0.29 to -0.11]	0.14 [95%CI: 0.09 to 0.20]	-0.33
	4	-0.20 [95%CI: -0.28 to -0.12]	0.12 [95%CI: 0.08 to 0.17]	-0.32
	5 (Least Deprived)	-0.08 [95%CI: -0.16 to -0.00]	0.17 [95%CI: 0.13 to 0.21]	-0.25

Heart Disease

For heart disease, I evaluated a total of 104,2281 admissions between 2003 and 2017. At the beginning of the study (2003), there was an average of 34.29 admissions per 100,000 people for the year 2003. At the introduction of the NHS Health Check (2009), there was an average of 30.09 admissions per 100,000 people for the year 2009. At the end of the study (2017), there was an average of 27.76 admissions per 100,000 people for the year 2017. Figure 3-12 suggests that autocorrelation of data points over a 14 month rolling period exists; this suggests that any given data point is predictable using the previous 14 data points and may suggest that since the introduction of the NHS Health check trends did not drastically change.

Between the start of the study and the introduction of the NHS Health Check, there was a month-to-month decrease of -1.61 admissions per month per 100,000 people [95% CI: -1.85 admissions/100,000 to -1.36 admissions/100,000). Therefore, prior to the introduction of the NHS Health Check, there was already a month-to-month decrease in admission rates. Thus, to show an improvement, the post-NHS Health Check trend requires a faster rate of month-to-month decreases. After the introduction of the NHS Health Check until the end of the study, there was a month-to-month decrease of 0.33 admissions per month per 100,000 people [95% CI: -0.45 admissions/100,000 to -0.23 admissions/100,000]. The month-to-month changes between 2009 and 2017 were produced with an R^2 score of 0.24. As the confidence intervals were not overlapping, after the NHS Health Check, trends were considered different prior to the NHS Health Check. See Figure 3-13 for a graphical representation of the interrupted time series for coronary heart disease events.

Figure 3-12: Autocorrelation graph for heart disease. In this graph, the x-axis represents the lag measured in months, whilst the y-axis represents the correlation. The shaded area represents a 95% CI; points outside this are statistically significant. The last time point with statistically significant correlation was 14-months. Therefore, this graph suggests that datapoints in Figure 3-13 are predictable using the previous 14 data points.

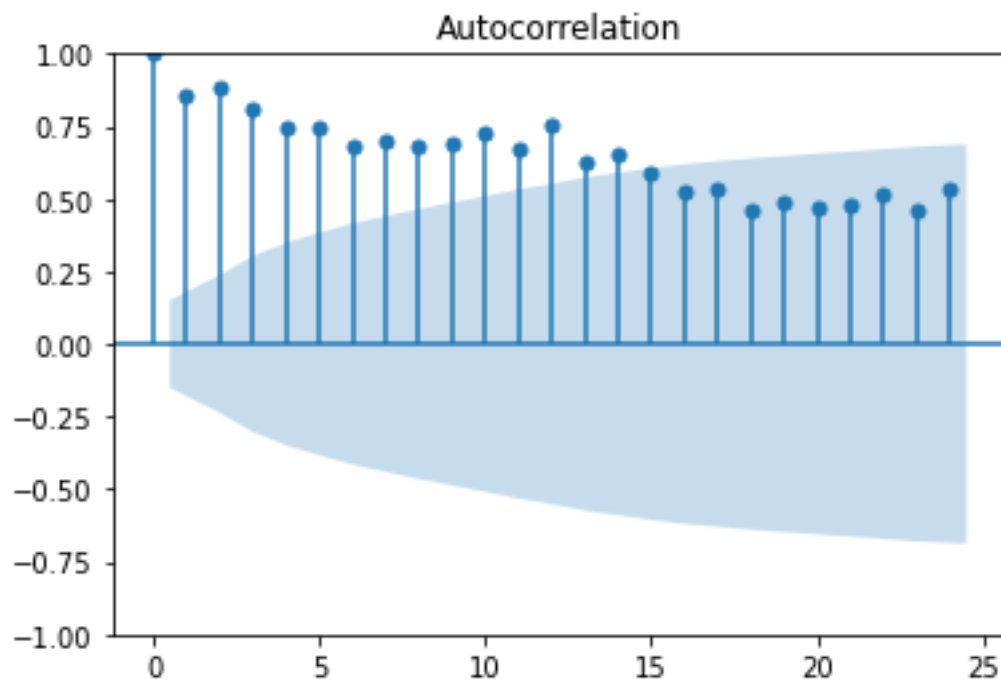
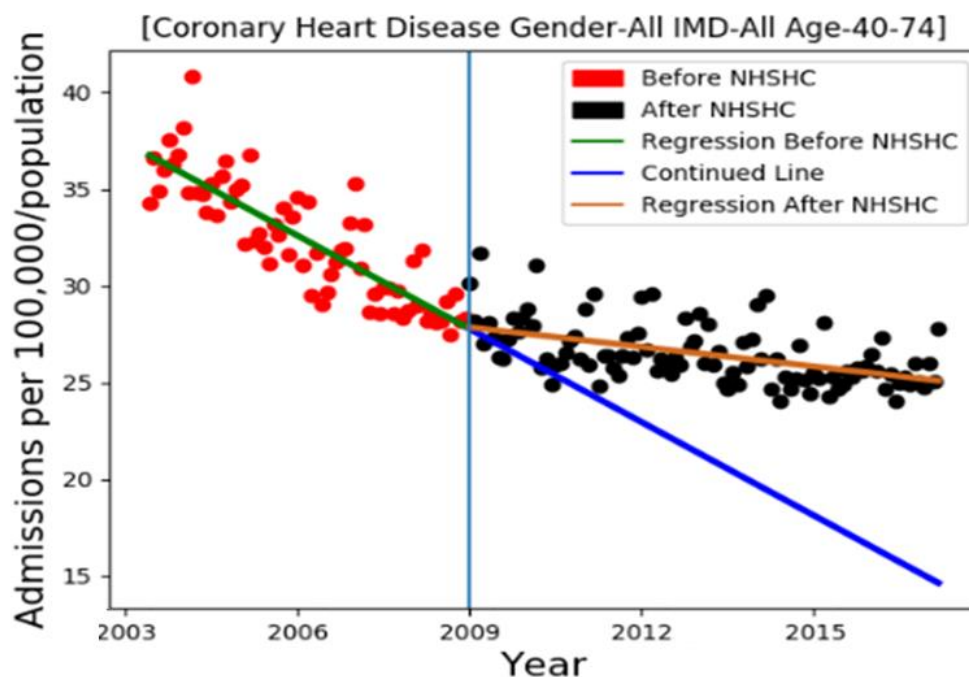


Figure 3-13: Interrupted time series graph for heart disease. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for heart disease when adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero



When stratifying for gender for coronary heart disease, before the introduction of the NHS Health Check, male admission rates were decreasing at a rate of 2.10 monthly admission per 100,000/people [95% CI: -2.46 to -1.74] whilst female admission rates were decreasing at 1.13 monthly admission per 100,000/people [95% CI: -1.30 to -0.97]. After the introduction of the NHS Health Check, male admission rates were decreasing at 0.36 [95%CI: -0.53 to -0.19] admissions per 100,000 people whilst female admission rates were decreasing at 0.30 [95%CI: -0.37 to -0.23] admissions per 100,000 people. Both genders saw a slower monthly decrease in admissions post health check compared to pre-health check. When stratifying for age for all-cause admissions, higher age is correlated with higher rates of monthly admission decreases prior to the introduction of the NHS Health Check; for 40–44-year-olds the rate was 0.28 admissions per 100,000 people [95%CI: -0.36 to -

0.19], whilst for 70–74-year-olds this was 4.47 admissions per 100,000 [95%CI: -5.11 to -3.85]. For all age groups, the rates of monthly decrease were slower post introduction of the NHS Health Check. For all age groups, the rates of monthly decreased admissions were slower post introduction of the NHS Health Check. After stratifying for index of multiple deprivation, higher deprivation was correlated with faster rates of monthly decreases in admissions prior to the introduction of the NHS Health Check; for the most deprived the rate was -2.51 [95%CI: -2.98 to -2.05] whilst for the least deprived the rate was -0.92 [95%CI: -1.09 to -0.75]. Higher deprivation was also correlated with faster rates of monthly decrease in admissions after the introduction of the NHS Health Check. For all IMD groups, post-NHS Health Check, there were lower rates of monthly decrease compared to prior to the NHS Health Check See Table 3-5 for a full breakdown of month-to-month admission rates for coronary heart disease when stratified down by gender, age group and IMD quintile.

Table 3-5: Interrupted Time Series for Coronary Heart Disease when broken down by gender, age group and index of multiple deprivation. Negative values denote a monthly decrease in admissions.

	Covariate	Trend Before	Trend After	Mean Difference
Gender	Male	-2.10 [95%CI: -2.46 to -1.74]	-0.36 [95%CI: -0.53 to -0.19]	-1.74
	Female	-1.13 [95%CI: -1.30 to -0.97]	-0.30 [95%CI: -0.37 to -0.23]	-0.83
Age Group	40 – 44	-0.28 [95%CI: -0.36 to -0.19]	-0.15 [95%CI: -0.20 to -0.11]	-0.13
	45 – 49	-0.55 [95%CI: -0.73 to -0.37]	-0.21 [95%CI: -0.29 to -0.13]	-0.34
	50 – 54	-0.64 [95%CI: -0.88 to -0.41]	-0.36 [95%CI: -0.46 to -0.25]	-0.28
	55 – 59	-0.95 [95%CI: -1.24 to -0.66]	-0.20 [95%CI: -0.33 to -0.07]	-0.75
	60 – 64	-2.70 [95%CI: -3.07 to -2.30]	-0.01 [95%CI: -0.19 to 0.15]	-2.69
	65 – 69	-3.54 [95%CI: -4.02 to -3.06]	-1.06 [95%CI: -1.28 to -0.84]	-2.48
	70 – 74	-4.47 [95%CI: -5.11 to -3.85]	-2.16 [95%CI: -2.44 to -1.88]	-2.31
IMD Quintile	1 (Most Deprived)	-2.51 [95%CI: -2.98 to -2.05]	-0.80 [95%CI: -1.00 to -0.60]	-1.71
	2	-2.00 [95%CI: -2.31 to -1.68]	-0.47 [95%CI: -0.62 to -0.32]	-1.53
	3	-1.54	-0.24	-1.30

	Covariate	Trend Before	Trend After	Mean Difference
		[95%CI: -1.78 to -1.28]	[95%CI: -0.35 to -0.13]	
	4	-1.26 [95%CI: -1.49 to -1.03]	-0.19 [95%CI: -0.31 to -0.09]	-1.07
	5 (Least Deprived)	-0.92 [95%CI: -1.09 to -0.75]	-0.14 [95%CI: -0.24 to -0.06]	-0.78

Diabetes

For diabetes, I evaluated a total of 168,182 admissions between 2003 and 2017. At the beginning of the study (2003), there was an average of 3.60 admissions per 100,000 people in the year 2003. At the introduction of the NHS Health Check (2009), there was an average of 5.57 admissions per 100,000 people in the year 2009. At the end of the study (2017), there was an average of 5.73 admissions per 100,000 people in the year 2017. As rates of diabetes were consistently rising between 2003 and 2017, there was a high rate of autocorrelation. Figure 3-14 suggests that autocorrelation of data points over a 24 month rolling period exists; this suggests that any given data point is predictable using the previous 24 data points and may suggest that since the introduction of the NHS Health check trends did not drastically change.

Between the start of the study and the introduction of the NHS Health Check, there was a month-to-month increase of 0.05 admissions per month per 100,000 people [95% CI: 0.00 admissions/100,000 to 0.11 admissions/100,000]. After the introduction of the NHS Health Check until the end of the study, there was a month-to-month increase of 0.06 admissions per month per 100,000 people [95% CI: 0.01 admissions/100,000 to 0.10 admissions/100,000]. The month-to-month admission rate between 2009 and 2017 was produced with an R^2 score of 0.07. As the confidence intervals did overlap, trends did not change after the introduction of the NHS Health Check. See Figure 3-15 for a graphical representation of the interrupted time series for diabetes.

Figure 3-14: Autocorrelation graph for diabetes. In this graph, the x-axis represents the lag measured in months, whilst the y-axis represents the correlation. The shaded area represents a 95% CI; points outside this are statistically significant. Points up to 24 months were statistically demonstrating autocorrelation. Therefore, this graph suggests that datapoints in Figure 3-15 are predictable using the previous 24 data points.

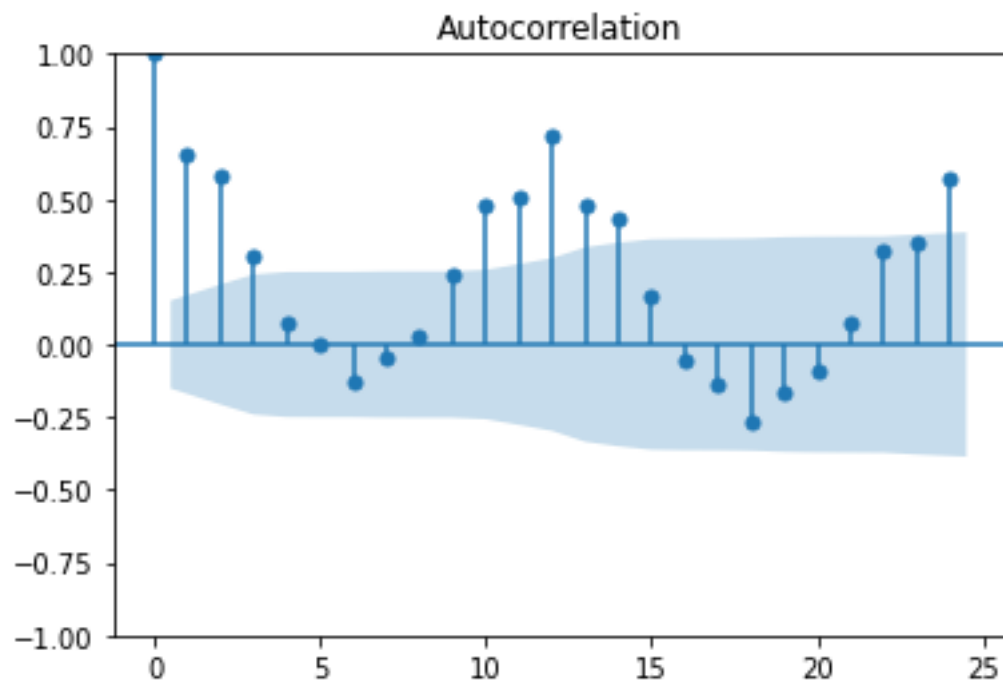
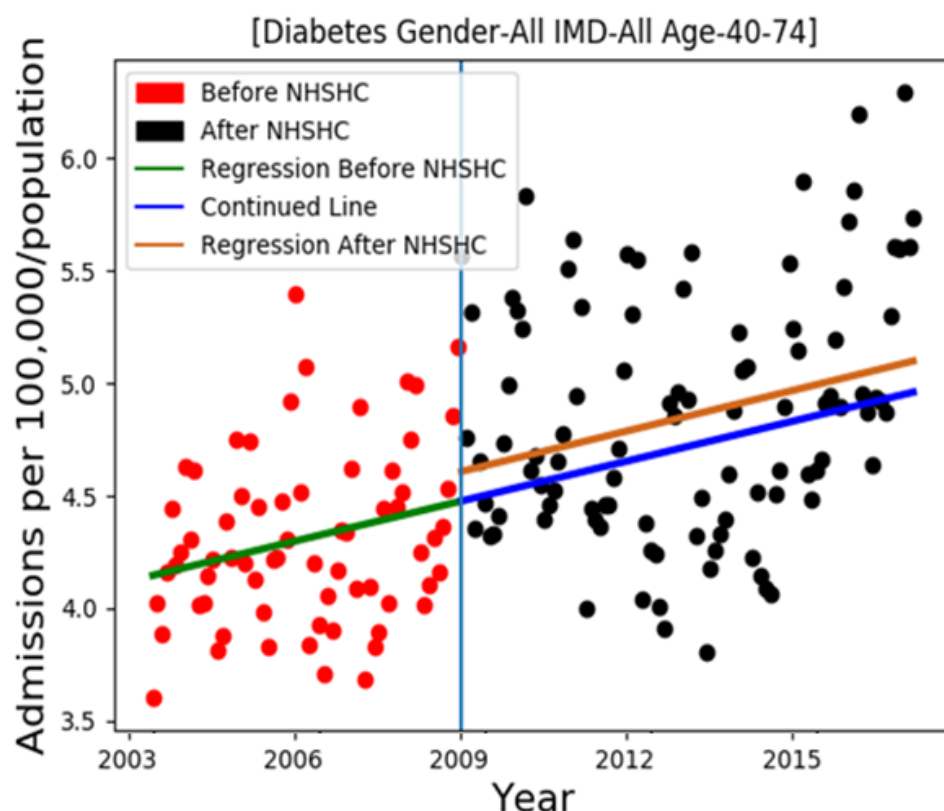


Figure 3-15: Graphical representation of the interrupted time series for diabetes. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for diabetes adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero



When stratifying for gender for diabetes, males and females were experiencing similar rates of growth both before and after the introduction of the NHS Health Check; for males this was 0.12 [95%CI: 0.04 to 0.19], whilst for females this was -0.00 [95%CI: -0.04 to 0.04]. Admission rates did not change after the introduction of the NHS Health Check for both males and females. When stratifying for age, the following age groups demonstrate no differences in trends before and after the introduction of the NHS Health Check: 40-44, 45-49, 50-54, 55-59 and 65-69. Age group 60-64 demonstrated an increase in monthly admissions after the introduction of the NHS Health

Check at 0.13 additional admissions/100,000 [95%CI: 0.08 to 0.18] compared to a monthly decrease of 0.08 admissions/100,000 [95%CI: -0.14 to -0.01] before the introduction of the NHS Health Check. Age group 70-74 experienced an accelerated rate of monthly decrease after the introduction of the NHS Health Check at 0.21 admissions/100,000 [95%CI: -0.28 to -0.15] compared to 0.00 admissions/100,000 [95%CI: -0.13 to 0.12]. When stratifying for the index of multiple deprivation, all IMD groups demonstrated overlapping confidence intervals for their trends before and after the introduction of the NHS Health Check. See Table 3-6 for a full breakdown of month-to-month admission rates for diabetes when stratified down by gender, age group and IMD quintile.

Table 3-6: Interrupted Time Series for diabetes when broken down by gender, age group and index of multiple deprivation. Negative values denote a monthly decrease in admissions.

	Covariate	Trend Before	Trend After	Mean Difference
Gender	Male	0.12 [95%CI: 0.04 to 0.19]	0.05 [95%CI: -0.00 to 0.11]	0.07
	Female	-0.00 [95%CI: -0.04 to 0.04]	0.07 [95%CI: 0.04 to 0.10]	-0.07
Age Group	40 – 44	0.09 [95%CI: 0.02 to 0.17]	0.06 [95%CI: 0.01 to 0.11]	0.03
	45 – 49	0.14 [95%CI: 0.06 to 0.22]	0.06 [95%CI: 0.01 to 0.11]	0.08
	50 – 54	0.14 [95%CI: 0.08 to 0.21]	0.11 [95%CI: 0.06 to 0.16]	0.03
	55 – 59	0.11 [95%CI: 0.05 to 0.18]	0.11 [95%CI: 0.06 to 0.16]	0.00
	60 - 64	-0.08 [95%CI: -0.14 to -0.01]	0.13 [95%CI: 0.08 to 0.18]	-0.21
	65 – 69	-0.07 [95%CI: -0.16 to 0.01]	-0.03 [95%CI: -0.09 to 0.03]	-0.04
	70 – 74	-0.00 [95%CI: -0.13 to 0.12]	-0.21 [95%CI: -0.28 to -0.15]	0.21
IMD Quintile	1 (Most Deprived)	0.12 [95%CI: 0.01 to 0.24]	0.09 [95%CI: 0.00 to 0.18]	0.03
	2	0.03 [95%CI: -0.06 to 0.14]	0.07 [95%CI: 0.01 to 0.14]	-0.04

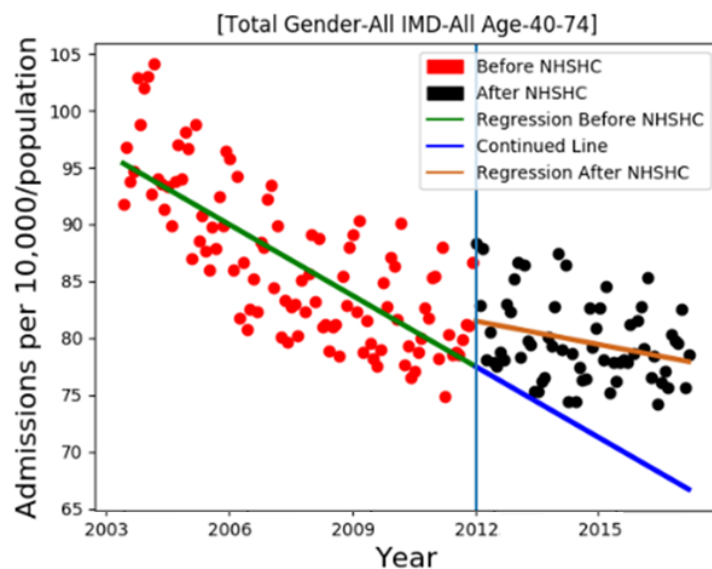
	Covariate	Trend Before	Trend After	Mean Difference
	3	0.06 [95%CI: -0.00 to 0.12]	0.06 [95%CI: 0.02 to 0.11]	0.00
	4	0.03 [95%CI: -0.01 to 0.08]	0.04 [95%CI: 0.01 to 0.08]	-0.01
	5 (Least Deprived)	0.05 [95%CI: 0.02 to 0.09]	0.00 [95%CI: -0.02 to 0.03]	0.05

Sensitivity Analyses

Sensitivity Analysis 1: Three Year Lag

To model the impact of the gradual introduction of the NHS Health Check, a 3-year lag period was implemented which shifted the introduction of the NHS Health Check from 2009 to 2012. When implementing this 3-year lag, there was an average reduction of 2.08 monthly admissions /100,000 [95%CI: -2.44 to -1.74] between the beginning of the study and the NHS Health Check (+ 3-year lag). Between the introduction of the NHS Health Check (+ 3-year lag) until the end of the study, there was a monthly decrease of 0.68 admissions/100,000 [95%CI: -1.27 to -0.10]. Therefore, when modelling for a 3-year lag, the introduction of the NHS Health Check did not accelerate monthly decreases in admission rates. See Figure 3-16 for a visual representation of this interrupted time-series study.

Figure 3-16: Interrupted time series for combined causes, with a 3-year lag after the introduction of the NHS Health Check. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for combined diseases adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero



Sensitivity Analysis 2: Cerebrovascular Events readjustment

Due to the quality of coding, there was inconsistent use of the ICD codes I6*, leading to an inconsistent trend in cerebrovascular events. See Figure 3-17 for a visual representation of this issue. Therefore, an interrupted time series analysis is less likely to be suitable for this. To tackle this issue, I resampled the time series by establishing the last data point in the time series that caused a positive correlation (Pearson's rank coefficient) between such data points and the introduction of the NHS Health Check. This was determined to be 34-months prior to the NHS Health Check (See Chapter 3 Figure 18). Therefore, the adjusted start date for the interrupted time series was March 2006. This method was used so that it maximises the number of data points before the introduction of the NHS Health Check while preserving the consistency of the ICD10 code used to establish cerebrovascular events.

Figure 3-17: Due to inconsistent use of ICD10 codes, there is evidence that admission rates experienced temporal variability. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for cerebrovascular events adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero.

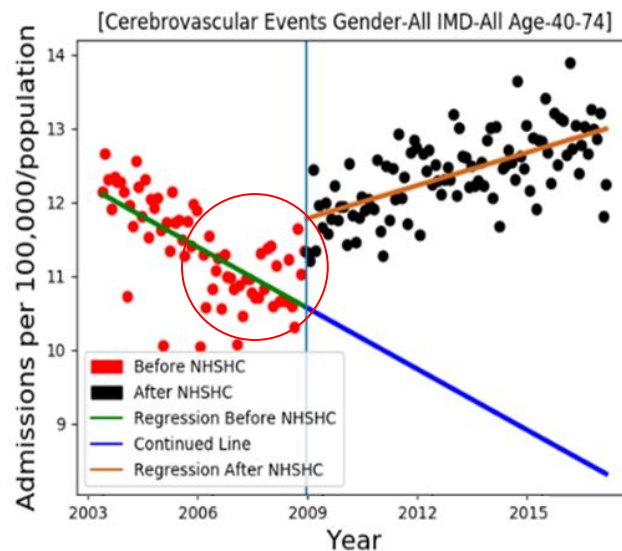
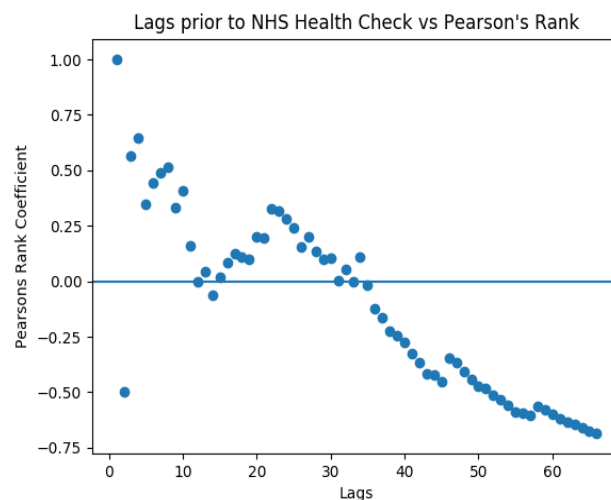
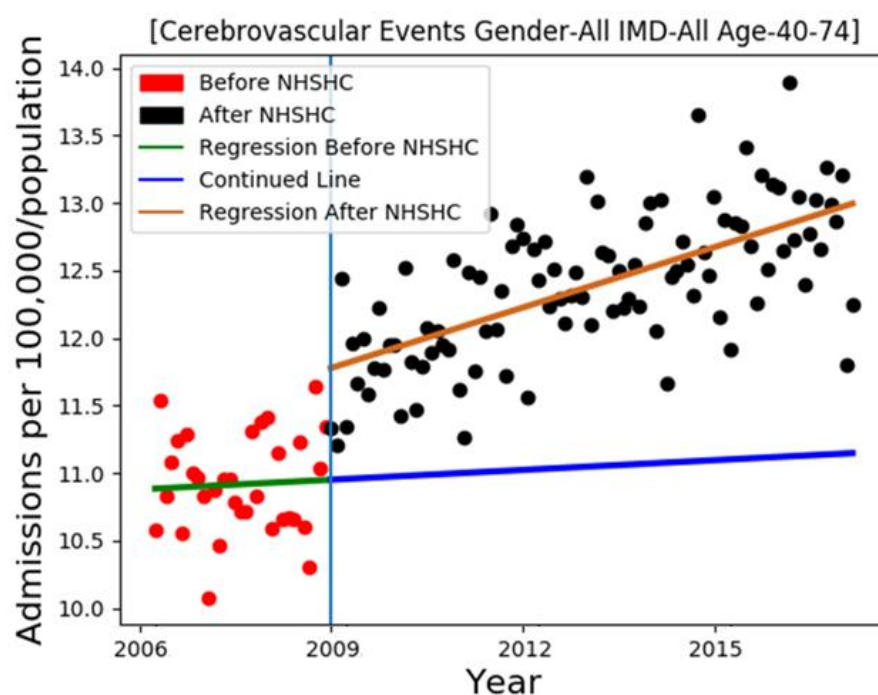


Figure 3-18: Graph depicting the effect of changing the start of the study period against Pearson's correlation.



After adjusting the start date of the study, the pre-NHS Health Check monthly admissions were rising at a rate of 0.02 admissions/100,000 [95%CI: -0.14 to 0.18] with an R^2 score of 0.00. When adjusting the start of the study, the post-NHS Health Check monthly admissions were rising at a rate of 0.14 admissions/100,000 [95%CI: 0.11 to 0.18] with an R^2 score of 0.42. Therefore, as the monthly admission rates had overlapping confidence intervals, there was no evidence that the introduction of the NHS Health Check changed admission rates of cerebrovascular events. See Figure 3-19 for a graphical representation of the interrupted time series when adjusting the study start date to March 2006.

Figure 3-19: Interrupted Time series for the adjusted study start date. In this graph, the x-axis represents time in years, whilst the y-axis represents the admission rates for cerebrovascular events adjusted for population size for the given year. Warning: graph's Y-axis does not start at zero



Discussion

Key Results

Overall, my primary analysis and my sensitivity analyses suggest that there was no detectable change in hospital admissions for coronary heart disease, stroke or diabetes associated with the introduction of NHS Health Check. Therefore, I failed to reject the null hypothesis that the NHS Health Check does not impact monthly hospital admissions for cerebrovascular disease, coronary heart disease and diabetes. This is supported by the autocorrelation graphs, which demonstrate that trends post the introduction of the NHS Health Check were more likely to be influenced by pre-NHS Health Check trends up to 14 months. One possible reason for such results is the mechanism and fidelity of the NHS Health Check as a prevention programme. This is because while the NHS Health Check programme is intended to be a preventative programme, it often uncovers previously undetected cases of coronary heart disease, chronic kidney disease, diabetes, and hypertension. Therefore, the prevalence of such diseases could be artificially inflated. Future studies could overcome this problem by analysing incidence rates instead of admission rates; although alternative study designs should consider admission rates as the NHS Health Check also aims to reduce the severity of cardiovascular disease by detecting it earlier, leading to lower long-term admission rates. This study also provides some evidence that different groups experience changes in admission rates at different levels, especially in differential deprivation groups. Therefore, future policies targeting cardiovascular health should take into consideration the social determinants of health as one of the aims of the NHS Health Check is to reduce health inequities.

Strengths

Due to HES' universal coverage, my study avoids the geographical constraints of previous studies, which may not have been representative of the population.

Interrupted time series studies are suitable for evaluating government policies and are able to examine evidence of population level changes in outcomes that include both effectiveness and uptake. While this study design is simple compared to other observational studies which use methods such as multiple imputation, propensity score matching and Cox regression, this study design answers the simple question of whether admissions rates from cardiovascular diseases nationally changed when the NHS Health Check was introduced.

Limitations

This study was limited by the fact that it was not possible to differentiate between incident and prevalent cases of disease and the low uptake of the NHS Health Check at population level and the lag between intervention and likely impacts on the outcomes. Additionally, missing population data, coding issues, and history of biases are also important limitations to this analysis which I review briefly below as studies in later chapters of the thesis aim to explicitly address these issues.

Furthermore, this analysis could not differentiate between NHS Health Check participants and non-participants, as the intervention is provided in primary care, whilst the outcome for this study is conducted using outcomes in secondary care. Thus, my study did not differentiate between the proportion of admissions which were in individuals who received an NHS Health Check; consequently, a controlled interrupted time series design could not be done; that is an interrupted time series study a control and intervention group.

Additionally, this analysis was limited to activity captured in admitted patient care and did not analyse outpatient care, accident and emergency or the critical care datasets; therefore, this analysis only considers a subset of hospital activity in England. Furthermore, this analysis is limited to hospital activity in England, irrespective of residency of the patient; consequently, English residents who seek treatment outside of England were not included,

whilst non-English residents who seek treatment English NHS hospitals were included in this analysis (who are not eligible for the NHS Health Check).

Missing data

I was unable to evaluate the impact of missing data for genders, age groups, and index of multiple deprivation data on the estimation of outcome events. This limitation exists because the reason for missingness in HES records may be different from that in the Office of National Statistics population data. Therefore, it is not possible to simply divide missing data points from HES by missing data points from the ONS particularly if the missingness is systemic (i.e., missing not at random). However, the levels of missing data were small (86 out of 1,645,644 admissions), therefore this should not introduced substantial bias to the results.

Coding inconsistencies

While the NHS Health Check was developed to reduce the rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes, I could not evaluate chronic kidney disease and hypertension due to inconsistent use of ICD10 codes for these disease groups. Therefore, I had to limit my study outcomes to coronary heart disease, diabetes, and cerebrovascular disease. My initial analysis only included type 2 diabetes; however, I found that by evaluating type 1 and type 2 diabetes, completeness and consistency of coding was better.

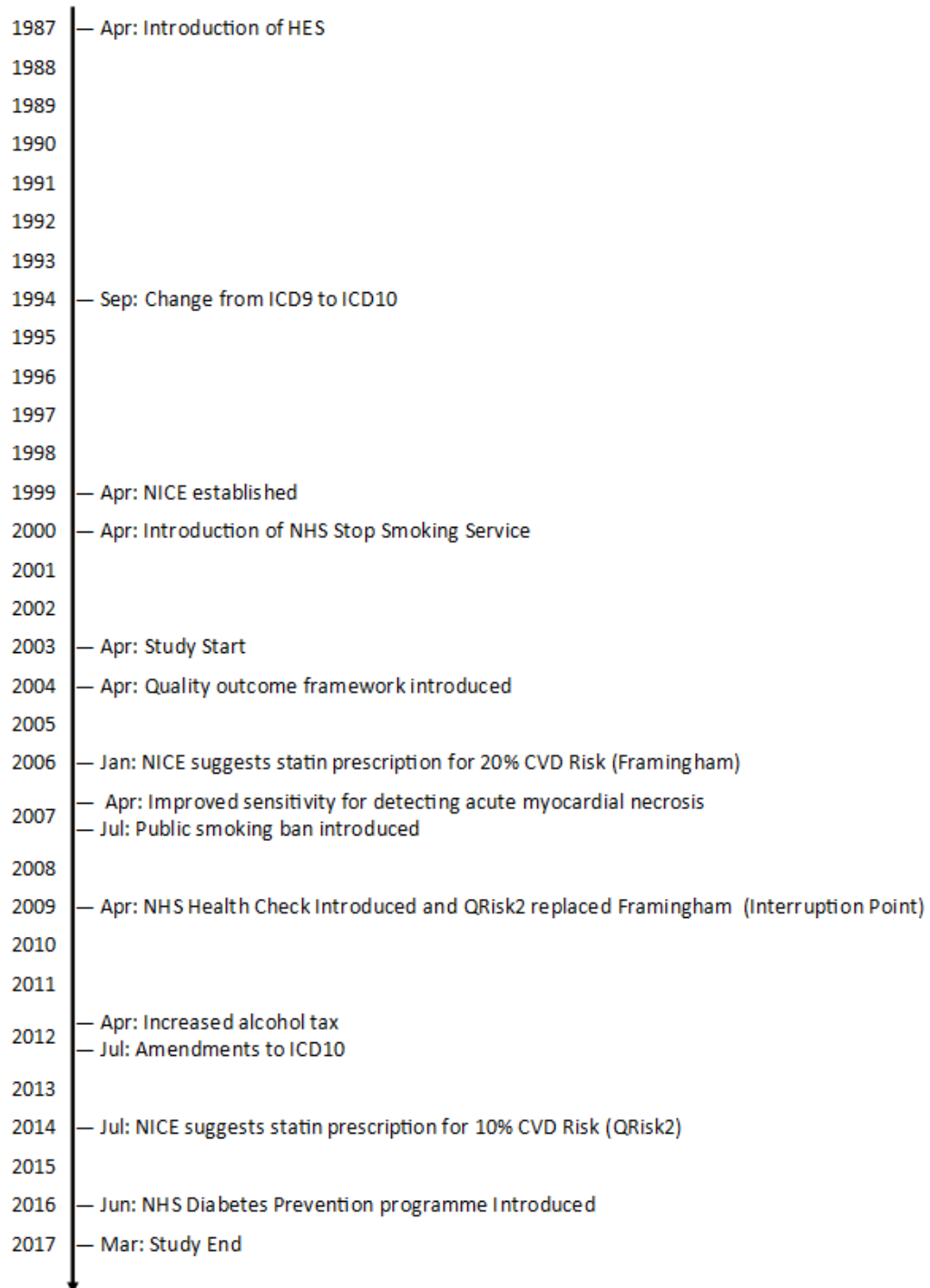
History of Bias

An important concern when evaluating public health interventions using an interrupted time series analysis is that there could be other events and co-interventions, which also has a national impact on the outcomes of interest. To identify these events, I generated a timeline of events related to Hospital Episode Statistics, changes in NICE guidelines impacting cardiovascular events or introductions of programmes aimed at preventing cardiovascular

disease. See Figure 3-20 for a chronological timeline of events which may have impacted hospital admissions of cardiovascular disease. However, some of these events were part of the NHS Health Check's aims and designs (e.g., statin prescriptions and NHS Diabetes Prevention Programme referrals); therefore, their "co-intervention" status should not be considered as a competing intervention, but a partner intervention.

Of the events in the timeline (Figure 3-20), I suspect the event that impacted this study the most is potentially the ICD10 amendments. This is because I noticed that specific codes were inconsistently used (Figure 3-20), and consequently, I had to evaluate specific subgroups of diseases together, for example, type 1 and type 2 diabetes as opposed to type 1 diabetes on its own. As the NHS Health Check uses NICE guided cardiovascular disease risk scores (Framingham and QRisk2) to evaluate patients, changes in guidelines were considered part of the NHS Health Check, and therefore should not have affected my analysis. As the NHS Diabetes Prevention Programme is one of the NHS preventative programmes the NHS Health Check refers to its patients too, I considered it part of the NHS Health Check; therefore, it should not impact my analysis.

Figure 3-20: A timeline of events which may introduce bias in evaluations of the NHS Health Check using an interrupted time series study design



Difficulties in establishing inferences.

One final limitation of this study (and of other non-controlled trials) is the use of analysing prevalence cases instead of incidence cases without a comparable control group of coronary heart disease, stroke, and cardiovascular disease; this an important distinction as the goal of this PhD is to evaluate the NHS Health Check as a preventative programme.

Generalisability

Based upon other studies which analysed the change in prevalence in primary care, this study acts as external validity by validating their results that the NHS Health Check does not seem to impact rates in the secondary care setting. Since the publication of Caley et al., 2014 (Caley et al., 2014) and Robson et al., 2016 (Robson et al., 2016) established that attendance of the NHS Health Check is lower than initially modelled for; therefore, even if the NHS Health Check was effective, it is hard to detect a significant change nationally using an interrupted time series design unless uptake was higher.

Overall evidence

Overall, there is lack of evidence that the NHS Health Check decreases monthly rates of admissions for cerebrovascular disease, coronary heart disease and diabetes nationally.

Next Steps

Further analysis of the NHS Health Check should consider using different datasets or study designs to understand the preventative effect of the NHS Health Check on the incidence of cerebrovascular disease, coronary heart disease, diabetes, hypertension, and stroke akin to a randomised controlled trial.

Chapter 4 – Reducing inaccuracies in identifying NHS Health Check and NHS Diabetes Prevention Programme participants in primary care records and phenotyping their cardiovascular disease, hypertension, stroke, and type 2 diabetes outcomes: a systematic review.

Abstract:

Introduction and research gap: Electronic health records can be used in conducting analyses of the NHS Health Check and the NHS Diabetes Prevention Programme. To create a structured and searchable set of records, electronic health records are dependent on clinical coding systems such as READ, International Classification of Diseases version 10 (ICD10) and Systematized Nomenclature of Medicine Clinical Terminology (SNOMED-CT) to allow researchers to extract relevant data. However, this leaves an opportunity for misclassification due to using an incorrect set of clinical codes and phenotyping algorithms. Whilst traditional studies have used two researchers (often a clinical coder and a clinician), this study explores the use of systematic reviews to create clinical code lists and phenotyping algorithms in the evaluation of the NHS Health Check and NHS Diabetes Prevention Programme. Using systematic reviews, I was able to collate the combined efforts of many research teams. Therefore, the objective of this chapter is to use systematic reviews to generate a list of phenotypes to be used in further chapters. The research gaps this chapter aims to target is the lack of systematically collected clinical code lists for phenotyping the NHS Health Check population and cardiovascular, diabetic, and chronic kidney disease-based outcomes in primary care datasets.

Methods: I conducted a systematic review using PubMed and Google in search for articles and clinical code repositories which described: the NHS

Health Check, the NHS Diabetes Prevention Programme, cardiovascular disease, diabetes, hypertension, and stroke phenotypes in primary care datasets such as the Clinical Practice Research Datalink, QResearch and The Health Improvement Network. I exclude other clinical coding systems such as the ICD10. I then grouped clinical codes grouped by disease and the number of references to establish how widely they have been used in the literature.

Results: I screened a total of 13,182 articles, with a total of 167 articles identified that provided READ codes describing heart disease, hypertension, stroke, and type 2 diabetes. 4,018 codes describing heart disease, 2,551 codes describing hypertension, 951 codes describing stroke, 1,991 codes describing type 2 diabetes were identified. Seven articles from 1,030 were deemed eligible when searching for clinical codes and algorithms to establish participation in the NHS Health Check in primary care datasets. Four hundred twelve codes describe the NHS Health Check with “9mC” codes having the most citations with three citations each. Due to the recent deployment of the NHS Diabetes Prevention Programme, only two policy documents were reviewed. This provided 5 READ codes with two citations each.

Conclusion and Discussion: This chapter produced a clinical code list to evaluate the NHS Health Check and the NHS Diabetes prevention programme using existing peer-reviewed articles and clinical coding guideline documents. Furthermore, this chapter introduces methods for quantifying often specific clinical codes are used in the peer-reviewed literature.

Next Steps: This study has systematically created a list of codes that can be used to evaluate the preventative effect of the NHS Diabetes Prevention Programme and the NHS Health Check on the incidence of type 2 diabetes.

Complementary Reading Material: To aid readers in this chapter, the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist has been provided in Appendix 4.1.

Introduction

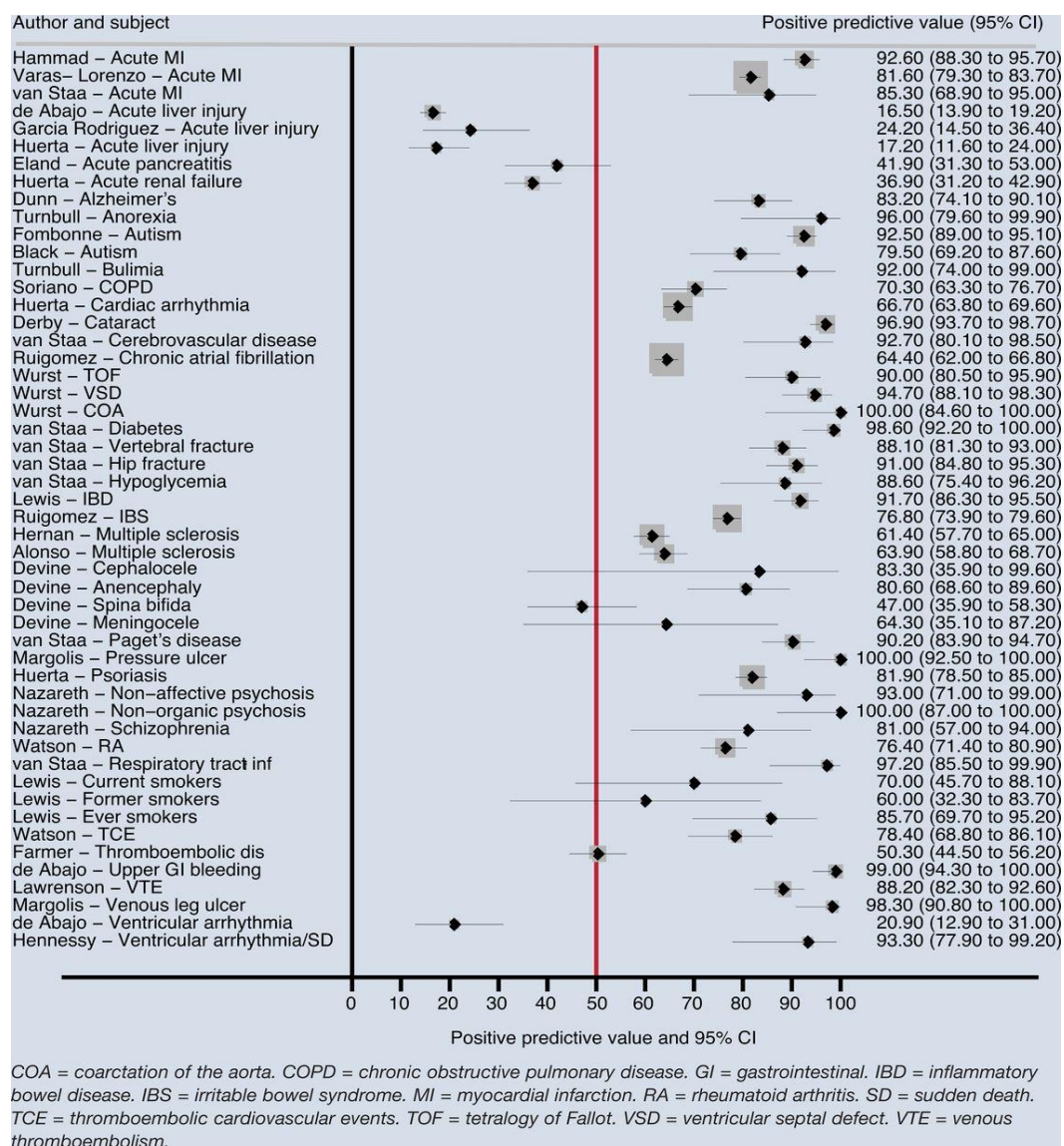
Chapter Three used a quasi-experimental interrupted time series analysis to investigate the yearly growth (or decline) of cardiovascular disease before and after the introduction of the NHS Health Check in England. This study used aggregated national data that required the use of national population estimates to calculate rates of hospital admission and was subject to historical biases due to other co-interventions implemented at the same time. Alternative study designs that could be used include randomised controlled trials (RCT). Whilst an RCT would evaluate the long-term impact of the NHS Health Check on healthcare outcomes would provide high-quality evidence of effectiveness and impact, using this method would be expensive and require long-term follow up (Soljak et al., 2013). An RCT is also likely to be unacceptable to decision-makers because NHS Health Check is widely used in practice. Additionally, because of the widespread implementation of the NHS Health Check already, finding appropriate control groups would require the withdrawal of the intervention to some individuals eligible and as a result may be unacceptable to many stakeholders.

Observational study designs using electronic health records are an alternative and pragmatic approach to examine the effectiveness of the NHS Health Check as they offer real-world data, high statistical power with longitudinal results and they are efficient to conduct. To conduct an observational study that analyses the NHS Health Check in England, the following primary care datasets can be used: Clinical Practice Research DataLink (CPRD), QResearch and The Health Improvement Network (THIN) (Vezyridis and Timmons, 2016) and QResearch (University of Nottingham, 2012). The CPRD is an ongoing primary care dataset whose records are contributed to by 674 general practices in the United Kingdom with a population of 4.4 million active patients (Herrett et al., 2015). CPRD is considered to be representative of the English population (Herrett et al., 2013). The THIN database currently hosts 3.7 million active patients amongst 562 general

practices in the United Kingdom. Finally, the QResearch database has access to 1500 contributing general practices in the United Kingdom with 24 million (total) patients (University of Nottingham, 2012). Each dataset has been linked to secondary care datasets such as Hospital Episode Statistics and such linkage has been demonstrated to improve the identification of conditions such as myocardial infarction (Herrett et al., 2013). However, conducting an observational study to evaluate the effectiveness of the NHS Health Check using primary care electronic health record data is challenging due to several biases and confounders, including, for example, confounding by indication; that is non-randomised treatment that is often based upon need (through severity of disease).

Another major limitation of retrospective observational studies conducted using electronic health records to analyse the effectiveness of the NHS Health Check relates to the challenge of establishing cohorts and healthcare outcomes due to inaccuracies in clinical coding (Chang et al., 2016) (See Figure 4-1). (Tate et al., 2017) estimate that inaccuracies in clinical coding between 2004-2014 have led to 10% of patients coded as having diabetes from 102 CPRD practices being misdiagnosed as having the wrong type of diabetes e.g. type 1 or type 2; in this PhD, I was only interested in type 2 diabetes as it is preventable through improved diet and weight management control whilst type 1 diabetes is an autoimmune disease (Salsali and Nathan, 2006). Whilst the policymakers produce READ codes as part of a series of Quality Outcome Framework (QOF) (a programme aimed at improving measurable healthcare quality through contractual obligations with a general practice), there is still a disparity in the list of clinical codes used by different studies and general practices which can heavily impact the results from studies using these codes as exposures or outcomes (Tate et al., 2017)

Figure 4-1: Positive Predictive Values for READ Codes in the General Practice Research Database (GPRD) (Khan, Harrison & Rose, 2010). There are other measures such as negative predicted value, sensitivity and specificity.



Evaluating the NHS Health Check using primary care data in the UK requires the use of READ codes; a clinical coding system primarily found in the United Kingdom primary care and New Zealand. READ Codes were developed to provide a code for all different terminologies used in medical records (including signs, symptoms, diseases) and then provide a hierarchical grouping of these codes. By using such clinical coding terminology,

researchers can easily access records by using structured medical concepts as compared to analysing “free text”. For example, the code “C10F.00” is used to represent the concept “Type 2 diabetes mellitus”. Many other record systems worldwide use the International Classification of Diseases (version 10), which are generated based on the understanding of the taxonomy of different categories of disease.

To overcome weaknesses in clinical coding such as variation in coding practices and errors in clinical coding, this chapter uses systematic reviews to identify and combine previously used and validated codes and to identify established phenotyping algorithms. I chose this method to identify many existing code lists that meet the requirements of this PhD. Taking this approach also has the advantage that it collates the collective efforts of multiple studies when phenotyping a given disease.

To be invited to the NHS Health Check, participants must be between 40 and 74 years old without an existing recording of chronic kidney disease, cardiovascular disease, hypertension, stroke, or type 2 diabetes at the time of their invitation. Therefore, to conduct a study using primary care observational data, READ code lists must be generated for identifying NHS Health Check participants and clinical code lists for heart disease, hypertension, stroke, or type 2 diabetes. By establishing an accurate list of the diseases, I can accurately eliminate patients at the beginning of the study who were not eligible for the NHS Health Check by virtue of having any of these conditions. The same codes can then also be used to establish healthcare outcomes post-intervention. Consequently, studies using these validated code lists are less likely to overestimate the impact of the NHS Health Check by under-reporting the incidence of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes. Once the eligible cohort is established, the NHS Health Check participation status could be established.

The aim of this study was, therefore, is to identify READ codes and phenotyping algorithms previously used to identify the incidence of heart disease, hypertension, stroke and type 2 diabetes and delivery of the NHS Health Check and the NHS Diabetes Prevention Programme.

Methods

To aid in my literature search, the Population, Intervention, Comparison, and Outcome (PICO) were as specified to facilitate the design of the search terms required for all studies using primary care datasets to analyse and identify the NHS Health Check, heart disease, diabetes, hypertension, and stroke. See Table 4-1 for the PICO dimensions.

With input from Professor Laurie Tomlinson (Associate Professor, London School of Hygiene and Tropical Medicine and Consultant Nephrologist) and their team, I've learnt that solely using READ codes to estimate chronic kidney disease would potentially underestimate the incidence of chronic kidney disease (Iwagami et al., 2017). Therefore, I did not include chronic kidney disease in my systematic review; instead, for future chapters, I will take Professor Laurie Tomlinson's team advice of using measures of serum creatinine and estimated glomerular filtration rate to estimate chronic kidney disease in electronic health records. Similarly, due to the recent deployment of the NHS Diabetes Prevention Programme (in 2016), I did not conduct a literature review in the same manner as the NHS Health Check. Instead, I reviewed policy documents to identify relevant code lists.

Table 4-1: Population, Intervention, Comparison and Outcome properties used when searching for Literature which reviews the NHS Health Check, Cardiovascular Disease, Diabetes, Hypertension and Stroke using Primary Care Databases

Concept	Population	Intervention	Primary Outcomes	Secondary Outcomes
NHS Health Check	Patients in England eligible for the NHS Health Check	READ Codes used to identify those who took part in the NHS Health Check	All healthcare outcomes were considered	To avoid errors and omissions by clinical coders, Secondary outcomes included Algorithms to identify those who have taken part in the NHS Health Check
Heart Disease	Studies that used Electronic Healthcare Records to evaluate heart disease healthcare outcomes were considered	All interventions which impacted primary heart disease outcomes were considered	READ Codes used to identify heart disease patients. Including codes that identify healthcare outcomes in heart disease	Algorithms used to identify those in English Primary Care who suffer from heart disease
Diabetes	Studies that used Electronic Healthcare Records to evaluate Diabetes healthcare outcomes were considered	All interventions which impacted Diabetic outcomes were considered	READ Codes used to identify Diabetic patients. Including codes that identify healthcare outcomes in Diabetes	Algorithms used to identify those in English Primary Care who suffer from Diabetes

Concept	Population	Intervention	Primary Outcomes	Secondary Outcomes
Hypertension	Studies that used Electronic Healthcare Records to evaluate Hypertension healthcare outcomes were considered	All interventions which impacted Hypertension outcomes were considered	READ Codes used to identify Hypertension patients. Including codes which identify healthcare outcomes in Hypertension	Algorithms used to identify those in English Primary Care who suffer from Hypertension.
Stroke	Studies that used Electronic Healthcare Records to evaluate Stroke healthcare outcomes were considered	All interventions which impacted Stroke outcomes were considered	READ Codes used to identify Stroke patients. Including codes that identify healthcare outcomes in Diabetes	Algorithms used to identify those in English Primary Care who suffer from Stroke.

Study and Code Selection

My primary search strategy was conducted using PubMed. MESH terms were used where possible; see Table 4-2 for the search terms used. Appendix 4.2 contained detailed search strings used. A secondary search strategy was conducted using Google's first 10 pages as many published studies do not publish their code lists in their paper. Whilst traditional literature searches do not use search engines, Google was also used to search for READ code databases and Clinical Coding Guidelines (non-academic). Searches were conducted on the 13 October 2017.

Table 4-2: MESH Terms used in the search criteria.

Concept Group	Concept	Terms
Public Health Intervention	NHS Health Check	"NHS" OR "National Health* Service" OR "Health Check"
	NHS Diabetes Prevention Programme	"NHS" OR "National Health* Service" OR "Diabet* Screen*"
Disease	Cardiovascular Disease	Cardiovascular Disease
	Diabetes	"Diabet*" OR "mellit"
	Hypertension	"Hypertensi*"
	Stroke	"Stroke"
Electronic Health Record System	Primary Care datasets	"CPRD" OR "EHR" OR "GPRD" OR "Codes"

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to visualise the process of eliminating ineligible articles. Articles were imported into Microsoft Excel and then eliminated first by title, then by Abstract then by full text, including appendices and references; this was conducted by a single author as studies did not need to be weighted (i.e., missing a study is less likely to impact the result when compared to studies that pool results). The primary type of article included studies that used READ codes to identify the incidence of heart disease, hypertension, stroke, and type 2 diabetes. The secondary type of journal article included studies that used the CPRD/GPRD/THIN/QResearch datasets to identify the incidence of cardiovascular disease, hypertension, stroke, or type 2 diabetes; this is to include any proxy measures such as HbA_{1c}, eGFR and product codes as described in Chapter 2. Using Google, my primary aim was to search for guidelines aimed at clinical coders stating how READ codes should be interpreted. These guidelines must include guidance in reviewing heart disease, hypertension, stroke, or type 2 diabetes. Finally, I also analysed websites that acted as databases for READ codes, for example, Clinicalcodes.org

I also included READ codes from the database held by University College London's Clinical Research using Linked Bespoke studies and Electronic Health Records (CALIBER) team; the resources from CALIBER have undergone multiple validation studies (Denaxas et al., 2012). The structure of CALIBER contains the following datasets and linkage files across them: the Clinical Practice Research Datalink, Hospital Episode Statistics, the Myocardial Ischaemia National Audit Project, and the Office of National Statistics linkage (for death registrations and deprivation linkage). Further, bespoke linkages could be conducted, including the UK Biobank dataset. Consequently, the team in CALIBER provide researchers access to their clinical code database which collates clinical codes available in the datasets

within CALIBER. I was granted access to the CALIBER's team's clinical code database on the 18th of October 2017. This dataset was compiled in October 2016 and contains a set of READ codes and their corresponding concepts. READ codes were firstly filtered by applying the following search terms: hypertensi*, diabet*, stroke, ischemi*, infarc*, cerebra*, and haemorrhag*. From this subset, each READ code was analysed sequentially to check for eligibility. Once filtered, the READ codes from CALIBER were added to my matrix with the reference "(UCL, 2016)". I included codes that described heart disease, hypertension, stroke, and diabetes. I included codes for treatments specifically associated with having a positive diagnosis for heart disease, hypertension, stroke, and diabetes. I also included codes for treatments used in treating patients who have a positive diagnosis for heart disease, hypertension, stroke, and type 2 diabetes. I excluded studies that used other coding systems such as the International Classification of Diseases (ICD) and studies that used another coding system such as SNOMED-CT as these terminologies are not used in primary care datasets in England.

Data Extraction and Analysis

To extract the relevant codes from the studies, the codes and their corresponding READ concepts were copied into an n*3 matrix (See Table 4-3 for an example). This contained the following dimensions: The study reference (Harvard), the READ Code and the READ Concept. To achieve this, each study was analysed for READ codes in the body of the study (excluding tables), the tables presented in the studies, the supplementary data (files), references and the appendixes. For codes in the body in the text or tables, I manually inserted the values into the matrix. For authors who provided their READ codes using Stata Data Files (dta format), the Haven library in R programming language (version 1.1.0) was used to convert the files to a format readable by Microsoft Excel (comma separated variables). For studies that stated they used the CPRD/THIN/QResearch database but

did not provide the READ codes, I emailed the corresponding author with a request for the Codes they used.

Table 4-3: Example Matrix for storing READ codes, their source, and concept.

Source	Code	Concept
(Mosholder et al., 2017)	G61..11	CVA- cerebrovascular accident due to intracerebral hemorrhage
(Mosholder et al., 2017)	G61..12	Stroke due to intracerebral hemorrhage
(Mosholder et al., 2017)	G610.00	Cortical hemorrhage
(Mosholder et al., 2017)	G611.00	Internal capsule hemorrhage

Once the matrix was populated, I transformed this into a second matrix that grouped unique READ codes by the studies which cite them (Chapter Table 4-4). As some studies did not state the READ concept for the codes they used, I used CALIBER's concept for each READ code without a concept. If there was no corresponding concept from CALIBER, I used the raw value stated by the study which cited it.

Table 4-4: Example transformed table which groups unique READ codes by the studies which cited them.

# Of Studies	Code	Concept	Study ₁	Study ₂	Study _{2<x<n}	Study _n
22	C10FJ11	Insulin-treated Type 2 diabetes mellitus	(Caleyac hetty et al., 2017)	(Toulis et al., 2017)		(UCL, 2016)
22	C10F900	Type 2 diabetes mellitus without complication	(Caleyac hetty et al., 2017)	(Toulis et al., 2017)		(UCL, 2016)
22	C10FJ00	Insulin-treated Type 2 diabetes mellitus	(Caleyac hetty et al., 2017)	(Toulis et al., 2017)		(UCL, 2016)

# Of Studies	Code	Concept	Study ₁	Study ₂	Study _{2<x<n}	Study _n
X						
X						
1	C109.13	TYPE 2 DIABETES MELLITUS	(Li, Neogi&Ji ck, 2017)	NULL	NULL	NULL

To analyse the READ codes, I counted the number of references per READ code. From this frequency, I used descriptive statistics to analyse: the average number of citations per code, codes that were cited the most, and codes that were least cited. I also counted the number of READ codes that were referenced by a single study; this is because I correlate the number of quotations per code with the confidence academics have when it comes to phenotyping heart disease, hypertension, stroke, and type 2 diabetes for that specific code. Therefore, using these counts, subgroup analysis could be conducted to establish the sub-set of codes that contribute the most towards identifying cases of cardiovascular disease, hypertension, stroke, and type 2 diabetes.

Results

Phenotyping cardiovascular disease, hypertension, stroke, and type 2 diabetes

From 13,182 articles, I considered 167 articles as eligible to identify READ codes used to identify the incidence of cardiovascular disease, hypertension, stroke, or type 2 diabetes (see Figure 4-2). For all diseases, the most common reason for removal was the use of ICD codes instead of READ

codes; this was either stated in the title or the abstract. A total of 8664 READ and product codes were found for all diseases from the eligible 167 studies. 1,770 codes were associated with diabetes, 4,019 with heart disease, 2,551 for hypertension and 766 for stroke. It should be noted that as the READ code system considers stroke a type of cardiovascular disease, many codes were classified under heart disease and stroke. See Table 4-5 for a summary of the most cited READ codes.

Figure 4-2: PRISMA describing the process of finding eligible studies As the first 10 pages of Google were evaluated, providing 10 result each, there were always 100 results attributed to Google; some of which may have been duplicates but were removed during de-duplication.

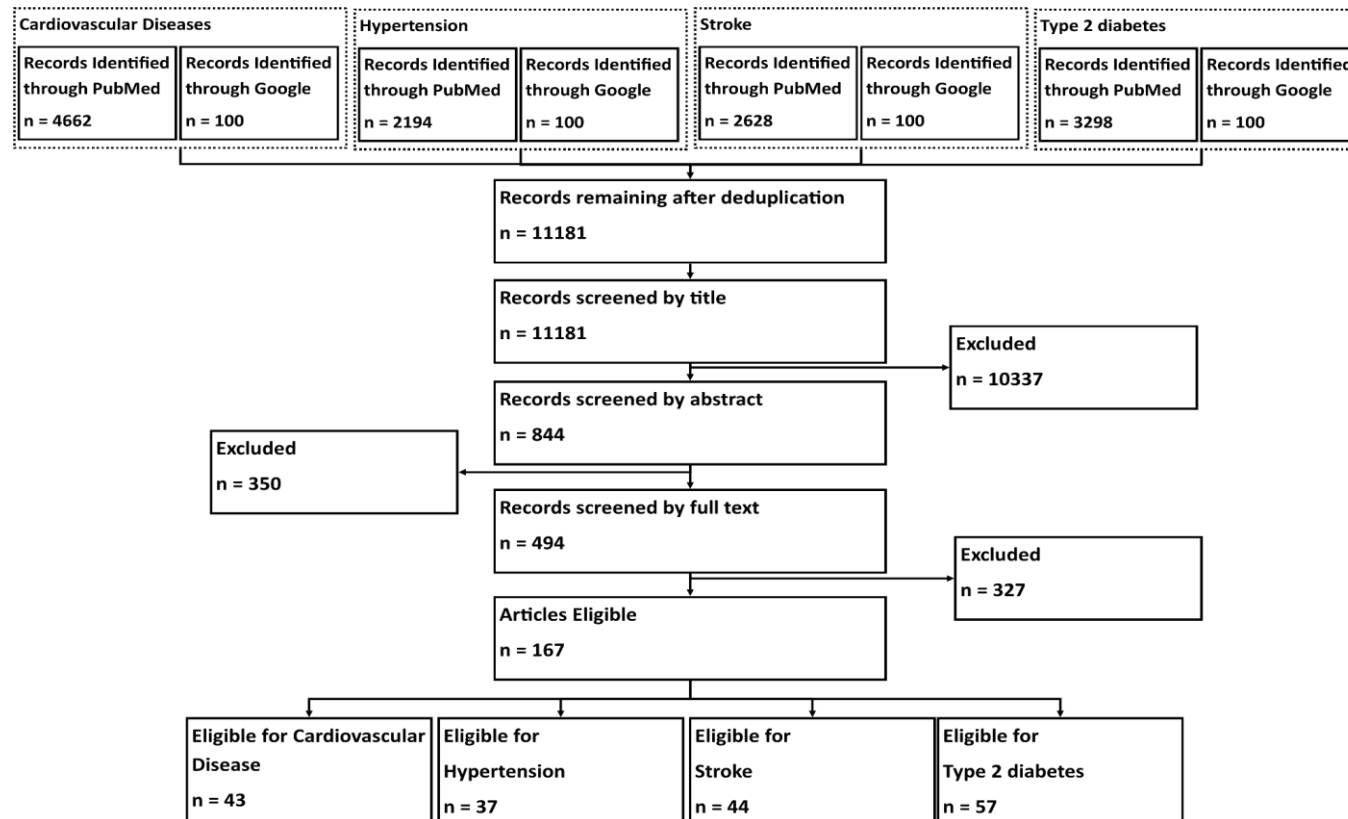


Table 4-5: Top 5 Referenced READ Codes for each Disease

Disease Group	Code	Concept	Citations
Heart Disease	G30..15	MI - acute myocardial infarction	19
	G30..00	Acute myocardial infarction	19
	G30..17	Silent myocardial infarction	18
	G30X.00	Acute transmural myocardial infarction of unspecified site	18
	G306.00	True posterior myocardial infarction	18
Hypertension	G24zz00	Secondary hypertension NOS	18
	G200.00	Malignant essential hypertension	18
	G20z.00	Essential hypertension NOS	18
	G201.00	Benign essential hypertension	18
	G24..00	Secondary hypertension	18
Stroke	G66..11	Cerebrovascular Accidents Accident unspecified	26
	G667.00	Left sided Cerebrovascular Accidents	26
	G640000	Cerebral infarction due to thrombosis of cerebral arteries	25
	G64..13	Stroke due to cerebral arterial occlusion	25
	G66..00	Stroke and cerebrovascular accident unspecified	25
Type 2 diabetes	C10FJ11	Insulin treated Type 2 diabetes mellitus	22
	C10F900	Type 2 diabetes mellitus without complication	22
	C10FJ00	Insulin-treated Type 2 diabetes mellitus	22
	C10FA00	Type 2 diabetes mellitus with mononeuropathy	22
	C10F011	Type 2 diabetes mellitus with renal complications	22

Forty-Three articles provided READ codes for heart disease, including 23 studies identified using PubMed and 20 web pages from Google. Eight corresponding authors responded to my READ code request and provided me with the appropriate codes: 1) Blackburn et al., 2017; 2) Collins and 3) Altman, 2011; 4) de la Iglesia et al., 2011, 2011; 5) Johnson et al., 2016; 6) Karch and Thomas, 2014; 7) Langley et al., 2012; and 8) Turner et al., 2016.

From all 43 sources, 9,163 codes were provided with a total of 4,018 unique READ codes to describe heart disease. Twenty studies produced more than 100 READ codes describing heart disease (Taylforth, 2015), providing the most codes with 2,046. The mean number of citations per code is 1.87 (95% CI: ± 0.08). The most cited codes started with “G30” and describe variants of myocardial infarction; these had at least 19 citations each. 2914 Codes out of 4018 were only referenced once. From CALIBER’s 111445 clinical codes, 188 concepts met my inclusion criteria (UCL, 2016).

Thirty-seven articles provided READ codes describing hypertension with 24 studies identified using PubMed and 20 web pages from Google. Three corresponding authors responded to my READ code request and provided me with the appropriate codes: (Ahmed et al., 2016; Bhaskaran et al., 2012; Robson et al., 2016). From all 37 sources, 3,662 codes were provided with a total of 2,551 unique READ codes to describe Hypertension. Seven studies produced more than 100 READ codes describing Hypertension with Sinnott *et al.*, 2017 providing the most codes with 2129 codes. The mean number of citations per code is 1.42 (95% CI: ± 0.07). The most cited codes started with “G2” describing variants of Secondary Hypertension; these had at least 18 citations each (Chapter 4 Table 11). 582 Codes out of 951 were only referenced once. From CALIBER’s 111,445 clinical codes, 185 concepts met my inclusion criteria (UCL, 2016). Following Iwagami et al., 2017 I will also

use systolic and diastolic blood pressure readings on entry to complement cases of hypertension in further chapters of this PhD

Forty-four studies described stroke having provided 3,182 codes with a total of 951 unique READ. Twelve studies produced more than 100 READ codes describing Stroke with (Zhong et al., 2018) providing the most codes with 203. The mean number of citations per code is 3.35 (95% CI: ± 0.34). The most cited codes started with "G6" and describe variants of cerebrovascular Accidents (Table 14); these had at least 26 citations each. Five hundred and eighty-two codes out of 951 were only referenced once. From CALIBER's 111,445 clinical codes, 188 concepts met my inclusion criteria for describing Stroke (UCL, 2016).

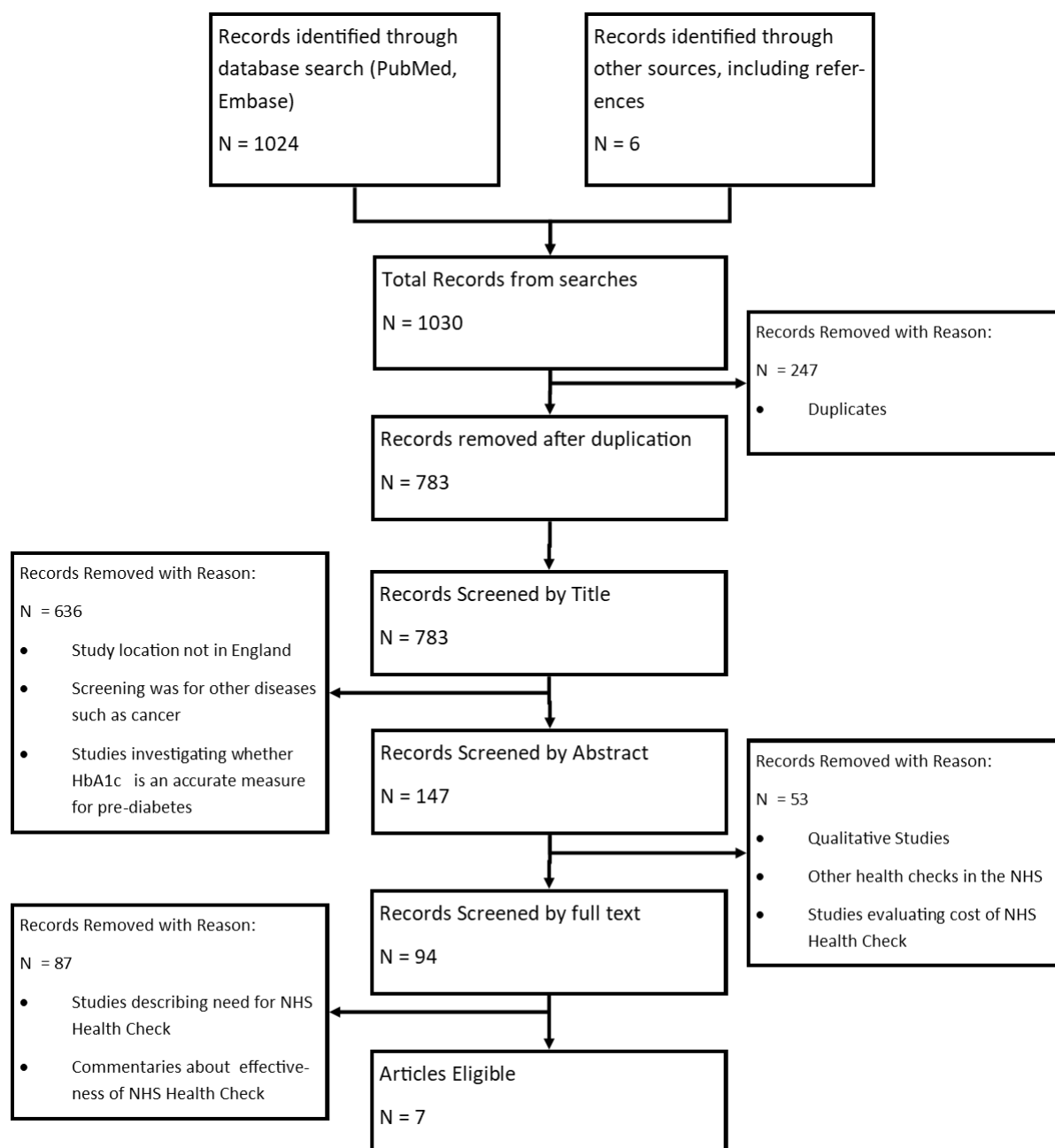
Fifty-Seven sources provided READ codes for diabetes with 9,188 codes, of which 1,992 were unique. Twenty-four studies produced more than 500 READ codes describing diabetes with CALIBER providing the most codes with 693. From the 1,992 unique codes, 182 described type 1 Diabetes, 195 described type 2 diabetes and 1,615 codes were unclear. The most cited codes started with "C10F" and describe variants of type 2 diabetes; these had 25 citations each. 1,076 codes from the unsure group were cited once. Following Iwagami et al., 2017, I will also analyse glycated haemoglobin levels (HbA_{1c}) and fasting plasma glucose (FPG) to complement diagnoses of diabetes in future chapters of this PhD

Phenotyping the NHS Health Check

A total of seven articles were deemed eligible from an original 1030 regarding the NHS Health Check. Many studies were excluded as they described cancer screening programmes based outside of the United Kingdom. No corresponding authors provided their READ code lists. The eligible articles are Artac et al., 2013; Chang et al., 2015; Forster et al., 2014; McDaid and

Hepplestone, 2011; Robson et al., 2017; Strother Smith and Hepplestone, 2012; Thomas, 2011. See Figure 4-3 for the PRISMA flowchart.

Figure 4-3: PRISMA Diagram for the NHS Health Check



For the NHS Health Check, 421 READ codes were obtained from all the studies mentioned except (Artac et al., 2013). (McDaid and Hepplestone,

2011) contributed the most codes with 316 whilst the mean number of READ codes provided per source is 74.625 (95% CI: ± 68.15891). From these codes, 421 unique READ codes were obtained with an average of 1.311 (95% CI: ± 0.056481) citations per code. The most cited READ codes had 3 citations each (Table 6) and either represent chronic kidney disease or the Invitation method of the NHS Health Check. Conversely, 317 READ codes were only cited by a single source. Most codes described the exclusionary criteria for the NHS Health Check ($n = 154$). This was followed by observations conducted as part of the NHS Health Check ($n = 82$), NHS Health Check specific READ codes ($n = 71$), and demographics READ codes ($n = 22$). See Table 4-6 for the most cited READ codes describing the NHS Health Check.

Table 4-6: Most popular READ Codes used in the NHS Health Check

Programme	Read Code	Concept	Citations
NHS Health Check	9mC.	NHS Health Check invitation	3
	9mC0.	NHS Health Check telephone invitation	3
	9mC1.	NHS Health Check invitation first letter	3
	9mC2.	NHS Health Check invitation second letter	3
	9mC3.	NHS Health Check invitation third letter	3

Algorithms to identify those who have taken part in the NHS Health Check, (Artac et al., 2013) used a combination of criteria to imply participation in the NHS Health Check. This includes collecting all the following readings if they were taken 3 months after joining the general practice on the same day:

- A blood pressure observation was recorded.
- A cholesterol reading was taken.

- The patient's Body Mass Index was recorded.
- A familial history of Chronic Heart Disease was recorded,
- The patient's ethnicity was recorded,
- The patient's smoking status was recorded.
- The patient's exercise level was recorded.

Phenotyping the NHS Diabetes Prevention Programme

Due to the recent deployment of the NHS Diabetes Prevention Programme, I was only able to evaluate two policy documents provided to general practices and local authorities. I found 5 READ codes to describe the NHS Diabetes Prevention Programme. See Table 4-7 or the READ codes extracted to describe the NHS Diabetes Prevention programme.

Table 4-7: Most popular READ Codes used in the NHS Diabetes Prevention Programme

Programme	READ Code	Concept	Citations
NHS Diabetes Prevention programme	679m4	Referred to NHS Diabetes Prevention Programme	2
	679m3	Referral to NHS Diabetes Prevention Programme declined	2
	679m2	NHS Diabetes Prevention Programme started	2
	679m1	NHS Diabetes Prevention Programme completed	2
	679m0	NHS Diabetes Prevention Programme not completed	2

Discussion

In total, I discovered 9,215 READ codes to evaluate the NHS Health Check with 4,018 codes describing heart disease, 2,551 codes describing hypertension, 951 codes describing stroke, 1,991 codes describing type 2 diabetes and 412 codes describing the NHS Health Check. My study has also described the most frequently used READ codes to describe heart disease, hypertension, stroke, and type 2 diabetes. This study also identified Artac *et al.*, 2013's algorithms to reduce misclassification in coding in terms used to identify NHS Health Check participants. My study combines the efforts of peer-reviewed articles to systematically identify heart disease, hypertension, stroke, and type 2 diabetes in primary care databases. Weaknesses of this study are that I was the only individual to screen studies. In this chapter I have not examined the validity of the code lists identified; however, in chapters 5 and 6 which use the READ codes and algorithms, I will also present analyses that examine their validity against externally validated datasets.

Whilst this study could have been conducted by using clinical coders, clinicians, and clinical expert reference groups to identify codes, Tate *et al.*, (2017) has already suggested that variation exists from different general practices, therefore, conducting this study using clinical coders, clinical and clinical expert reference groups may add to such variation as opposed to resolving it. Although I did not extract specific data on these points, it is likely that many of the studies referenced in this systematic review have used clinicians and clinical coders, therefore, this study has possibly combined the efforts of multiple clinicians and multiple clinical coders.

Acknowledgements

I thank my colleagues from University College London who provided access to the Calibre READ code dataset that greatly assisted the research, although they may not agree with all the interpretations/conclusions of this chapter. I

would also like to acknowledge the following studies that responded to my READ code request, who may not also agree with all the interpretations/conclusions of this chapter:

- Collins and Altman, 2011
- de la Iglesia et al., 2011
- Langley et al., 2012
- Bhaskaran et al., 2012
- Karch and Thomas, 2014
- Yulong et al., 2015
- Bruderer et al., 2015
- Turner et al., 2016
- Johnson et al., 2016
- Zghebi et al., 2016
- Robson et al., 2016
- Vinogradova et al., 2016
- Nielen et al., 2016
- Gitsels et al., 2016
- Eastwood et al., 2016
- Ahmed et al., 2016
- Blackburn et al., 2017
- Datta-Nemdharay et al., 2016

Chapter 5 - Investigating the effect of the NHS Diabetes Prevention on the prevention of type 2 diabetes in England: A population-based cohort study using linked CPRD primary care and HES secondary care health records

Abstract

Background and research gap: To reduce new cases of type 2 diabetes cases in England, the National Health Service (NHS) piloted the NHS Diabetes Prevention Programme. The NHS Diabetes Prevention Programme aims to prevent type 2 diabetes by providing adults at high risk with access to 13 face-to-face sessions over nine months that focus on diet and weight management. The NHS Diabetes Prevention Programme has been shown to improve intermediate outcomes for type 2 diabetes prevention, including weight loss and glycated haemoglobin (HbA_{1c}) reduction. However, there is a lack of observational studies emulating randomised controlled trials to evaluate the preventative effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes.

Methods I applied target trial emulation using retrospective observational cohort data using linked electronic health records from primary (Clinical Practice Research Datalink), and secondary (Hospital Episode Statistics) care between June 2016 to January 2019. I compared rates of incident type 2 diabetes diagnoses among eligible adults who were referred to the NHS Diabetes Prevention Programme with rates for propensity score-matched (ratio of 1:4) controls who were eligible for the NHS Diabetes Prevention Programme but were not invited. Eligibility for the NHS Diabetes Prevention Programme was defined as having HbA_{1c} levels of 42-47 mmol/mol or fasting

plasma glucose (FPG) levels of 5.5-6.9 mmol/L on entry. Adults with type 2 diabetes within 90 days of start of follow-up (earliest NHS DPP activity) were excluded as these were considered prevalent cases. Time to the first phenotypical recording of type 2 diabetes was modelled using Cox regression with age, alcohol intake, body mass index, ethnicity, sex, HbA_{1c}, index of multiple deprivations and smoking status included as covariates.

Results I identified 2205 individuals who participated in the NHS Diabetes Prevention Programme and 8,820 matched controls of a similar age, sex, HbA_{1c} and FPG. During the 2.5-year study period, 4.13% (95%CI: 3.3% - 5.0%) of NHS Diabetes Prevention Programme individuals have a new recording of type 2 diabetes vs 6.42% (95%CI: 5.9% - 7.0%) of matched controls. My results indicate that NHS Diabetes Prevention Programme referrals were associated with a 59% reduction in recorded type 2 diabetes incidence rates [adjusted hazard ratio=0.41;95%CI=0.38-0.44]. My findings are comparable to results produced by randomised controlled trials which evaluate similar diabetes prevention programmes worldwide.

Discussion and Conclusions My study found evidence that the NHS Diabetes Prevention Programme reduced incident type 2 diabetes in high-risk groups compared to usual care. The results provide support for the effectiveness of the NHS Diabetes Prevention Programme in reducing type 2 diabetes onset and are compatible with findings for similar interventions in other settings whose effectiveness were established using randomised controlled trials.

Next Steps Due to the limitations of this study, primarily surrounding missing data and low numbers compared to validated datasets, future studies should explore methods to reduce these biases.

Abstract Presentations intended to be turned into full paper: Nguyen, V., Aldridge, R., Blackburn, R., Hayward, A., Greaves, F. and Flowers, J. (2020). Does the NHS Diabetes Prevention Programme prevent diabetes? A population-based matched cohort study. *European Journal of Public Health*, [online] 30(Supplement_5). doi:10.1093/eurpub/ckaa165.1184.

Complementary Reading Material: To aid readers in this chapter, the REporting of studies Conducted using Observational Routinely collected Data (RECORD) checklist has been provided in Appendix 5.1.

Introduction

The National Health Service (NHS) Diabetes Prevention Programme was piloted in England in 2016 with the primary goal of preventing or postponing type 2 diabetes in England in high-risk individuals (Barron et al., 2018). A more detailed description of the NHS Diabetes Prevention Programme can be found in Chapter 1 - The proposed targeted solution: NHS Diabetes Prevention Programme.

Due to the recent phased deployment of the NHS Diabetes Prevention Programme in 2016, there is limited research with studies analysing patient uptake (Valabhji et al., 2020), and proxy measures such as weight loss and change in HbA_{1c} levels (Barron et al., 2018). Whilst randomised controlled trials evaluating similar programmes in the USA and Finland have shown a beneficial effect on the incidence of type 2 diabetes (Diabetes Prevention Programme Group, 2015, 2002)), (Ilanne-Parikka et al., 2013), there is no study that evaluates whether the NHS Diabetes Prevention Programme changes the risk of developing type 2 diabetes in high-risk adults when compared to a comparable control group in England at an individual level.

Therefore, in this chapter, I aim to evaluate the NHS Diabetes Prevention Programme's ability to prevent the incidence of type 2 diabetes for eligible adults in a manner that emulates a randomised controlled trial. To achieve this aim, this chapter has the following objectives:

- 1) Identify randomised controlled trials which evaluated programmes similar to the NHS Diabetes Prevention Programme to define a target randomised controlled trial which evaluates the effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes.
- 2) Using READ codes and phenotypes I identified in chapter 4 to reduce misclassification when establishing a cohort of eligible patients, their treatment status, and their healthcare outcomes.

- 3) Validate the cohort identified as having NHS Diabetes Prevention Programme activity by comparing their baseline covariates to an externally validated source.
- 4) Applying established epidemiological methods to reduce biases in observational studies such as missing data, misclassification, and confounding.
- 5) Validate the results of this chapter by comparing the results of this observational study informed by a target trial design to randomised controlled trials which have evaluated similar interventions outside of the UK.

Methods

Study Design

In this study, I used an observational, retrospective longitudinal cohort design with the “trial emulation” framework applied to reduce confounding by indication (Hernán et al., 2022).

Bias and Target Trial Description

The target trial for this study emulates the study designs used by randomised controlled trials which evaluated similar programmes internationally; Diabetes Prevention Programme Group, 2015, 2002 and Ilanne-Parikka et al., 2013.

These studies were chosen as they were mentioned in prior literature produced by Public Health England as studies that evaluated diabetes prevention programmes with a hard outcome of the incident of type 2 diabetes (Barron et al., 2018).

The target population for this study mirrors that of the NHS Diabetes Prevention Programme with the following inclusion/exclusion criteria (on entry):

- Inclusion:
 - At least 18 years old
 - AND
 - Fasting plasma glucose between 5.5-6.9 mmol/L
 - OR
 - HbA1c level 42 to 47 mmol/L
- Exclusion: Prior diagnosis of type 2 diabetes (includes discovering diabetes on entry after being invited)

Group assignment and trial-arm in this study design is allocated based upon invitation status (e.g., invited versus not invited rather than uptake of the intervention versus no uptake) akin to an intention-to-treat assignment analysis. The primary outcome used is the incidence of type 2 diabetes after

invitation to the NHS Diabetes Prevention Programme. See Table 5-1 for the target trial emulation framework used to conceptualise this study.

Table 5-1: Details of the trial emulation framework, used to conceptualise the observational study as a controlled trial.

	Ideal Randomised Controlled Trial	Target Trial emulation
Eligibility Criteria	No diagnosis of any diabetes on entry At least 18 years old on entry Fasting plasma glucose between 5.5-6.9 mmol/L or 42 to 47 mmol/L	No recorded phenotype of diabetes on entry, emulated using a 90-day prevalence period. At least 18 years old on entry Fasting plasma glucose between 5.5-6.9 mmol/L or 42 to 47 mmol/L on (estimated) entry
Study Period	1 June 2016 (introduction of the NHS Diabetes Prevention Programme) until 1 January 2019	1 June 2016 (introduction of the NHS Diabetes Prevention Programme) until 1 January 2019
Follow-up duration	Entry until: -Diagnosis of type 2 diabetes -Dropout -End of study	From estimated entry until first chronological recording of: -First phenotypic recording of type 2 diabetes -Dropout e.g., death record, end of CPRD follow-up -End of study
Outcome	Diagnosis of Type 2 diabetes	First recording of type 2 diabetes:
Treatments to be compared	NHS Diabetes Prevention Programme group assignment Usual care group assignment	Invitation to the NHS Diabetes Prevention Programme Usual Care assume via no

	Ideal Randomised Controlled Trial	Target Trial emulation
		invitation to the NHS Diabetes Prevention Programme
Estimand	Intention to treat based upon group assignment	Intention to treat based upon invitation (not uptake) to the NHS Diabetes Prevention Programme
Analysis Plan	Survival Analysis (Kaplan Meier)	Multiple Imputation to reduce missingness, preserve sample sizes, particularly for populations who are disproportionately impacted by data quality. Propensity Score Matching to reduce baseline differences between intervention and control groups. Survival Analysis (Multivariable Cox Proportional Hazards models to control for further differences not reduced by propensity score matching)

Data resource and Setting

To analyse the NHS Diabetes Prevention Programme, the CPRD dataset was used as it is widely applied in epidemiological studies and provides approximately 4.4 million active patients from 674 general practices in England and Wales (Herrett et al., 2015). The primary clinical coding system used in the CPRD is the READ code terminology (see Chapter 4 for further details). I used CPRD extracts that were anonymised and obtained through the UCL institutional licence. To identify additional cases of type 2 diabetes not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death

records were performed. The linkage period for my study for HES data started from April 1997 until November 2018, while the linkage period for ONS death records began in January 1998 until January 2019. Personal index of multiple deprivation data (version 2015) was also linked to primary care records to evaluate the socio-economic inequalities concerning the NHS Diabetes Prevention Programme. HES, ONS and IMD extracts were conducted by NHS Digital, who provided various “ranks” of matching success (See 5 Table 5-2 for a full breakdown of matching criteria). To enable consistent matching, the top 2 ranks were used as birthdates (to calculate age) and sex are fixed characteristics which were adjusted for as they are social determinants of health and health seeking behaviour; therefore, I did not use ranks 3 to 5 in this analysis as these mismatches may lead to biases; for example, if the matched individual in HES was older, then it is expected the risk of type 2 diabetes is higher. Overall, using ranks 1 and 2, 90% of primary care records were matched to a secondary care record.

Table 5-2: Definition of CPRD match ranks between primary care and secondary care records

Rank	Explanation
1	Exact match on NHS number, date of birth, sex and postcode
2	Exact match on NHS number, date of birth and sex only
3	Exact match on NHS number, partial match on date of birth, exact match on sex and postcode
4	Exact match on NHS number, partial match on date of birth, and exact match on sex only
5	Exact match on NHS number and postcode only

Participants (Study Population)

My study period was from 1 June 2016 (introduction of the NHS Diabetes Prevention Programme) until 1 January 2019 (latest available CPRD build at the time of being granted access). I used the same eligibility criteria as those

of the NHS Diabetes Prevention programme. I included people who were at least 18 years old on entry with a HbA_{1c} reading between 42-47 mol/mmol or an FPG reading between 5.5-7.0 mmol/L. I excluded those with a previous diagnosis of type 1 or type 2 diabetes (see primary outcomes section for how this was defined).

Patients from general practices whose records were not up to standard (UTS) for one year before the introduction of the NHS Diabetes Prevention Programme were excluded. The CPRD specification defines the UTS date as the “date at which the practice data is deemed to be of research quality” (Herrett *et al.*, 2015) and is based upon an assessment including valid dates (e.g. empty registration rate), in-valid values (e.g. genders other than male/female/indeterminate or age greater than 115 years old), consultations and deaths within the practice. Full details of UTS is described in full detail in Herrett *et al.*, 2015. As values for age and sex are important social determinants of health, and consultations and death recordings are important to understand the start and end of follow-up using non-UTS data may lead to misclassification. Consequently, I only used UTS data.

Primary Outcome Variable

My primary outcome of interest was incident cases of type 2 diabetes, which were defined using the first recording of:

1. A primary care (CPRD) diagnosis for type 2 diabetes using READ codes and medical codes.
2. A secondary care (HES) diagnosis for type 2 diabetes using ICD10 codes.
3. A death record (ONS) for type 2 diabetes, identified using ICD10 codes.
4. A HbA_{1c} reading of 48 mmol/L or higher from primary care records (CPRD)
5. An FPG reading of 7 mmol/L or higher from primary care records (CPRD)

READ codes for type 2 diabetes were established in a previous systematic review in Chapter 4. ICD-10 codes were chosen using codes available in the NHS data dictionary. I also used covariates such as measures of blood glucose (HbA_{1c} and FPG) to complement missing clinical codes; this mirrors their use as outcome measures in randomised controlled trials evaluating similar programmes worldwide (Diabetes Prevention Programme Group, 2015, 2002; Ilanne-Parikka et al., 2013),

Intervention

I excluded patients who had a previous diagnosis of diabetes before the introduction of the NHS Diabetes Prevention programme. However, this does mean that certain patients may discover that they have a previously undiagnosed case of type 2 diabetes because of participating in the NHS Diabetes Prevention Programme. Prevalent and previously undiagnosed cases of type 2 diabetes are excluded in controlled studies (often during a screening process), which I emulated by excluding patients who had a diagnosis within 90 days of entry (See Discussion for strengths and limitations of this method). While in a prospective study, entry is primarily defined using the screening process, there were no consistently used READ code for this within CPRD. Therefore, I defined the entry date (and participation in the NHS Diabetes Prevention Programme) as the first chronological READ code recording of 679m4 (NHS DPP referral), 679m0 (NHS DPP not completed), 679m1 (NHS DPP completed) and 679m2 (NHS DPP started). Patients who declined participation in the DPP (READ Code: 679m3) were included in the intervention group, akin to an intention-to-treat assignment analysis in a randomised controlled trial.

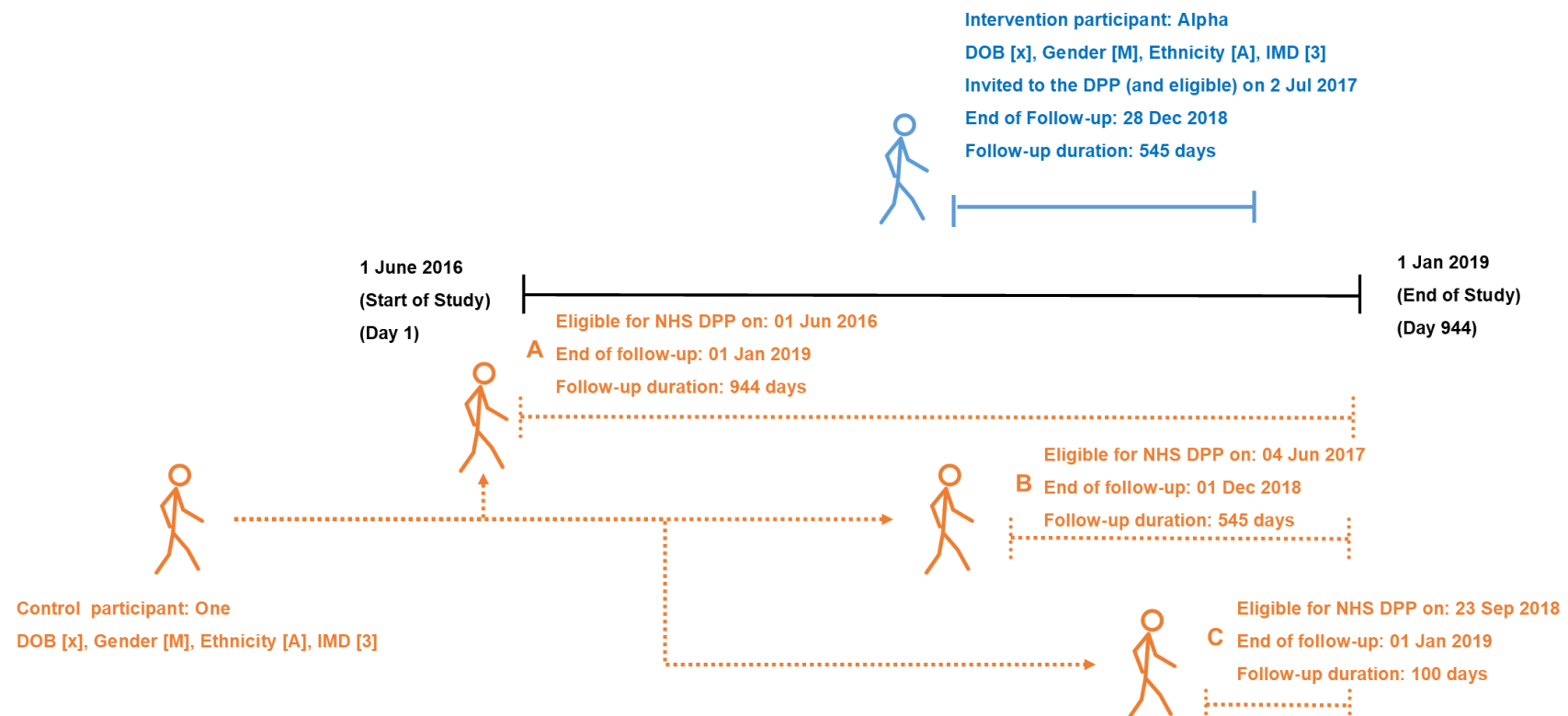
Control Populations

In this study, I modelled control participants as those who did not have any NHS Diabetes Prevention Programme activity recorded during the study

period; those who rejected an NHS Diabetes Prevention Programme are considered intervention participants akin to an intention-to-treat assignment analysis in a randomised controlled trial. Therefore, these individuals could have been invited to the NHS Diabetes Prevention Programme after the end of this study (1 January 2019) but were considered control participants as data beyond this was not available. As READ code usage for the NHS Diabetes Prevention Programme was previously estimated to be low (Barron et al., 2018), I used control patients solely from general practices not offering the NHS Diabetes Prevention Programme; I derived this by generating a set of practices where no NHS Diabetes Prevention Programme READ activity code was recorded in the study period. By using patients from practices that did not participate in the NHS Diabetes Prevention Programme as control patients, I aimed to reduce misclassification (by mistakenly including them in the intervention group) as patients from non-referring practices are unlikely to have participated in the NHS Diabetes Prevention Programme. Similar to the intervention group, I excluded patients with a previous diagnosis of diabetes before the NHS Diabetes Prevention Programme introduction and removed recorded cases of type 2 diabetes within 90 days of entry (because these were assumed to be prevalent previously undiagnosed cases). To estimate the entry date for control patients, I used multivariable linear regression analysis and estimated how long they would have been followed using the following covariates from their intervention counterparts: birthdate, gender, ethnicity, and index of multiple deprivation group. I choose these covariates as they are social determinants of health and were time-fixed; whilst index of multiple deprivation is time-varying, there were no changes recorded in this population. To generate the entry date for the control group, the I deducted the estimated duration from the exit date (see analysis section). I have chosen this method as it allows non-invited individuals who are similar to invited individuals to have similar follow up periods (See Figure 5-1). This is an alternative to choosing a random start of entry (and checking eligibility on that

date) where the average follow-up period would be the median/mean possible follow-up time. This is important because in a time-to-event analysis, those who have longer follow-up periods are disproportionately likely to have the event occur due to the cumulative definition of the hazard function and not controlling for follow-up period can impact the hazard ratio (Hernán et al., 2008).

Figure 5-1: Control Participant One (bottom) has multiple eligibility dates; choosing the right one is important as this could distort the time-to-event. If I choose the earliest possible date (labelled A in diagram), I would have extended this time. If I choose the shortest possible date (labelled C), I truncated this. Therefore, I used regression modelling to estimate which follow up duration to use in analysis so that it is more comparable to our Intervention Participant Alpha. Image not to scale.



To reduce differences in baseline characteristics between the control group and the intervention group, propensity score matching was used (see bias section for more details on the implementation of propensity score matching)

Sample Size

To understand sample sizes needed, I've compared the sample in this chapter to prior peer reviewed studies analysing similar interventions elsewhere in the world: Diabetes Prevention Programme Group study, 2002/2015 (USA) and Ilanne-Parikka *et al.*, 2013 (Finland). The Diabetes Prevention Programme Group study, 2002/2015 (USA) was a three-armed study consisting of: 1082 placebo participants, 1073 metformin participants and 1079 Diabetes Prevention Programme participants. Ilanne-Parikka *et al.*, 2013 contained a total of 522 participants with 257 control participants and 265 participants.

In this analysis, I've used all the population invited to the NHS Diabetes Prevention Programme to preserve numbers; this resulted in 2205 invited individuals and 8820 propensity matched non-invited individuals (see results).

Analysis

I conducted all analyses using R studio software and reported according to the REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement. To account for left censorship caused by the phased introduction of the NHS Diabetes Prevention Programme, right censorship due to leaving the CPRD (through general practice transfer or death), and the interest in the first diagnosis of type 2 diabetes, I conducted a time-to-event analysis using a multivariable Cox proportional hazards model. To understand the effect of the NHS Diabetes Prevention Programme, I only considered initiators of the programme (incident users). Therefore, patients in the intervention group of the NHS Diabetes Prevention Programme were assigned an entry date equivalent to their first chronological READ code entry from 679m4 (NHS DPP referral), 679m0 (NHS DPP not completed), 679m1

(NHS DPP completed), 679m2 (NHS DPP started) and 679m3 (NHS DPP declined). Therefore, in this analysis, the start of follow up is the earliest NHS DPP activity, and not at the start of the completion of the NHS DPP; this was decided because some individuals who started the NHS DPP could have developed type 2 diabetes during the programme. Furthermore, by starting the follow-up at the earliest NHS DPP activity, any preventative effect would be conservatively estimated as individuals may not complete the NHS DPP. Therefore, the maximum follow-up period is 2.5 years (1st June 2016 to 1st of January 2019). Control patients were assigned an entry date using multivariable regression (See Control Population section). All patients were followed until the first chronological phenotypic recording of a diagnosis of type 2 diabetes (by READ code or ICD10), a HbA_{1c} reading of 48 mmol/mol or higher, a fasting plasma glucose reading of 7 mmol/L or higher, dropout (for examples who those leave the CPRD either by changing general practice or through death) or end of study (1 January 2019). Patients were determined to have incident type 2 diabetes if they either having an ICD10 or READ recording of with type 2 diabetes (after 90 days of entry to allow for the removal of previously undiagnosed prevalent cases), had recorded a HbA_{1c} reading of 48 mmol/mol or higher, a fasting plasma glucose recording of 7 mmol/L or higher, or if one of their 15 causes of death were recorded as diabetes (see primary outcomes section).

Covariates

To account for the NHS Diabetes Prevention Programme's impact on patients from different backgrounds, I included demographic, socio-economic and clinically relevant covariates which are collected as part of the NHS Diabetes Prevention Programme. I used the latest readings up to 5-years before each

patient's (estimated) entry date. See Table 5-3 for a list of covariates used in this analysis and See Table 1-1 and Figure 1-2 to see how these are related.

Table 5-3: Covariates used in modelling the effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes.

Demographic and socio-economic covariates	Clinically relevant covariates
Age on (estimated) entry	Baseline body mass index
Ethnicity	Baseline HbA _{1c}
Index of Multiple deprivations (1 – 5) (See Table 5-4 for an explanation)	Baseline FPG
Gender	Smoking Status (1-4) (See Table 5-4 for an explanation)
	Alcohol Status (1-6) (See Table 5-4 for an explanation)

Index of multiple deprivation (IMD) data was provided through linkage at the individual patient level. Ethnicity data was primarily derived from primary care records, with hospital records complementing missing ethnicity data from primary care. Ethnicity groups were grouped into the Office of National Statistics supersets (White, Black, Asian, Mixed, Other) (England and Wales Census, 2018) because certain ethnic groups, particularly "Mixed – Black and Asian" would have caused statistical disclosure issues (i.e., less than 5 individuals) leading to statistical disclosure and non-convergence in regression analysis. Alcohol and smoking status were categorised by the CALIBER team at UCL. The UCL CALIBER team's categories were used in this study due to their experience in data linkage, phenotyping and the popularity of the CALIBER resources in observational research, making

categories that I used comparable to many other studies (Denaxas et al., 2012). See Table 5-4 for the categories used for the index of multiple deprivation, alcohol, and smoking status.

Table 5-4: Encoding explanation for Index of Multiple Deprivation, Alcohol Consumption and Smoking status.

Value	IMD
1	Most deprived quintile
2	Second most deprived quintile
3	Middle
4	Second least deprived quintile
5	Least deprived Quintile

Value	Alcohol
1	Non-Drinker
2	Ex Drinker
3	Occasional Drinker (less than once per week)
4	Current Drinker
5	Excess Drinker
6	Binge Drinker

Value	Smoking
1	Non-smoker
2	Ex-smoker
3	Ex or current smoker
4	Current smoker

Mitigating limitations

To reduce biases due to the observational study design, I identified and addressed such biases through careful study design and by incorporating a variety of sensitivity analyses. I concentrated on tackling recruitment bias, missing data and misclassifications, based upon known weaknesses of observational studies (Hammer et al., 2009).

Bias

After comparing my cohort size to studies that used proprietary datasets designed to evaluate the NHS Diabetes Prevention Programme (Valabhji et al., 2020), I realised that the CPRD recorded only a small fraction of referrals to the NHS Diabetes Prevention Programme; this is because I only found 2205 invitations versus Valabhji et al., 2020 who documented 324,699 invitations and 152,294 attendees using a custom dataset that NHS Diabetes Prevention Programme providers are obliged to contribute to (Valabhji et al., 2020). Therefore, to maximise the number of participants, the study period was from the introduction of the NHS Diabetes Prevention Programme, the latest CPRD-Gold database build. To tackle the phased introduction of the NHS Diabetes Prevention Programme, I conducted a time to event analysis using a Cox Proportional Hazards model to tackle left censorship (i.e., practices did not introduce the NHS Diabetes Prevention Programme at the same time).

Missing data

After assigning covariate data (see covariate section) to the cohort, there was a substantial amount of missing data, especially for HbA_{1c} and FPG (See 5 Table 5-4). The missingness in HbA_{1c} and FPG is likely due to general practices using only one measure or the other but not both simultaneously. Missingness was also disproportionately impacting those from non-white ethnicities (See Table 5-5) and this is in line with the literature on the social determinants of data quality in health care (Cook et al., 2021). To tackle missing data, I used multiple imputation by chained equations (MICE) (Azur et

al., 2011). Not only has multiple imputation been shown to preserve sample sizes, but it has also been shown to create cohorts that are more representative of ethnic-minority groups when compared to a full case analysis in cardiovascular research (Collins and Altman, 2010). MICE use chained equations to temporarily generate a non-missing dataset (except one covariate) to predict missing values (in the covariate as mentioned earlier). Using the first iteration of imputation for one missing covariate, MICE then repeat until all the data is estimated for the remaining covariates. A full explanation of MICE can be found elsewhere (Azur *et al.*, 2011). The following covariates were used in the MICE model, all of which were established using the closest recording before each individual's (estimated) entry date within 5-years: age on entry, gender, ethnicity, index of multiple deprivation, body mass index, glycated haemoglobin, fasting glucose plasma, alcohol status, smoking status and disease status (i.e., a type 2 diabetes diagnosis). The outcome (type 2 diabetes) was used as previous studies have found this to be a good predictor of the (missing) covariates (Sterne *et al.*, 2009). For numerical covariates (age, body mass index, glycated haemoglobin, fasting glucose plasma, CALIBER based alcohol and CALIBER based smoking categories) the MICE model used linear regression modelling and logistic regression for binary covariates (for example gender and dummy variables for ethnicity). I generated ten alternative datasets using MICE, with each dataset being propensity score-matched, analysed using Cox proportional hazards regression before being pooled using a fixed-effect meta-analysis. An important limitation of MICE is that it assumes the missingness at random (MAR) (Sterne *et al.*, 2009). Due to this assumption, MICE generates missing data from non-missing data within the dataset. As this may not be the case, I also conducted a full case analysis to explore further the effects of missingness within the data.

Baseline differences

One crucial bias that is often attributed to observational studies is imbalanced baseline covariates, due to the lack of randomisation (Austin, 2011), often referred to as confounding-by-indication where treatment assignment is related to the risk of disease. I observed this when I compared unmatched baseline covariates (See Results section). To mitigate this issue, I conducted propensity score matching on the imputed dataset(s) to reduce differences in observed characteristics between intervention and control groups. After multiple imputation (see above), each imputed dataset was matched using the latest recording within 5-years of each patient's entry date of the following: age, gender, ethnicity, alcohol consumption, smoking, body mass index, index of multiple deprivation, HbA_{1c} and FPG.

As propensity score matching under-samples the control group to match the intervention group, this results in a smaller number of patients compared to an unmatched analysis. Therefore, to preserve statistical power, I used a 1:4 ratio for matching intervention patients to control patients as opposed to a 1:1 matching ratio which would have reduced statistical power.

Misclassification

After comparing my cohort size to studies using proprietary datasets (Valabhji et al., 2020), it became clear that the CPRD only captured a small fraction of the NHS Diabetes Prevention Programme related activity. Therefore, many participants of the NHS Diabetes Prevention Programme may not have been recorded as such, leading to misclassification. To reduce this problem, my primary control group only consisted of individuals from practices not providing the NHS Diabetes Prevention Programme. Similarly to the misclassification of the intervention group, I was concerned about the misclassification of type 2 diabetes. Therefore, to avoid misclassification of type 2 diabetes, I used previous work which used systematic reviews to

generate an evidence-based list of READ codes and phenotyping algorithms within primary care databases such as the CPRD, THIN and QResearch. Similarly to studies evaluating other non-communicable diseases (Herrett *et al.*, 2013), I also complemented missing type 2 diabetes diagnoses in the CPRD by using linkage to secondary care datasets and Office of National Statistics death records. In trials evaluating other programmes aimed at preventing diabetes (Diabetes Prevention Programme Group, 2002), type 2 diabetes was diagnosed using covariates such as HbA_{1c} readings; therefore, I also used HbA_{1c} as a proxy for diagnosing type 2 diabetes to keep the analyses consistent. As FPG could also be used to diagnose type 2 diabetes, I also used FPG values as an alternative healthcare outcome.

External validity

As studies have described the demographic, socio-economic and clinical characteristics of people participating in the NHS Diabetes Prevention Programme (Valabhji *et al.*, 2020), I used this opportunity to compare my cohort to these external data. I restricted the comparisons to the covariates that both studies used to include gender, age, ethnicity, index of multiple deprivation, body mass index and baseline HbA_{1c}. (Valabhji *et al.*, 2020) provided descriptive statistics for patients who were referred to the NHS Diabetes Prevention Programme as well as patients who were referred and attended an initial assessment. As the initial assessment recorded ethnicity and body mass index, I included both "referred" and "referred and attended an initial assessment" in my comparison of baseline descriptive statistics.

Since the Diabetes Prevention Programme Group in the USA (Diabetes Prevention Programme Group, 2015, 2002) and Ilanne-Parikka *et al in Finland* (Ilanne-Parikka *et al.*, 2013) have established the effect of similar programmes in other settings. I compared the studies using the Centre of Evidence-Based Medicine's (CEBM, 2018) evidence appraisal toolkit to compare the studies. I included both the 2002 and the 2015 study from the

Diabetes Prevention Group as the follow-up time in the earlier 2002 study was similar to my analysis (3 years versus 2.5 years) and the follow-up time for the later 2015 study is similar to that of Ilanne-Parikka *et al.*, 2013 (15 years versus 13 years). I chose these studies not only because they were compared to the NHS' Diabetes Prevention Programme by Public Health England (Barron *et al.*, 2018), but because they were conducted using gold-standard randomised controlled trials.

Ethics and approvals

Approval for this study was granted as part of an application to the CPRD's Independent Scientific Advisory Committee: protocol 18_179. Data extractions were completed by the CALIBER team under NHS research ethics approval (09/H0810/16) and ECC approval (ECC 2-06(b)/2009 CALIBER dataset).

Information governance

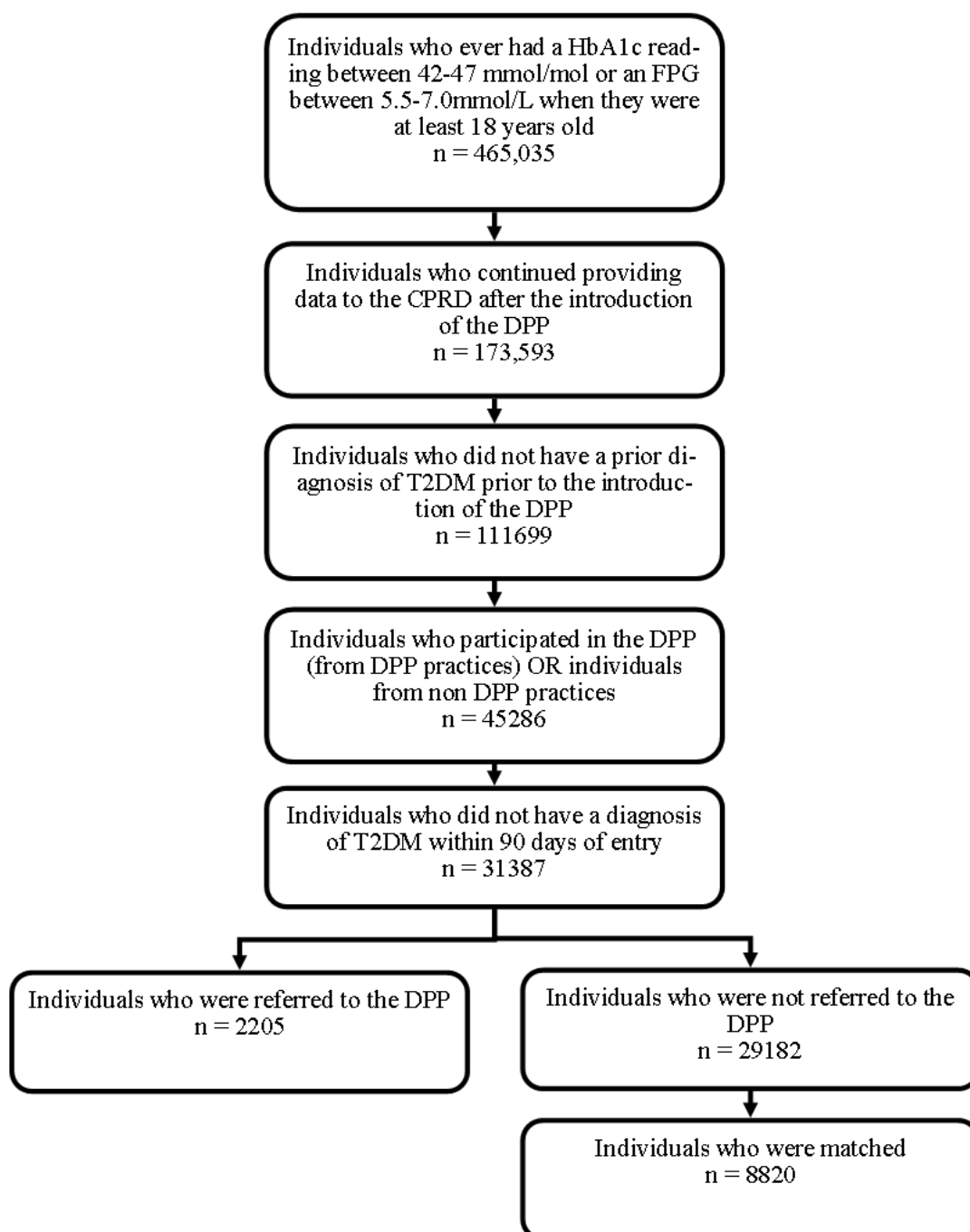
I completed all analyses were in the UCL data safe-haven. The pseudonymised dataset will be securely destroyed after four years in the first occurrence in line with the latest Independent Scientific Advisory Committee's guidance. In line with CPRD policy, I did not report any data with a cell containing <5 events and where necessary I have protected these counts with secondary suppression.

Results

Numbers Analysed

I found 465,035 individuals in the CPRD had a HbA_{1c} reading between 42-47 mmol/L or an FPG reading between 5.5-7.0 mmol/L when they were at least 18 years old in CPRD from 1987 until January 2019 (Figure 5-2). After the introduction of the NHS Diabetes Prevention Programme, only 173,593 eligible individuals continually provide data (i.e., they did not leave the CPRD dataset through general practice transfer or death). After removing individuals who had a previous diagnosis of type 2 diabetes before the introduction of the NHS Diabetes Prevention Programme, there were 111,699 individuals left. After removing the non-NHS Diabetes Prevention Programme participants from general practices which provide the NHS Diabetes Prevention Programme, there were 45,286 individuals left. Once I removed individuals who had a recording of type 2 diabetes within 90 days of their estimated entry date (i.e., likely prevalent cases), 31,387 individuals were left. Of the 31,387 individuals in the cohort, 2,205 were referred to the NHS Diabetes Prevention Programme; whilst 29,182 were not. After propensity score matching, I matched 8,820 individuals from the 29,182 control individuals as part of the matching process. See Figure 5-2 for a diagram for a graphical representation of the cohort generating process.

Figure 5-2: Consort diagram depicting how patients were filtered to generate the cohort.



Population and Characteristics

Of the 2,205 NHS Diabetes Prevention Programme referred individuals, 172 were included in my full case analysis, and 1,486 of the 29,182 control individuals were included. Missingness was similar between both groups, except for HbA_{1c} and FPG, where intervention patients had a lot less missingness; this is because those in the intervention group were more likely to have these covariates measured through their participation to establish eligibility. See Table 5-5 for a breakdown of missingness by covariate.

Table 5-5: Percentage of missingness for each covariate; lower is better.

Note: gender and date of birth are fully complete in the CPRD dataset

Covariate	Control (n = 29182)	Intervention (n = 2205)	Total (n = 31,387)
Within 5 years of entry			
Ethnicity	10,689 (37%)	860 (39%)	11,613 (37%)
Linked IMD	16,891 (58%)	1257 (57%)	18,204 (58%)
BMI	5836 (20%)	7779 (16%)	6,277 (20%)
Smoking	2,918 (10%)	176 (8%)	3,139 (10%)
Alcohol	19,844 (68%)	1,521 (69%)	21,343 (68%)
HbA_{1c}	10,214 (35%)	419 (19%)	10,358 (33%)
FPG	18,093 (62%)	1,147(52%)	19,146 (61%)

Under a full-case cohort

With a full-case cohort, there were more men than women, for both the control group and the intervention group. Under the full-case cohort, certain demographic groups were unaccountable or had a few people, for example, there were no excess or binge drinkers, and there were few individuals who were of mixed ethnicity. Before matching under the full-case cohort, there were imbalances between the intervention and control group for mean HbA_{1c},

deprivation proportions, and alcohol intake proportions. After propensity score matching on the full case dataset, there were no significant differences in means or proportions between the intervention group and the matched control group. See Table 5-6 for a full breakdown of the cohort.

Imputed Cohort

After applying multiple imputation by chained equations, proportions for those analysed changed for gender, ethnicity, deprivation (least deprived), alcohol status and smoking status for the intervention group (Table 5). After applying MICE, there were more females eligible than males, with lower age, BMI, but higher FPG compared to a full case cohort. After applying MICE but before propensity score matching, there were measured baseline imbalances between the intervention and control groups in all covariates except for, BMI and, FPG, ethnicity (black and mixed-race). After applying propensity score matching on the imputed dataset, there were imbalances between the intervention and control groups only for the following covariates: Ethnicity – White and Asian, all IMD groups and alcohol status (except binge drinkers), and smoking status (except non-smoker and ex-smoker).

See Table 5-6 for a full breakdown of the baseline demographics of the cohort and the impact of using multiple imputation by chained equations as well as propensity score matching

Table 5-6: Cohort distribution of covariates, by imputation method, matching method and intervention group

	Full Case			MICE		
Covariate	Intervention (n = 172)	Unmatched Control (n = 1314)	Matched Control (n = 688)	Intervention (n = 2205)	Unmatched Control (n = 29182)	Matched Control (n = 8820)
Gender						
Male	93 (54.07%)	671 (51.07%)	372 (54.07%)	1065 (48.32%)	15073 (51.65%)	4264 (48.35%)
Female	79 (45.92%)	643 (48.93%)	316 (45.93%)	1140 (51.68%)	14109 (48.35%)	4556 (51.65%)
Mean Age [95% CI]	69.96 [68.27, 71.66]	68.26 [65.75,70.78]	69.96 [68.27,71.66]	65.19 [65.01,65.38]	64.02 [63.96, 64.08]	65.34 [65.25, 65.44]
Mean BMI [95% CI]	30.21 [29.24,31.18]	29.94 [29.58,30.30]	30.24 [29.75,30.74]	29.59 [29.51, 29.67]	29.53 [29.50,29.55]	29.63 [29.58, 29.66]
Mean HbA1c [95% CI]	43[43,43]	40 [40, 40]	43[43,43]	43 [43,43]	41 [41, 41]	43 [43, 43]
Mean FPG [95% CI]	5.5[5.4,5.6]	5.7[5.6,5.7]	5.5 [5.5, 5.6]	5.6 [5.6, 5.6]	5.6 [5.6, 5.6]	5.6 [5.6, 5.6]

	Full Case			MICE		
Covariate	Intervention (n = 172)	Unmatched Control (n = 1314)	Matched Control (n = 688)	Intervention (n = 2205)	Unmatched Control (n = 29182)	Matched Control (n = 8820)
Ethnicity						
White	145 (84.30%)	1157 (88.05%)	598 (86.92%)	1591 (72.17%)	23894 (81.88%)	6571 74.50%
Black	7 (4.07%)	71 (5.40%)	36 (5.23%)	131 (5.96%)	1833 (6.28%)	561 (6.36%)
Asian	16 (9.30%)	68 (5.18%)	44 (6.40%)	393 (18.05%)	2629 (9.01%)	1363 (15.45%)
Mixed	NA	9 (0.68%)	NA	24 (1.11%)	344 (1.18%)	101 (1.15%)
Other	NA	9 (0.68%)	6 (0.87%)	60 (2.73%)	482 (1.65%)	224 (2.54%)
Index of Multiple Deprivation						
(Most Deprived) 1	57 (33.14%)	262 (19.94%)	183 (26.60%)	698 (31.64%)	5831 (19.98%)	2430 (27.55%)
2	37 (21.51%)	214 (16.29%)	128 (18.60%)	495 (22.44%)	5886 (20.17%)	2104 (23.86%)
3	32 (18.60%)	315 (23.97%)	166 (24.13%)	436 (19.76%)	6674 (22.87%)	1976 (22.40%)
4	37 (21.51%)	305 (23.21%)	125 (18.17%)	331 (15.03%)	6166 (21.13%)	1456 (16.51%)
(Least Deprived) 5	9 (5.23%)	218 (16.59%)	86 (12.50%)	245 (11.13%)	4625 (15.85%)	854 (9.68%)

	Full Case			MICE		
Covariate	Intervention (n = 172)	Unmatched Control (n = 1314)	Matched Control (n = 688)	Intervention (n = 2205)	Unmatched Control (n = 29182)	Matched Control (n = 8820)
Drinking Status						
Non-Drinker	138 (80.23%)	906 (68.94%)	552 (80.23%)	1323 (60.01%)	12507 (42.86%)	4974 (56.39%)
Ex Drinker	NA	78 (5.94%)	16 (2.33%)	117 (5.29%)	2539 (8.70%)	736 (8.35%)
Occasional Drinker	28 (16.28%)	309 (23.52%)	112 (16.28%)	665 (30.16%)	11962 (40.99%)	2784 (31.56%)
Current Drinker	NA	21 (1.60%)	8 (1.16%)	73 (3.30%)	1331 (4.56%)	224 (2.54%)
Excess Drinker	NA	NA	NA	26 (1.19%)	797 (2.73%)	98 (1.11%)
Binge Drinker	NA	NA	NA	NA	47 (0.16%)	NA
Smoking Status						
Non-Smoker	84 (48.84%)	661 (50.29%)	336 (48.84%)	1152 (52.24%)	14512 (49.73%)	4320 (48.98%)
Ex-Smoker	55 (31.98%)	467 (35.54%)	220 (31.98%)	577 (26.17%)	9324 (31.95%)	2767 (31.37%)
Ex or current smoker	NA	NA	NA	8 (0.35%)	76 (0.26%)	25 (0.28%)
Current Smoker	33 (19.19%)	186 (14.17%)	132 (19.19%)	468 (21.24%)	5270 (18.06%)	1708 (19.37%)

Outcomes and Estimations

Unadjusted incidence of type 2 diabetes

Of 11,025 individuals (2205 intervention + 8,820 matched control) who were identified after imputation and matching, 5.96% (n = 657; 95%CI: 5.5% - 6.4%) have newly recorded diabetes within the 2.5 years (between June 2016 and January 2019) study period. Of the 2205 intervention patients, 4.13% (n = 91) have a new recording of diabetes within two and a half years of initiating the NHS Diabetes Prevention Programme. Of the 8,820 control (matched) patients, 6.42% (n = 566) have a new recording of diabetes within two and a half years of initiating the NHS Diabetes Prevention Programme. This created a hazard ratio of 0.64 (95%CI: 0.51 to 0.79). See Table 5-7 for a breakdown of incident of type 2 diabetes after follow-up.

Table 5-7: Unadjusted type 2 diabetes incidence rates for control and intervention groups between June 2016 and January 2019.

		Control [Imputed and Matched] N = 8820	Intervention [Imputed] N = 2205	Total N = 11,025
Outcome	Type 2 Diabetes during follow up	566 6.42% 95%CI: 5.9% - 7.0%	91 4.13% 95%CI: 3.3% - 5.0%	657 5.96% 95%CI: 5.5% - 6.4%
	No Type 2 diabetes during follow up	8254 93.6% 95%CI: 93.1% - 94.1%	2114 95.9% 95%CI: 94.9% - 96.6%	10368 94.04% 95%CI: 93.6% - 94.5%

Adjusted Results

After adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, Index of multiple deprivation quintile, baseline alcohol intake, baseline smoking consumption, baseline BMI, and age on entry, the hazard ratio for a referral to the NHS Diabetes Prevention Programme demonstrated that

referred patients were 59% (Hazard Ratio - HR: 0.41 [95% CI: 0.38 – 0.44]) less likely to have a new recording of type 2 diabetes compared to the imputed and matched control group. See Table 5-8 for a full breakdown of the hazard ratios for each covariate.

Table 5-8: Covariates and their adjusted hazard ratio. HR < 1 = protective to type 2 diabetes. HR > 1 = more likely to develop type 2 diabetes.

Covariate	Control (n = 2210)	Intervention (n = 8820)	Adjusted Hazard Ratio [95% CI:]
NHS DPP status			
Not referred (reference)	-	8820 (100%)	1.00 [Ref]
Referred	2210 (100%)	-	0.41 [0.38, 0.44]
Age on entry	65.34 [65.25, 65.44]	65.19 [65.01, 65.38]	1.00 [1.00 – 1.00]
Gender			
Male (reference)	4264 (48.35%)	1065 (48.32%)	1.00 [Ref]
Female	4556 (51.65%)	1140 (51.68%)	0.82 [0.78 – 0.87]
Ethnicity			
Asian (reference)	1363 (15.45%)	393 (18.05%)	1.00 [Ref]
Black	561 (6.36%)	131 (5.96%)	0.68 [0.62 – 0.76]
Mixed	101 (1.15%)	24 (1.11%)	0.57 [0.44 – 0.72]
Other	224 (2.54%)	60 (2.73%)	0.50 [0.44 – 0.72]
White	6571 (74.50%)	1591 (72.17%)	0.56 [0.52 – 0.60]
Index of Multiple Deprivation (Continuous)			1.04 [1.02 – 1.06]
(Most Deprived) 1	698 (31.64%)	2430 (27.55%)	-
2	495 (22.44%)	2104 (23.86%)	-
3	436 (19.76%)	1976 (22.40%)	-
4	331 (15.03%)	1456 (16.51%)	-

Covariate	Control (n = 2210)	Intervention (n = 8820)	Adjusted Hazard Ratio [95% CI:]
(Least Deprived) 5	245 (11.13%)	854 (9.68%)	-
Blood glucose measures			
Fasting Plasma Glucose	5.6 [5.6, 5.6]	5.6 [5.6, 5.6]	1.38 [1.32 – 1.45]
HbA_{1c}	43 [43,43]	43 [43, 43]	1.33 [1.31 – 1.35]
Baseline Body Mass Index	29.63 [29.58, 29.66]	29.59 [29.51, 29.67]	1.02 [1.02 – 1.02]
Baseline smoking status (Continuous)			1.02 [1.00 – 1.04]
Non-Smoker	4320 (48.98%)	1152 (52.24%)	-
Ex-Smoker	2767 (31.37%)	577 (26.17%)	-
Ex or current smoker	25 (0.28%)	8 (0.35%)	-
Current Smoker	1708 (19.37%)	468 (21.24%)	-
Baseline alcohol status (Continuous)			0.99 [0.97 – 1.02]
Non-Drinker	4974 (56.39%)	1323 (60.01%)	-
Ex Drinker	736 (8.35%)	117 (5.29%)	-
Occasional Drinker	2784 (31.56%)	665 (30.16%)	-
Current Drinker	224 (2.54%)	73 (3.30%)	-
Excess Drinker	98 (1.11%)	26 (1.19%)	-
Binge Drinker	NA	NA	-

External Validity

Cohort Comparison

When comparing my sample cohort with the population cohort as described by (Valabhji et al., 2020), both studies had a higher percentage of women compared to men. The age breakdown for both studies was similar, except for the ≥ 75 age group as this study had a higher proportion of elderly patients (Valabhji et al., 2020: 19% ≥ 75 years old vs this study 25% ≥ 75 years old). The age differences reflected in the slightly higher mean age in my study at 65.2 years versus 62 years (referred) and 64 years (referred and attended initial assessment). The ethnicity breakdown for White, Other, Black, and Mixed patients was similar (within 2% difference). While Valabhji et al., 2020 had an equal distribution across all IMD groups, my sample did not and had more participants in the IMD 1 (most deprived) group compared to the IMD 5 (least deprived) group. BMI proportions were similar for both studies for overweight and obese participants of the NHS Diabetes Prevention Programme. The underweight/normal BMI proportions for this study were slightly higher as Valabhji et al., 2020; this could be because they included an unknown category. Valabhji et al 2020 reported that the baseline HbA_{1c} of those who completed the NHS Diabetes Prevention Programme was 41.8 mmol/mol; my mean HbA_{1c} was 43.2 mmol/mol for those who were referred to the NHS Diabetes Prevention Programme. See Table 5-9 for a comparison of descriptive baseline statistics between the two studies.

Table 5-9: Comparison between Valabhji et al., 2020 and this study in terms of initiators of the NHS Diabetes Prevention Programme. Highlighted values are those which appear to be different from Valabhji et al., 2020.; *HbA_{1c} value is for those who completed the NHS Diabetes Prevention Programme n = 16083

	Population Valabhji et al., 2020				Imputed cohort	
	Referred to NHS DPP N = 324,699		Referred and attended an initial assessment. N = 152,294		Referred to NHS DPP N = 2205	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Sex						
Male	147,890	46	68,780	45	1,066	48
Female	172,252	53	82,637	54	1,139	52
Age band (years)						
<40	17,797	5	5,818	4	88	4
40–44	15,811	5	5,593	4	110	5
45–49	22,604	7	8,449	6	132	6
50–54	32,021	10	12,735	8	176	8
55–59	37,938	12	16,647	11	243	11
60–64	40,880	13	19,656	13	265	12
65–69	46,787	14	25,481	17	287	13
70–74	48,106	15	26,616	17	353	16
≥75	62,641	19	31,281	21	551	25
Unknown	114	0	18	0		—
Mean age	62	—	64	—	65	—
SD	13.4	—	12.4	—	13.7	—

	Population Valabhji et al., 2020				Imputed cohort	
	Referred to NHS DPP N = 324,699		Referred and attended an initial assessment. N = 152,294		Referred to NHS DPP N = 2205	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Ethnicity						
Asian	—	—	17,364	11	397	18
Black	—	—	9,567	6	132	6
Mixed	—	—	2,539	2	22	1
Other	—	—	1,432	1	66	3
White	—	—	105,315	69	1588	72
Unknown	—	—	16,077	11	—	—
Index of Multiple Deprivation quintile						
(Most deprived) 1	68,616	21	29,388	19	706	32
2	65,469	20	29,604	19	485	22
3	62,733	19	30,141	20	441	20
4	61,798	19	30,446	20	331	15
(Least deprived) 5	65,108	20	32,247	21	243	11
BMI grouping at I.A.						
Underweight/ healthy	—	—	22,953	15	507	23
Overweight	—	—	50,850	33	772	35
Obese	—	—	67,390	44	926	42
Unknown	—	—	11,101	7	—	—
Mean (kg/m ²)	—	—	30.3	—	29.59	—

	Population Valabhji et al., 2020				Imputed cohort	
	Referred to NHS DPP N = 324,699		Referred and attended an initial assessment. N = 152,294		Referred to NHS DPP N = 2205	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
S.D. (kg/m ²)	—	—	6.1	—	6.4	—
Mean HbA _{1c}	—	—	41.8*	—	43.2	—

Results comparison

When comparing my evaluation of NHS Diabetes Prevention Programme to studies of comparable interventions analysed by Ilanne-Parikka *et al.*, 2013 and the Diabetes Prevention Programme Group, 2002/2015, the NHS Diabetes Prevention Programme is the least restrictive in terms of the inclusion criteria, especially when considering age and BMI requirement as there are no BMI requirements in the NHS Diabetes Prevention Programme. All interventions concentrated on improved nutrition and increased physical activity; however, the Diabetes Prevention Programme Group, 2002/2015 and Ilanne-Parikka *et al.*, 2013 also had an aim of losing a specific percentage of each participant's initial weight. While the NHS's Diabetes Prevention Programme also had weight control as an outcome, participants were not given a specific amount of weight to aim to lose. (Ilanne-Parikka *et al.*, 2013) was even more specific in terms of their nutritional education by including lessons on tracking macronutrients. All studies had a comparison group; however, the Diabetes Prevention Programme Group, 2002/2015 used a three-arm trial, with the third group receiving metformin. For my external validity comparison, I only analysed the diabetes prevention programmes versus usual care. While this study used a retrospective observational cohort design, the other studies used the randomised controlled trial design. Due to

interactive sessions, blinding was not possible for any implementation of a diabetes prevention programme.

The Diabetes Prevention Programme Group, 2002/2015 study did not report any baseline differences, while Ilanne-Parikka et al, 2013 did not provide baseline covariates. After propensity score matching, this study demonstrated baseline differences in the proportions of ethnicity, index of multiple deprivation and alcohol status. All studies demonstrated that the intervention group had a type 2 diabetes incidence rate between 4% to 5%. Control group incidence rates differed between studies. This study and the Diabetes Prevention Programme group's 2002 study in America produced similar hazard ratios, demonstrating approximately a 60% reduction in type 2 diabetes incidence rates. Ilanne-Parikka et al, 2013, in Finland, produced a 39% reduction in incidence rates. The Diabetes Prevention Group's 2015 study (in the United States of America) produced similar hazard ratios with Ilanne-Parikka et al., 2013 (from Finland) when increasing the study time to 15 years. All studies demonstrate that their respective "diabetes prevention programme" reduces the incidence of type 2 diabetes. See Table 5-10 for a comparison of all three studies using evaluation tools developed by the centre of evidence-based medicine.

Table 5-10: Comparison between studies evaluating various forms of the diabetes prevention programme.

	This Study	Diabetes Prevention Programme Group study, 2002/2015 (USA)	Ilanne-Parikka <i>et al.</i>, 2013 (Finland)
Population	-Age: At least 18 on entry -BMI: Any -FPG: 5.5 – 6.9mmol/L or HbA_{1c}:42 to 47 mmol/L -No prior diagnosis of type 2 diabetes	-Age: At least 25 years old -BMI: At least 24 kg/m² or higher (22 kg/m² or higher in Asians) -Fasting Plasma: 5.3 to 6.9mmol/L -No prior diagnosis of type 2 diabetes	-Age: 40 – 65 years old -BMI: Over 25 kg/m² -Plasma glucose between 7.8-11.0mmol/l, two hours after oral administration of 75g of glucose -No prior diagnosis of type 2 diabetes
Intervention	-Personal lifestyle advice -16 hours of face-to-face interactions over 13 sessions within 36 weeks -Mixture of one-to-one and group sessions -Lesson Themes: -Nutrition and health -Add physical activity to a lifestyle -Staying motivated -Solve problems that can get in the way of healthy change -Gain life-changing skills and knowledge	-Intensive lifestyle intervention -Aim of losing 7% of initial body weight -16-lesson curriculum covering diet, exercise and behaviour within 24-weeks -Individual meetings -Lesson Themes: -Be a fat detective -Three ways to eat less fat -Healthy eating -Move those muscles -Be active -Tip the calorie balance -Take charge of what's around you -Problem solving	-Detailed advice about weight loss, dietary advice and exercise advice -Aims of losing 5% of initial body weight -Personalised dietary advice with aims of: -Total fat to make up less than 30% of daily intake -Saturated fat to make up less than 10% of daily intake -Increase fibre to at least 15 g/1000kcal -Frequent ingestion of whole-grain products, vegetables, fruits, low-fat milk meat products, soft margarine and vegetable oils rich in monounsaturated fatty acids

	This Study	Diabetes Prevention Programme Group study, 2002/2015 (USA)	Ilanne-Parikka <i>et al.</i>, 2013 (Finland)
	for long term success	-Four keys to healthy eating out -Talkback to negative thoughts -Slippery slope of lifestyle change -Jumpstart activity plan -Make social cues work for you -Manage Stress -Ways to stay motivated	-Delivered through seven sessions with a nutritionist during the first year and one session every three months thereafter -Personal guidance on physical activity: -Aim to have at least 30 minutes of exercise daily -Supervised, progressive, individually tailored circuit-type training sessions were also offered
Comparison	-Intervention vs Usual care	-Intervention vs usual care	Intervention vs Usual care (health leaflets)
Outcome	-Incidence of type 2 diabetes through first recording of: -READ code -ICD code - HbA_{1c} -FPG reading	-Incidence of type 2 diabetes through HbA _{1c} of 7 mmol/l or higher through the 1997 American Diabetes Association Criteria	- Incidence of type 2 diabetes through the 1985 World Health Organisation criteria: a fasting plasma glucose concentration of 7.8mmol/l or higher
Time	-Three years – 2016 - 2019	2002 study Three years – 1996 to 1999 2015 study Fifteen years – 1996 - 2014	- Thirteen-years – 1993 to 2009
Study Type	Retrospective observational cohort	Randomised controlled trial	Randomised controlled trial

	This Study	Diabetes Prevention Programme Group study, 2002/2015 (USA)	Ilanne-Parikka <i>et al.</i>, 2013 (Finland)
1.a Randomised Treatment	No	Yes	Yes
1.b. Baseline similarities	Baseline differences were in: -Ethnicity -White and Asian -IMD - 1,3,4,5 -Alcohol status: all values	"Baseline characteristics including all measured risk factors for diabetes were similar among the study groups."	Unknown
Results	No of participants: Intervention: 2,205 Control: 8,820 Three-year incidence rate: Intervention: 4.11% Control: 6.61% Adjusted Hazard ratio: 0.41;95%CI=0.38-0.44]	No of participants: Intervention: 1,079 Placebo: 1,082 Three-year incidence Rate Intervention: 4.8% Control: 11% Three years Adjusted hazard ratio: 0.42 [95CI: 0.34 -0.51] Fifteen-year adjusted hazard ratio: 0.73[95% CI 0.65-0.83]	No of participants: Intervention: 265 Control: 257 Thirteen-year incidence rate: Intervention: 4.5% Control: 7.2% Thirteen year - Adjusted Hazard Ratio 0.614 [95% CI 0.48 - 0.79]

Sensitivity Analyses

When conducting a full case analysis, a total of 1,486 individuals provided data for the full case analysis in both the intervention and control groups. This produced a total of 74 events, less than the 423 required as part of the sample size calculations. Under a full case analysis without propensity score matching, the hazard ratio for NHS Diabetes Prevention Programme participation changed to 0.60 [95%CI: 0.32 – 1.12]. Under a full case analysis with propensity score matching, the hazard ratio for NHS Diabetes Prevention Programme participation changed to 0.59 [95% CI: 0.30 – 1.12]. When conducting an unmatched analysis using MICE, the hazard ratio for NHS Diabetes Prevention Programme referral did not change at 2 decimal places 0.41 [95%CI: 0.38 – 0.44]. See Table 6 to view the effect of imputation and matching on the hazard ratio associated with participating in the NHS Diabetes Prevention Programme. See Table 5-11 for the adjusted hazard ratio of the NHS Diabetes Prevention programme under the various sensitivity analyses.

Table 5-11: Results of alternative analyses based upon imputation method and matching method.

Imputation Method	Matching Method	Cohort size	No of events	Hazard Ratio for Treatment [95% CI:]	Analysis type
Full Case	No Matching	Intervention: 172 Control: 1314	74	0.60 [0.32 – 1.12]	Sensitivity
	Propensity Score Matching	Intervention: 172 Control: 688	55	0.59 [0.30 – 1.12]	Sensitivity
MICE	No Matching	Intervention: 2205 Control: 29182	1334	0.41 [0.38 – 0.44]	Sensitivity
	Propensity Score Matching	Intervention: 2205 Control: 8820	609	0.41 [0.38 - 0.44]	Primary

Discussion

Key Results

My primary analysis provides evidence that the NHS Diabetes Prevention prevents incident cases of type 2 diabetes in high-risk adults with an estimated 59% (HR: 0.41 [95% CI: 0.38 – 0.44]) 2.5-year risk reduction. Unsurprisingly, those with a higher baseline fasting plasma glucose (H.R.: 1.38 [95CI: 1.32 – 1.45]) or baseline HbA_{1c} (H.R.: 1.33 [95%CI: 1.31 – 1.35]) were more likely to develop type 2 diabetes compared to those with a lower baseline blood glucose reading; although this should be read with caution as this is not the primary exposure. My cohort breakdown is consistent with previous work by Valabhji et al., 2020, a study of the NHS Diabetes Prevention's initial population, providing evidence to support the validity of the phenotypes developed in chapter 4. Furthermore, through the use of target trial emulation, guided by similar diabetes prevention programmes which were evaluated using randomised controlled trials, my point estimates for NHS Diabetes Prevention Programme participation over a control group was similar to the aforementioned trials; HR 0.41 [95%CI=0.38-0.44] for this study, 0.42 [95CI: 0.34 -0.51] for the Diabetes Prevention Group's 3 year trial and 0.614 [95% CI 0.48 - 0.79] for Ilanne-Parikka *et al.*, in (Finland).

When evaluating other covariates, such as alcohol and smoking there was no evidence that they were associated with a reduction in the incidence of type 2 diabetes. This may be as a result of the relatively small proportion of patients who were drinkers and smokers in the cohort. My results also show that for each increment in deprivation quintile, there is a 4% increase in developing type 2 diabetes (H.R.: 1.04 [1.02 – 1.06]) , therefore potential further research (potentially using the target trial emulation framework) could investigate the impact of NHS Diabetes Prevention Programme on individuals within the same deprivation group to understand whether the NHS Diabetes Prevention Programme is equally effective across deprivation groups.

My results also indicate that participants who were recorded as being Asian also had an increased risk of developing type 2 diabetes compared to their non-Asian counterparts. This falls in line with findings from Valabhji *et al.*, 2020, which demonstrated that Asian patients who participated in the NHS Diabetes Prevention Programme had less weight loss compared to their non-Asian counterparts.

Furthermore, by comparing my imputed cohort to Valabhji *et al.*, 2020's cohort, I had confidence in the results produced in this chapter, although there were some surprising values in my imputed cohort. For example, in my cohort, there were more individuals aged 75 or over (19% vs 25%), of Asian descent (11% vs 18%), most deprived (21% vs 32%) and most surprisingly, individuals who were underweight or healthy at baseline (15% vs 23%). I postulate these different estimates are due to the fact that I used the outcome of type 2 diabetes in the imputation model which imputed values which are correlated with a recording of type 2 diabetes.

Strengths

The study design chosen aims to reduce bias and confounding in observational studies through the careful choice of inclusion/exclusion criteria on entry to emulate a randomised controlled trial, along with the use Cox proportional hazard models, multiple imputation and propensity score matching. My findings are comparable to results from randomised controlled trials evaluating a similar intervention for similar periods (Diabetes Prevention Programme Group study, 2002/2015). I also demonstrated that my sample breakdown from the CPRD is similar to those taking part in the NHS Diabetes Prevention Programme established by Valabhji *et al.*, 2020 which used a custom dataset that captured the whole cohort taking part in the NHS Diabetes Prevention Programme between June 2016 and December 2018.

My study design used data that included linkage between the CPRD, HES and ONS mortality records, and as a result, benefited from using the largest primary care observational dataset that was further complemented through linkage to secondary care and death records. This enabled me to lower the risk of misclassification, especially if there was an under-recording of type 2 diabetes incidence in any single dataset.

Limitations

My study has a smaller sample size when compared to Valabhji et al., 2020, therefore, multiple imputation played an important role in avoiding the reduction of analytical power. A challenge surrounding missing data was using the combination of HbA_{1c} and fasting plasma glucose; this is because general practitioners often used one value or the other but not both. Whilst the missingness for HbA_{1c} and fasting plasma glucose was high, the results of the imputed dataset were comparable to other external studies (Valabhji et al., 2020).

Clinical coding of the NHS Diabetes Prevention Programme is relatively new due to the recent phased introduction of the intervention starting from 2016. The data I used consisted of records from 01 June 2016 to 01 January 2019 and therefore, I suspect that I may have missed a proportion of participants that recently participated in the NHS Diabetes Prevention Programme from participating general practices. To tackle this, I only used control participants from general practices who did not offer the NHS Diabetes Prevention Programme during this period; this may have resulted in a selection bias especially if the general practices which provide the NHS Diabetes Prevention Programme had done so due to having higher rates of type 2 diabetes. Alternatively, if practices did not record NHS Diabetes Prevention Programme activities, then my study would misclassify participants from these general practices in the control group despite having participated in the NHS Diabetes

Prevention Programme, this result may conservatively estimate the impact of NHS Diabetes Prevention Programme activity on the incidence of type 2 diabetes.

Despite using a target trial emulation framework, as I used the retrospective observational data, certain baseline characteristics were significantly different even after matching, suggesting that there could be unmeasured confounding variables. I attempted to tackle this by conducting multivariable analysis and externally comparing my results to validate them. When comparing my results with those of similar studies, each study defined a diagnosis of type 2 diabetes differently. Due to the retrospective nature of my study, to identify the incidence of type 2 diabetes, I used a combination of READ codes, ICD10 codes, HbA_{1c} readings and FPG readings in line with the 2010 American Diabetes Association (American Diabetes Association, 2010) criteria for diagnosing type 2 diabetes. The Diabetes Prevention Programme Group, 2002/2015 used the 1997 American Diabetes Association Criteria for diagnosing type 2 diabetes, and Ilanne-Parikka *et al.*, 2013 used the 1985 World Health Organisation criteria for diagnosing type 2 diabetes. Therefore, my study is likely to pick up more cases of type 2 diabetes compared to those only using clinical codes alone; however, these rates were similar to prior studies analysing diabetes prevention programmes worldwide using randomised controlled trials (Diabetes Prevention Programme Group, 2002/2015, Ilanne-Parikka *et al.*, 2013).

To exclude previously undiagnosed cases of type 2 diabetes, I removed participants with a diagnosis of type 2 diabetes within 90 days of entry. Type 2 diabetes is an exclusion criterion for referral to the NHS Diabetes Prevention Programme, therefore individuals in the intervention group are actively assessed for type 2 diabetes by their general practitioner and can only be referred to the NHS Diabetes Prevention Programme if they have

non-diabetic hyperglycaemia. For the control group who are not invited to the NHS Diabetes Prevention Programme, there is less certainty of whether a recording of type 2 diabetes shortly after the start of follow-up (i.e., up to 90 days after the start of follow up) is due to a pre-existing undiagnosed case, or truly an incident of type 2 diabetes. If people in the control arm with a recording of type 2 diabetes within 90 days of their start of follow up were included, this may overestimate the impact of the NHS Diabetes Prevention Programme. Therefore, my estimate of the impact of the NHS Diabetes Prevention Programme is likely to be conservative due to these features of my study design.

Finally, in this analysis, by using a target trial emulation framework, I attempted to conduct an intention-to-treat analysis by emulating the treatment assignment with an NHS Diabetes Prevention Programme invitation. Consequently, this does not represent the impact of completing the NHS Diabetes Prevention Programme. Therefore, this analysis may underestimate the impact of the NHS Diabetes Prevention Programme when compared to a per-protocol analysis.

Generalisability

Based upon studies that analyse the impact of the NHS Diabetes Prevention Programme on weight loss (Wise, 2018), my analysis contributes toward the more comprehensive evidence base to suggest a positive preventative effect of the NHS Diabetes Prevention Programme. My study generated results similar to studies based in the United States (Diabetes Prevention Programme Group, 2015). Based upon the triangulation against randomised controlled trials of similar interventions (Diabetes Prevention Programme Group, 2015 and Ilanne-Parikka *et al.*, 2013), there is confidence about the estimate of our effectiveness of the NHS Diabetes Prevention Programme.

In addition to comparing the impact of the NHS Diabetes Prevention Programme on rates of type 2 diabetes, it is important to understand the eligibility of the NHS Diabetes Prevention Programme when compared to that of prior studies evaluating similar interventions (Diabetes Prevention Programme Group, 2015 and Ilanne-Parikka *et al.*, 2013). Of the various diabetes prevention programmes compared in this chapter, the NHS Diabetes Prevention Programme did not have any eligibility based upon body mass index, a lower age limit that is 7 years younger than the Diabetes Prevention Group in the USA and Ilanne-Parikka *et al.*, in Finland. If the event rates of 6% within 2.5 years within the NHS Diabetes Prevention Programme is considered too low to policy makers, the eligibility criteria could be updated to include body mass index criteria and increased age eligibility similarly to studies in the United States and Finland.

Interpretation

This analysis suggests that an invitation to the NHS Diabetes Prevention Programme may reduce short-term type 2 diabetes incidence in high-risk adults. By evaluating the preventive effect of having access to a NHS Diabetes Prevention Programme with a control group, my evaluation has demonstrated similar results to that of randomised controlled trials evaluating similar programmes worldwide at 2.5 years in the prevention of the incidence of type 2 diabetes (Diabetes Prevention Programme Group Study, 2002). It is likely that future evaluations of the NHS Diabetes Programme would converge the effect from 59% reduction at 3-years towards the 30% reduction at 15-years in line with findings from the Diabetes Prevention Programme Group Study, 2015 and Ilanne-Parikka *et al.*, 2013.

With a 59% reduction in type 2 diabetes rates in patients referred to the NHS Diabetes Prevention Programme relative to eligible adults who were not referred, this study supports findings from other observational and randomised controlled trials that the NHS Diabetes Prevention Programme is

effective in reducing short-term type 2 diabetes incidence in high-risk adults. As the NHS Diabetes Prevention Programme aims to close healthcare inequities, future research and iterations to the NHS Diabetes Prevention Programme could seek to understand the barriers experienced by deprived and particularly Asian patients who are at high risk of developing type 2 diabetes.

Chapter 6 . - Investigating the effect of the NHS Health Check on reducing incident cases of type 2 diabetes: A population-based cohort study using linked CPRD primary and HES secondary care health records in England

Abstract

Background and research gap: To reduce the incidence of cardiovascular disease in England, the National Health Service introduced the NHS Health Check in 2009. The NHS Health Check aims to identify those at high risk of developing preventable diseases such as chronic kidney disease, type 2 diabetes, heart disease, hypertension, and stroke. Current research suggests that rates of heart disease between invitees of cardiovascular health checks programmes similar to the NHS Health Check are comparable to patients who were not invited to take part in these programmes. Prior evaluations of the NHS Health Check have used outcomes that included prevalent, previously undiagnosed cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension and stroke which were discovered during the screening process. As a result of including prevalent and not incident cases, these existing evaluations are not examining the preventative effect of an NHS Health Check. This study aims to address this gap in the evidence base by attempting to estimate the preventative effect of the NHS Health Check by comparing the incidence of type 2 diabetes between eligible invitees and non-invitees of the NHS Health Check.

Methods: I applied target trial emulation in a retrospective observational cohort study using linked electronic health records from primary (Clinical Practice Research Datalink), and secondary (Hospital Episode Statistics) care. The study time period was January 2009 to January 2019. I compared rates of incident type 2 diabetes among eligible adults who were invited to the

NHS Health Check with rates for propensity score-matched controls who were eligible for the NHS Health Check but were not invited. Eligibility for the NHS Health Check was defined as being between 40-74 without a previous diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke at the start of follow-up. To emulate the NHS Health Check, I also excluded those who had a previous diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke on entry, akin to a randomised controlled trial. Those with a recorded event of type 2 diabetes within 90 days of entry were also excluded as these were likely prevalent (i.e., previously undiagnosed cases) identified during the NHS Health Check. Time to the first phenotypical record of type 2 diabetes was modelled using Cox regression with age, alcohol intake, body mass index, serum creatinine, ethnicity, sex, HbA_{1c}, index of multiple deprivations and smoking status included as covariates.

Results: I identified 105,382 individuals who participated in the NHS Health Check and 105,382 matched controls with a similar breakdown in age, sex, deprivation, and relevant clinical covariates. During the 10-year study period, 1.04% (95%CI: 0.98% - 1.11%) of NHS Health Check individuals have a new recording of type 2 diabetes versus 2.06% (95%CI: 1.98% - 2.15%) of usual care individuals. Individuals with an NHS Health Check referral had a 54% reduction in recorded type 2 diabetes incidence rates [adjusted hazard ratio= 0.46, 95% CI:0.45 – 0.47].

Discussion and Conclusions Rates of incident type 2 diabetes were low when compared to the NHS Diabetes Prevention Programme, which is likely due to the NHS Health Check's invitation of "healthy" individuals, compared to the higher risk individuals invited to the NHS Diabetes Prevention Programme. I found evidence that the NHS Health Check reduces the risk of type 2 diabetes when compared to usual care. These contrasts previous

findings of similar rates and is likely due to differentiating “newly recorded type 2 diabetes” as an incident case as opposed to a combination of previously undiagnosed case and incident cases.

Next Steps Due to the limitations of my study, primarily surrounding missing data, future studies should explore methods to reduce these biases.

Complementary Reading Material: To aid readers in this chapter, the REporting of studies Conducted using Observational Routinely collected Data (RECORD) checklist has been provided in Appendix 6.1.

Introduction

The NHS Health Check was introduced in 2009 as a general practice-driven intervention with the aim of reducing new cardiovascular-related diagnoses such as chronic kidney disease, coronary heart disease, hypertension, stroke and type 2 diabetes (Abdallah and Soljak, 2015). See Chapter 1 for a full description of the NHS Health Check (Chapter 1 - Introduction to the NHS Health Check and NHS Diabetes Prevention Programme). See Figure 6-1 for a flow chart of the NHS Health Check process.

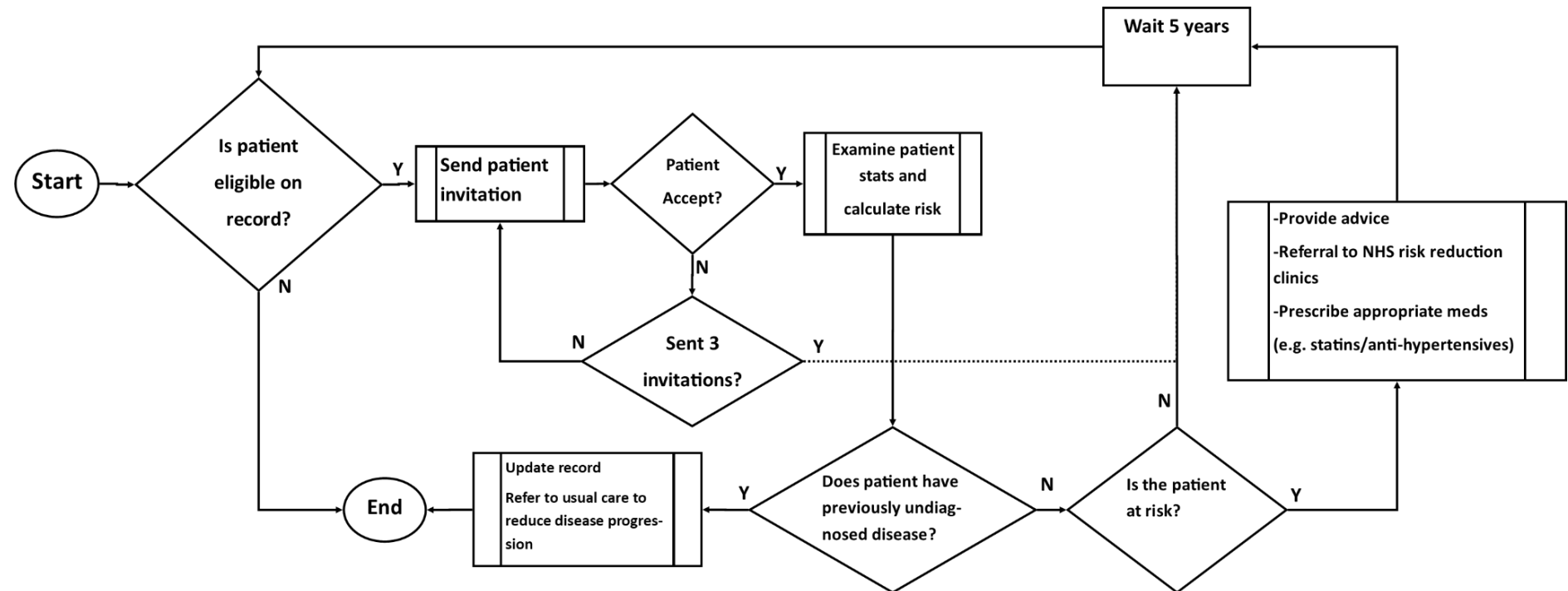
As stated in previous chapters, the primary concern about evaluating the NHS Health Check is that previous studies have evaluated new detection, and this combines previously undiagnosed cases (important to prevent disease progression) and incident cases of type 2 diabetes. Therefore, there is limited understanding on whether the NHS Health Check reduces the incidence of disease in a disease-free population, in this case, type 2 diabetes.

Aims and Objectives

Chapter 2 and other systematic reviews of the NHS Health Check suggest that there is a lack of evidence evaluating the preventative effect of the NHS Health Check with a comparable control group (Martin et al., 2018). To fill this gap in the existing literature in this study, I aim to investigate the preventative effect of the NHS Health Check by excluding individuals with previously undiagnosed chronic kidney disease, coronary heart disease, hypertension, stroke, or type 2 diabetes detected during the screening process and compare rates of incident of type 2 diabetes with a comparison group that was not invited to the NHS Health Check. The study design used aims to emulate a randomised controlled trial. To achieve this aim, this chapter has the following objectives:

- 1) To define a target trial description for the NHS Health Check in a similar manner that I had done for the NHS Diabetes Prevention Programme
- 2) To use READ codes and phenotypes developed in chapter 4 to reduce recording biases when establish a cohort of eligible patients, their treatment status and outcome of the incidence of type 2 diabetes.
- 3) Externally validate my sample by comparing to previous studies that evaluated the NHS Health Check' ability to detect new previously unrecorded type 2 diabetes (including both previously undiagnosed cases and incident cases)
- 4) Understand whether the NHS Health Check could prevent incident type 2 diabetes by emulating a "screening" process for eligibility and removing those who were found to have a previously unrecorded disease on entry.
- 5) Apply methods to reduce other biases such as missing data and differential baseline covariates between invitees and non-invitees of the NHS Health Check

Figure 6-1: Algorithm of patients journey through the NHS Health Check. Note an invitation is sent to a participant who on record is eligible. This may no longer be the case after the initial consultation where previously undiagnosed cases are found and patients are no longer eligible for further NHS Health Check activity. In this figure, Y = Yes, N = No



Methods

Study Design

This study used the observational, retrospective longitudinal cohort design with the “trial emulation” framework applied to reduce confounding by indication (Hernán et al., 2022).

Target Trial Description

The target trial for this study uses the inclusion and exclusion criteria for the NHS Health Check and treats the screening consultation of the NHS Health Check akin to a randomised controlled trial eligibility screening so that the NHS Health Check can be evaluated as a preventative programme. The target population for this study includes the following inclusion/exclusion criteria on entry:

- Inclusion: Aged between 40 - 74 on entry
- Exclusion: Prior diagnosis/signs of chronic kidney disease, diabetes, heart disease, hypertension, or stroke on entry

Group assignment and trial-arm was allocated based upon invitation status akin to an intention-to-treat analysis with an outcome of the incidence of type 2 diabetes after entry. See Table 6-1 for the target trial emulation framework used to conceptualise this study.

Table 6-1: Details of the trial emulation framework, used to conceptualise the observational study as a controlled trial.

	Ideal Randomised Controlled Trial	Target Trial emulation
Eligibility Criteria	Aged between 40 - 74 at start of follow-up. Exclusion: Prior diagnosis/signs of chronic kidney disease, diabetes, heart disease, hypertension, or stroke at start of follow up	Aged between 40 - 74 at start of follow-up. Exclusion: Prior phenotypical recording of chronic kidney disease, diabetes, heart disease, hypertension, or stroke at start of follow up
Study Period	1 Jan 2009 (introduction of the NHS Health Check) until 1 January 2019	1 Jan 2009 (introduction of the NHS Health Check) until 1 January 2019
Follow-up duration	Entry until: -Diagnosis of type 2 diabetes -Dropout -End of study	From estimated entry until first chronological phenotypical recording of: -First phenotypic recording of type 2 diabetes -Dropout e.g., death record, end of CPRD follow-up -End of study
Outcome	Diagnosis of Type 2 diabetes	First phenotypical recording of type 2 diabetes:
Treatments to be compared	NHS Health Check group assignment Usual care group assignment	Invitation to the NHS Health Check Usual Care assume via no invitation to the NHS Health Check
Estimand	Intention to treat based upon group assignment	Intention to treat based upon invitation (not uptake) to the NHS Health Check

	Ideal Randomised Controlled Trial	Target Trial emulation
Analysis Plan	Survival Analysis (Kaplan Meier)	Multiple Imputation to reduce missingness and increase sample size and representativeness. Propensity Score Matching Survival Analysis (Multivariable Cox Proportional Hazards models)

Data resource and setting

To analyse the NHS Health Check, I used the CPRD dataset. To identify additional cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension and stroke not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed (ONS death records were used for the outcome of type 2 diabetes only). See Chapter 4 for phenotyping and Chapter 5 for further details of the linkage periods and methods for the CPRD, HES and ONS datasets including which ranks of linkages were used.

Study Population

My study period was from 1 January 2009 (introduction of the NHS Health Check) until 1 January 2019 (latest available CPRD build). I used the same eligibility criteria as the NHS Health Check, defined as those between 40 – 74 who were “healthy” which is defined as individuals without a record indicating previous diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke. The primary difference between this study and general practice is that the “healthy” eligibility criteria in general practice is applied when inviting individuals; in this study, the “healthy” eligibility criteria is applied at the start of follow up. I excluded individuals who were likely to

have had pre-existing diagnoses of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke during the screening process i.e. exclusion of diagnoses that were recorded within 90 days of their start of follow-up to evaluate prevention and not discovery of pre-existing conditions (See Figure 6-2). Patients from general practices whose records were not up to standard (UTS) for one year before the introduction of the NHS Health Check were excluded to reduce misclassification bias (see Chapter 5 for definition of UTS).

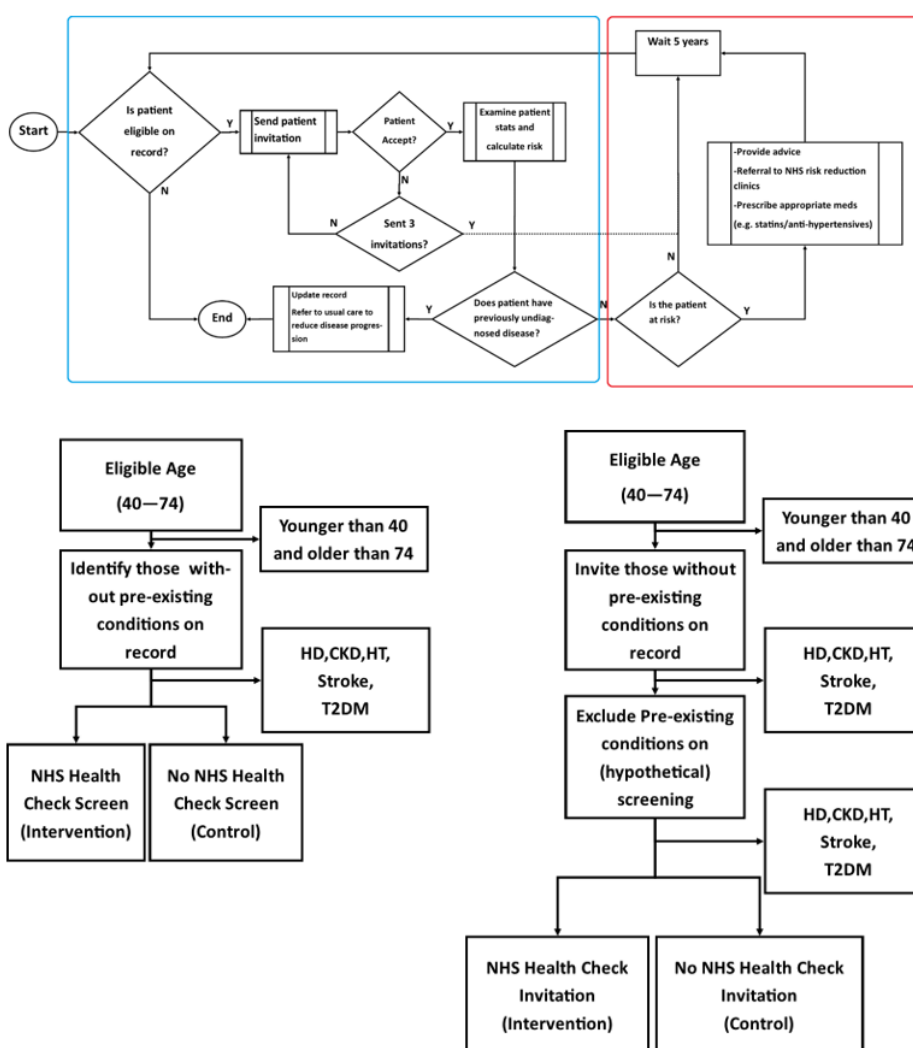
Primary Outcome Variable

The primary outcome of interest was incident cases of type 2 diabetes, which were defined using the first phenotypical recording of:

1. A primary care (CPRD) diagnosis for type 2 diabetes using READ codes and medical codes.
2. A secondary care (HES) diagnosis for type 2 diabetes using ICD10 codes.
3. A death record (ONS) for type 2 diabetes, identified using ICD10 codes.
4. A HbA_{1c} reading of 48 mmol/L or higher from primary care records (CPRD)
5. An FPG reading of 7 mmol/L or higher from primary care records (CPRD)

This phenotypic recording of type 2 diabetes was used to keep this chapter consistent with Chapter 5.

Figure 6-2: Top: This is the NHS Health Check Journey as described in Figure 6-1. The components of the NHS Health Check circled in blue are acting as a screening process for eligibility, whilst the components circled in red act as the intervention component. Bottom Left: how traditional studies have been analysing the NHS Health Check; that is those who attended a screening against those who have not, irrespective of whether they were “eligible” at the time. Right: How this study analyses the NHS Health Check. In this study, the NHS Health “NHS Health Check screen” is used as an “eligibility” screening process in the emulated controlled trial that eliminates previously unrecorded cases.



Intervention

My intervention was an invitation to the NHS Health Check. I defined the entry date (and participation in the NHS Health Check) with the first READ code

recording in Table 6-2 or by using a combination of covariate readings after registering for a general practitioner, whichever was first. Patients who were invited to have an NHS Health Check but declined or did not turn up for the NHS Health Check were included in the intervention group, akin to an intention-to-treat analysis in a randomised controlled trial.

To complement missing NHS Health Check READ codes, phenotyping algorithms were used to reduce misclassification. I used the Artac et al., 2013 algorithm and used a combination of blood pressure readings, body mass index records, smoking status, ethnicity, and cholesterol reading on the same day, after 3 months of registering for a general practice to denote participation in the NHS Health Check (Artac et al., 2013). In these instances, I used the earliest date where all these recordings were done to use as my entry date.

Table 6-2: READ Codes for identifying the NHS Health Check

READ Code	READ Term
6AH..00	NHS Health Check annual review
6B5..00	NHS Health Check Programme
8Ag.0	NHS Health Check Completed
8Aix.00	NHS Health Check Declined
8Bag000	NHS Health Check completed by third party
8BR2.00	NHS Health Check indicated
9mC..00	NHS Health Check invitation
9mC0.00	NHS Health Check telephone invitation
9mC1.00	NHS Health Check invitation first letter
9mC2.00	NHS Health Check invitation second letter
9mC3.00	NHS Health Check invitation third letter
9mC4.00	NHS Health Check verbal invitation
9mc5.00	NHS Health Check invitation email

READ Code	READ Term
9mC6.00	NHS Health Check invitation SMS text message
9Nie.00	Did not attend NHS Health Check annual review
9NiS.00	Did not attend NHS Health Check
9Nj5.00	Failed to respond to NHS Health Check invitation

Control Populations

In this study, I modelled as control participants those who did not have any NHS Health Check activity (i.e., no READ code or measurements of covariates on the same day) recorded during the study period; those who rejected an NHS Health Check are considered intervention participants akin to an intention-to-treat allocation in a randomised controlled trial. Therefore, these individuals could have been invited to the NHS Health Check after the end of this study (1 January 2019) but were considered control participants as data beyond this was not available. Similarly to the intervention group, I excluded patients with a previous diagnosis of diabetes before their start of follow-up when a hypothetical screening process could have taken place and removed cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke within 90 days of their estimated entry into the trial. See Chapter 5 for the data-driven method and graphical representation of how the start of follow up was estimated for control participants.

In an attempt to balance differential baseline characteristics between the control group and the intervention group, propensity score matching (See bias section)

Sample Size

To understand sample sizes in comparison to previous studies analysing the NHS Health Check, I've compared the sample in this chapter to prior studies

analysing the NHS Health Check on type 2 diabetic outcomes on an individual level which were identified during my systematic review in Chapter 2: (Robson et al., 2017) and (Chang et al., 2016).

Robson et al., 2017 contained 252,259 total participants, of which 85,122 attended an NHS Health Check; this was found to have 30% increased odds for new diabetes recording (OR: 1.30; 95%CI: 1.21 to 1.39). Chang et al, 2016 evaluated 138,788 individuals with 29,672 individuals receiving a health check; this was found to also have a 30% increase in diabetes diagnoses (Difference in difference = 1.31, 95% CI = 1.17 to 1.45).

In this chapter, I evaluated a total of 293,606 patients, of whom, 105,382 had NHS Health Check activity.

Analysis

I completed all analyses using R studio software and reported according to the REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement. To account for left censorship due to time-varying eligibility, right censorship due to leaving the CPRD (through general practice transfer or death), and the binary outcome of the phenotypic recorded incident of type 2 diabetes, I conducted a time-to-event analysis using a multivariable Cox proportional hazards model. To understand the preventative effect of the NHS Health Check, I only considered initiators of the programme (incident users). Therefore, patients in the intervention group of the NHS Health Check were assigned an entry date equivalent to their first chronological READ code entry or the first date where they had a combination of readings taken, 3 months after joining their general practice, whichever came first. Control patients were assigned a start of follow up using linear regression (See Control Population section). All patients were followed until the first chronological event of a diagnosis of type 2 diabetes (by READ code or ICD10), a HbA_{1c} reading of 48 mol/mol or higher, a fasting plasma glucose reading of 7 mmol/L or higher, dropout (for examples who those

leave the CPRD either by changing general practice or through death) or end of study (1 January 2019). Patients were considered determined to have type 2 diabetes if they were either diagnosed with type 2 diabetes in primary or secondary care, had a HbA_{1c} reading of 48 mmol/L or higher, a fasting plasma glucose reading of 7 mmol/L or higher, or if one of their 15 causes of death were recorded as diabetes (see primary outcomes section).

Covariates

To evaluate the NHS Health Check impact on patients from different backgrounds, I included demographic, socio-economic and clinically relevant covariates to the NHS Health Check. I used the latest readings up to 5-years before each patient's (estimated) entry date with missing values being imputed (see Biases Missing data section). Indexes of multiple deprivation, ethnicity, alcohol, and smoking categories were kept consistent from Chapter 5. See Table 6-3 for a list of covariates used in this analysis.

Table 6-3: Covariates used in modelling the effect of the NHS Health Check on the incidence of type 2 diabetes.

Demographic and socio-economic covariates	Clinically relevant covariates
Age on (estimated) entry	Baseline body mass index
Ethnicity	Baseline HbA _{1c}
Index of Multiple deprivations (1 – 5) (See Table 2 for an explanation)	Baseline FPG
Gender	Smoking Status (1-4) (See Table 4 for an explanation)
	Alcohol Status (1-6) (See Table 4 for an explanation)
	Baseline Diastolic Blood Pressure
	Baseline Systolic Blood Pressure
	Baseline Serum creatinine
	Baseline QRisk Score

Biases

To reduce biases due to the observational study design, I identified and addressed such biases through careful study design and by incorporating a variety of sensitivity analyses. Based upon weaknesses of observational studies (Hammer et al., 2009), I concentrated on tackling recruitment bias, missing data and misclassifications.

Missing data

Similarly to Chapter 5, missingness existed in the data, and more so as the eligible population for the NHS Health Check were “healthy” individuals who

were less likely to have clinical covariates measured compared to “high-risk” individuals in the NHS Diabetes Prevention Programme. This is because these “healthy” individuals were less likely to have laboratory tests when compared to their NHS Diabetes Prevention Programme counterparts.

Therefore, I also used multiple imputation in this chapter too. The following covariates were used in the MICE model, all of which were established using the closest recording before each individual's (estimated) entry date within 5-years: age on entry, gender, ethnicity, index of multiple deprivation, body mass index, glycated haemoglobin, fasting glucose plasma, diastolic blood pressure, systolic blood pressure, serum creatinine, alcohol status, smoking status and disease status (i.e., a type 2 diabetes diagnosis). The outcome of type 2 diabetes was used to improve the quality of imputation (Sterne et al., 2009). For numerical covariates (age, body mass index, glycated haemoglobin, fasting glucose plasma, alcohol status and smoking status) the MICE model used linear regression modelling and logistic regression for binary covariates (for example gender and dummy variables for ethnicity).

Biases in different baseline covariates

Similarly to Chapter 5, I've used propensity score matching to reduce differences in baseline covariates between invitees and non-invitees of the NHS Health Check. In this chapter, the following variables were used to match invitees and non-invitees of the NHS Health Check after multiple imputation was applied: age, ethnicity, gender, index of multiple deprivation, body mass index, blood glucose measures, smoking status, alcohol intake, blood pressure measures, serum creatinine and recorded QRisk2 score.

Misclassification

One concern was the misclassification of those who were and were not invited to the NHS Health Check based upon the eligibility criteria. To avoid misclassification of chronic kidney disease, type 2 diabetes, heart disease,

hypertension, stroke, I used previous work which used systematic reviews (Chapter 4) to generate an evidence-based list of READ codes and phenotyping algorithms within primary care databases such as CPRD, THIN and QResearch. I also used linkage to secondary care datasets to complement missing diagnoses of chronic kidney disease, type 2 diabetes, heart disease, hypertension, stroke in primary care as suggested by Herrett et al., 2013. I also used relevant clinical covariates to establish both the healthcare criteria and clinical outcomes, including serum creatinine for chronic kidney disease, HbA_{1c} and fasting plasma glucose for type 2 diabetes and diastolic/systolic blood pressure for hypertension. To complement any missingness in recording the NHS Health Check intervention, I used a combination of READ Codes and covariate readings which are often collected during an NHS Health Check; as these readings are often collected during the initial registration of a general practice, I only considered readings taken 3 or more months after joining the practice (Artac et al., 2013).

External Validity and understanding the role of detecting previously undiagnosed cases.

Unlike the NHS Diabetes Prevention Programme, there is limited data on the population of the NHS Health Check; therefore, I could not compare my cohort's distribution against a database that had universal recording of NHS Health Check activity. Therefore, to understand whether my study is comparable, I used Robson et al., 2017 as a comparator. I chose Robson et al., 2017 as it was the only study whose methods I could replicate to externally validate my results in the NHS Health Check population with an outcome of recording of type 2 diabetes. Therefore, I used the results from Robson et al., 2017 to 1) to understand whether the socio demographic trends are similar and 2) to understand the impact of not excluding those who had a first diagnosis of type 2 diabetes within 90 days of the start of follow-up. A-priori, I do not expect the socio-demographic distributions to be similar, but

the trends to be similar; this is because the geographical sample in Robson et Al., 2017 is vastly different from this study.

Ethics and approvals

Approval for this study was granted as part of an application to the CPRD's Independent Scientific Advisory Committee: protocol 18_179. Data extractions were completed by the CALIBER team under NHS research ethics approval (09/H0810/16) and ECC approval (ECC 2-06(b)/2009 CALIBER dataset).

Information governance

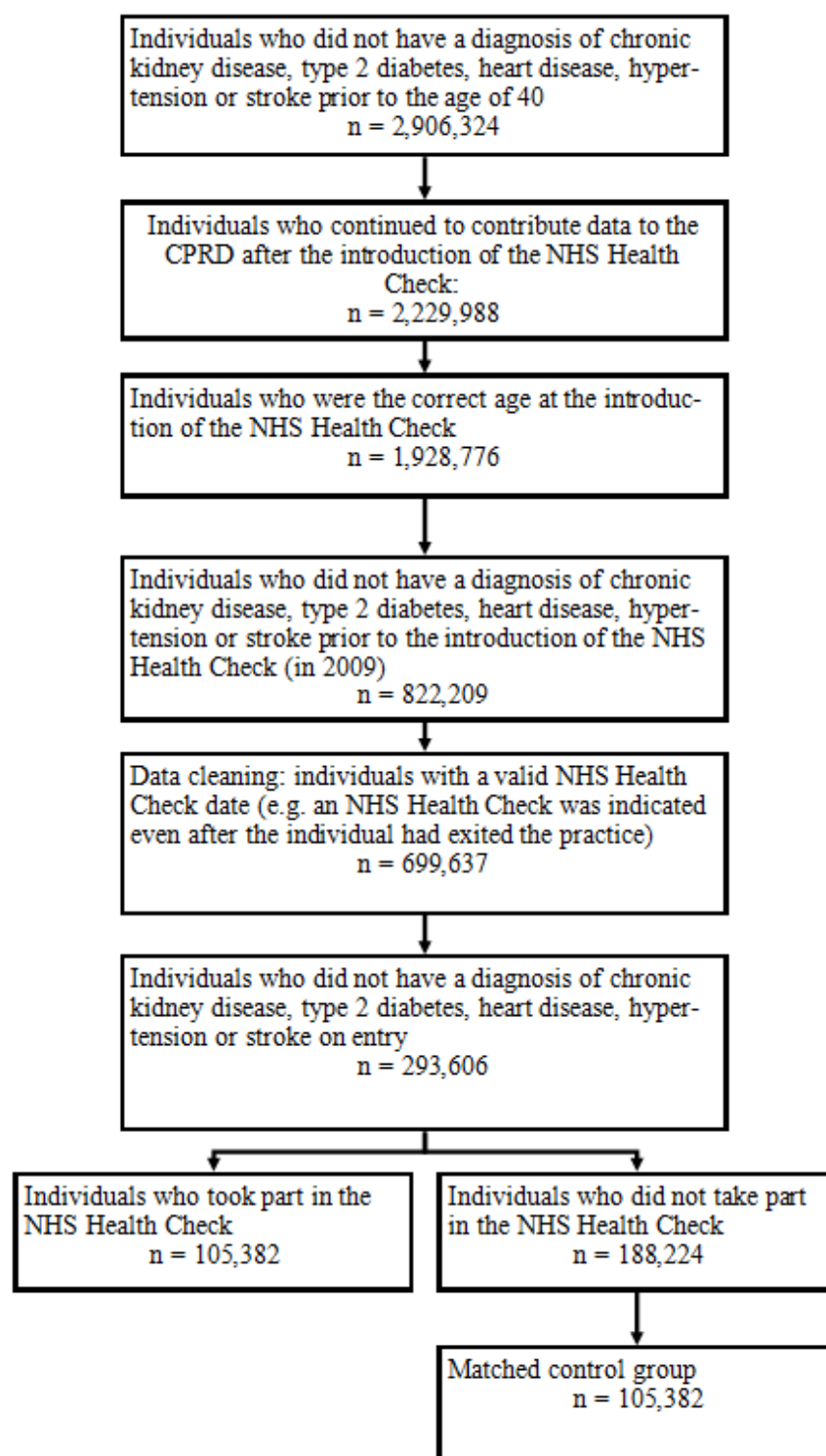
All analyses were completed on the UCL data safe haven. The pseudonymised dataset will be securely destroyed after four years in the first occurrence in line with the latest Independent Scientific Advisory Committee's guidance. In line with CPRD policy, I did not report any data with a cell containing <5 events and where necessary I have protected these counts with secondary suppression.

Results

Numbers Analysed

I found 2,906,324 individuals in the CPRD who did not have a diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension, or stroke prior to the age of 40. After removing those who did not contribute data after the introduction of the NHS Health Check, 2,229,988 participants remained. When removing individuals who were either too young or too old to have participated in the NHS Health Check between 2009 and 2019, 1,928,776 individuals remained. I then removed those with a previous diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke prior to the introduction of the NHS Health Check; this left me with 822,209 individuals. After cleaning data and removing those with a diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke on entry, 293,606 were considered part of my cohort with 105,382 intervention patients and 188,224 control patients. See Figure 6-3 for how the cohort was derived..

Figure 6-3: CONSORT diagram of how my cohort was derived.



Population and Characteristics

Due to the high missingness of certain covariates, a full case analysis was considered if all the following socio-demographic covariates were available for a patient: age, gender, ethnicity, and index of multiple deprivation quintile.

Under a full case analysis, 2026 were included as intervention patients whilst 7020 patients were considered controlled patients (prior to matching).

Missingness for sociodemographic covariates was less likely in the NHS Health Check group for all variables except for index of multiple deprivation - see Table 6-4. For clinical covariates such as QRisk Score, BMI, alcohol status, smoking status, and blood pressure, the intervention group was less likely to have missing data due to access to diagnostic tools. See table 6-5 for a breakdown of missingness in my matched group.

Table 6-4: Percentage of missingness per group and covariate. Smaller numbers are better (i.e., less missingness)

Covariate	Control (n = 105,382)	Intervention (n = 105,382)	Total (n = 210,764)
Ethnicity	67.24% (n=70857)	57.75% (n=60862)	62.50% (n=131719)
IMD	90.39% (n=95252)	95.90% (n=101059)	93.14% (n=196311)
Alcohol status	90.74% (n=95628)	85.09% (n=89674)	87.92% (n=185302)
BMI	68.11% (n=71779)	53.95% (n=56852)	61.03% (n=128631)
Serum Creatinine	99.96% (n=105024)	99.50% (n=104860)	99.58% (n=209884)
Q-Risk	99.73% (n=105102)	96.19% (n=101363)	97.96% (n=206465)
FGP	98.86% (n=104184)	98.15% (n=103429)	98.50% (n=207613)
HBA1C	99.72% (n=105088)	98.82% (n=104141)	99.27% (n=209229)
HDL LDL Ratio	99.99% (n=105377)	99.99% (n=105381)	99.99% (n=210758)
Smoking	46.18% (n=48666)	29.66% (n=31260)	37.92% (n=79926)
Diastolic BP	60.56% (n=63824)	47.72% (n=50285)	54.14% (n=114109)
Systolic BP	60.56% (n=63824)	47.72% (n=50285)	54.14% (n=114109)

Full Case Cohort

Under a full case analysis, there are significantly more males than females with a similar mean age for both the control and intervention group of 54 years of age on entry. Attendees were of “white” ethnicity with a small proportion of “mixed” ethnicity patients. Deprivation closely mirrors the general population at 20% per quintile, except for deprivation group 1 (least deprived). See Table 6-5 for a full breakdown of the baseline demographics of the cohort and the impact of using multiple imputation by chained equations as well as propensity score matching.

Imputed Cohort

After applying multiple imputation by chained equations, proportions for those analysed shifted for gender, ethnicity (Asian), deprivation quintile 1 with a lowered mean age compared to a full case analysis. After applying MICE but before applying propensity score matching, there were significant differences between the distribution of the deprivation quintiles and drinking status. After applying propensity score matching on the imputed dataset, the gap in these baselines’ differences had tightened. See Table 6-5 for a full breakdown of the baseline demographics of the cohort and the impact of using multiple imputation by chained equations as well as propensity score matching.

Table 6-5: Break down of the cohort by imputation status, matching status, trial-arm and covariates. Note a full case analysis was based upon the sociodemographic variables only.

	Full Case based upon sociodemographic measures only			Imputed - MICE		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
Total	n = 2026	n = 7020	n = 2026	n = 105,382	n = 188, 224	n = 105,382
Gender						
Male	63.43% (n = 1210)	58.02% (n = 4073)	63.57% [61.48 – 65.67]	59.76% (n = 62976)	58.29% (n = 109716)	59.72% (n = 62934)
Female	36.57% (n = 816)	41.98% (n = 2947)	36.43% [34.33 – 38.52]	40.24% (n = 42406)	41.71% (n = 78508)	40.28% (n = 42448)
Mean Age	54.52 [54.12 – 54.92]	55.14 [54.92 – 55.36]	54.64 [54.22 – 55.05]	50.44 [50.42 – 50.46]	50.71 [50.69 – 50.72]	50.41 [50.39 – 50.43]
Mean BMI	--	--	--	26.65 [26.61 – 26.69]	26.55 [26.52 – 26.58]	26.65 [26.61 – 26.69]
Mean HbA _{1c}	--	--	--	36.7 [36.72 – 36.74]	36.93 [36.92 – 36.93]	36.7 [36.72 – 36.73]

	Full Case based upon sociodemographic measures only			Imputed - MICE		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
Mean FPG	--	--	--	4.94 [4.94 – 4.94]	4.97 [4.97 – 4.97]	4.94 [4.94 – 4.94]
Mean Serum Creatinine	--	--	--	53.23 [53.22 – 53.25]	52.97 [52.96 – 52.99]	53.27 [53.26 -53.29]
Mean QRisk	--	--	--	5.28 [5.27 – 5.29]	5.11 [5.10 – 5.12]	5.25 [5.24 – 5.26]
Mean Dias BP	--	--	--	75.78 [75.77 – 75.79]	75.76 [75.75 – 75.77]	75.78 [75.77 – 75.79]
Mean Sys BP	--	--	--	122.54 [122.52 – 122.56]	122.59 [122.58 – 122.61]	122.53 [122.51 – 122.55]
Ethnicity						
White	82.38% (n = 1669)	81.31% (n = 5708)	81.89% (n =1659)	80.43% (n = 84759)	80.46% (n = 151445)	80.37% (n = 84696)
Black	6.27% (n = 127)	5.81% (n = 408)	6.71% (n =136)	5.97% (n = 6291)	5.71% (n = 10748)	6% (n = 6323)

	Full Case based upon sociodemographic measures only			Imputed - MICE		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
Asian	6.86% (n = 139)	8.05% (n = 565)	6.56% (n = 133)	8.61% (n = 9073)	8.89% (n = 16752)	8.62% (n = 9084)
Mixed	1.53% (n = 31)	1.54% (n = 109)	1.68% (n = 34)	1.76% (n = 1855)	1.61% (n = 3030)	1.75% (n = 1844)
Other	2.96% (n = 60)	3.28% (n = 230)	3.16% (n = 64)	3.24% (n = 3404)	3.32% (n = 6249)	3.26% (n = 3435)
Index of Multiple Deprivation						
(Least Deprived) 1	16.34% (n = 331)	16.65% (n = 1169)	15.4 [13.83 – 16.97]	18.25% (n = 19232)	20.31% (n = 38228)	17.88% (n = 18843)
2	18.81% (n = 381)	20.03% (n = 1406)	19.84 [18.11 – 21.58]	19.75% (n = 20813)	21.21% (n = 39922)	19.92% (n = 20992)
3	21.22% (n = 430)	22.36% (n = 1570)	20.98 [19.2 – 22.75]	21.38% (n = 22531)	21.54% (n = 40525)	21.57% (n = 22731)
4	20.38% (n = 413)	21.13% (n = 1483)	21.57 [19.78 – 23.36]	20.96% (n = 22088)	19.72% (n = 37118)	21.06% (n = 22193)

	Full Case based upon sociodemographic measures only			Imputed - MICE		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
(Most Deprived) 5	23.25% (n = 471)	19.83% (n = 1392)	22.21 [20.4 – 24.02]	19.67% (n = 20718)	17.23% (n = 32431)	19.57% (n = 20623)
Drinking Status						
Non-Drinker	--	--	--	41.8% (n = 44050)	45.07% (n = 84814)	41.66% (n = 43902)
Ex Drinker	--	--	--	5.46% (n = 5754)	5.28% (n = 9938)	5.19% (n = 5469)
Occasional Drinker	--	--	--	40.58% (n = 42753)	39.30% (n = 73972)	41.26% (n = 43481)
Current Drinker	--	--	--	7.87% (n = 8294)	6.90% (n = 12987)	7.75% (n = 8176)
Excess Drinker	--	--	--	4.01% (n = 4226)	3.23% (n = 6080)	3.85% (n = 4057)
Binge Drinker	--	--	--	0.28% (n = 295)	0.23% (n = 433)	0.29% (n = 306)

	Full Case based upon sociodemographic measures only			Imputed - MICE		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
Smoking Status						
Non-Smoker	--	--	--	47.33% (n = 49877)	48.18% (n = 90668)	47.41% (n = 49962)
Ex-Smoker	--	--	--	19.89% (n = 20960)	19.74% (n = 37155)	19.76% (n = 20823)
Ex or current smoker	--	--	--	0.1% (n = 106)	0.07% (n = 132)	0.07% (n = 74)
Current Smoker	--	--	--	32.69% (n = 34439)	32.02% (n = 60269)	32.76% (n = 34523)

Outcomes and Estimations

Unadjusted incidence rates of type 2 diabetes

Of 210,764 individuals (105,382 intervention + 105,382 matched control) who were identified after imputation and matching, 1.55% (n = 3,267) have a new recording of diabetes within the 10-year study period (between January 2009 and January 2019) within a maximum of 3547 days of initiating the NHS Health Check. Of the 105,382 intervention patients, 1.04% (n = 1,096, 95%CI: 0.98% - 1.11%) have a new recording of type 2 diabetes within 3512 of initiating the NHS Health Check with a median follow up time of 927 days and a mean follow up time 1068 days. Of the 105,382 control (matched) patients, 2.06% (n = 2,171, 95%CI: 1.98% - 2.15%) have a new recording of type 2 diabetes within 3547 days of initiating the NHS Health Check with a median follow-up time of 698 days and a mean follow-up time of 902 days. This created a crude hazard ratio of 0.50 (95%CI: 0.46 to 0.54). See Table 6-6 for the unadjusted incidence of recorded type 2 diabetes in the imputed and matched cohort.

Table 6-6: Unadjusted type 2 diabetes incidence rates for control and intervention groups between 2009 and 201. The minimum of 91 days of follow up is since those who had type 2 diabetes within 90 days were excluded.

		Control (n = 105,382)	Intervention (n = 105,382)	Total (n = 210,764)
Follow up time (days)	Min	91	91	91
	1st Qu	356	480	401
	Med	698	927	782
	Mean	902	1068	965
	3rd Qu	1278	1541	1397
	Max	3547	3512	3547
Outcome	No Type 2 diabetes during follow up	103,211 97.94% 95CI: 97.85 - 98.02	104,286 98.96% 95CI: 98.90 – 99.02	207,497 98.45% 95CI: 98.40 – 98.50
	Type 2 diabetes during follow up	2,171 2.06% 95%CI: 1.98 – 2.15	1,096 1.04% 95CI: 0.98 – 1.10	3,267 1.55% 95CI: 1.50 – 1.60

Adjusted Results

After adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, IMD, baseline alcohol intake, baseline smoking consumption, baseline BMI, age on entry, baseline blood pressure, and serum creatinine, the hazard ratio for a referral to the NHS Health Check demonstrated that referred patients were 54% (H.R.: 0.46 [95% CI: 0.45 – 0.47]) less likely to have a new recording of type 2 diabetes compared to the imputed and matched control group. See Table 6-7 for a full breakdown of the hazard ratios for each covariate.

Table 6-7: Covariates and their adjusted hazard ratio. HR < 1 = protective to type 2 diabetes. HR > 1 = more likely to develop type 2 diabetes.

Covariate	Intervention (n = 105,382)	Control (n = 105,382)	Adjusted Hazard Ratio [95% CI:]
NHS Health Check invitation			
Not invited (reference)	-	105,382 (100%)	1.00 [Ref]
Invited	105,382 (100%)	-	0.46 [0.45 – 0.47]
Age on Entry	50.44 [50.42 – 50.46]	50.41 [50.39 – 50.43]	0.93 [0.93 – 0.93]
Gender			
Female	40.24% (n = 42406)	40.28% (n = 42448)	1.68 [1.64 – 1.72]
Male (reference)	59.76% (n = 62976)	59.72% (n = 62934)	1.00 [Ref]
Ethnicity			
Asian (reference)	8.61% (n = 9073)	8.62% (n = 9084)	1.00 [Ref]
Black	5.97% (n = 6291)	6% (n = 6323)	1.01 [0.97 – 1.05]
Mixed	1.76% (n = 1855)	1.75% (n = 1844)	1.12 [1.04 – 1.20]
Other	3.24% (n = 3404)	3.26% (n = 3435)	1.25 [1.19 – 1.32]
White	80.43% (n = 84,759)	80.37% (n = 84696)	0.59 [0.58 – 0.61]
IMD2015			1.14 [1.13 – 1.15]
(Least Deprived) 1	18.25% (n = 19232)	17.88% (n = 18843)	-
2	19.75% (n = 20813)	19.92% (n = 20992)	-

Covariate	Intervention (n = 105,382)	Control (n = 105,382)	Adjusted Hazard Ratio [95% CI:]
3	21.38% (n = 22531)	21.57% (n = 22731)	-
4	20.96% (n = 22088)	21.06% (n = 22193)	-
(Most Deprived) 5	19.67% (n = 20718)	19.57% (n = 20623)	-
Blood Glucose measures			
Fasting Plasma Glucose	4.94 [4.94 – 4.94]	4.94 [4.94 – 4.94]	4.95 [4.86 – 5.04]
HbA _{1c}	36.7 [36.72 – 36.74]	36.7 [36.72 – 36.73]	1.22 [1.22 – 1.23]
Q-Risk	5.28 [5.27 – 5.29]	5.25 [5.24 – 5.26]	1.12 [1.11 – 1.12]
Smoking			0.90 [0.90 – 0.91]
Non-Smoker	47.33% (n = 49877)	47.41% (n = 49962)	-
Ex-Smoker	19.89% (n = 20960)	19.76% (n = 20823)	-
Ex or current smoker	0.1% (n = 106)	0.07% (n = 74)	-
Current Smoker	32.69% (n = 34439)	32.76% (n = 34523)	-
Alcohol Consumption			0.98 [0.97 – 0.99]
Non-Drinker	41.8% (n = 44050)	41.66% (n = 43902)	-
Ex Drinker	5.46% (n = 5754)	5.19% (n = 5469)	-
Occasional Drinker	40.58% (n = 42753)	41.26% (n = 43481)	-
Current Drinker	7.87% (n = 8294)	7.75% (n = 8176)	-
Excess Drinker	4.01% (n = 4226)	3.85% (n = 4057)	-
Binge Drinker	0.28% (n = 295)	0.29% (n = 306)	-
Blood Pressure			
Systolic Blood Pressure	122.54 [122.52 – 122.56]	122.53 [122.51 – 122.55]	1.00 [1.00 – 1.00]
Diastolic Blood Pressure	75.78 [75.77 – 75.79]	75.78 [75.77 – 75.79]	1.00 [1.00 – 1.00]
Serum Creatinine	53.23 [53.22 – 53.25]	53.27 [53.26 – 53.29]	1.00 [1.00 – 1.00]
Body Mass Index	26.65 [26.61 – 26.69]	26.65 [26.61 – 26.69]	1.00 [1.00 – 1.00]

Sensitivity Analyses

When conducting a full case analysis, a total of 9046 (2026 intervention and 7020 control) individuals provided data in the intervention and control groups. Under a full case analysis without propensity score matching, the hazard ratio for developing type 2 diabetes in those invited to undergo an NHS Health Check changed to 0.63 [95%CI: 0.54 – 0.73]. Under a full case analysis with propensity score matching, the hazard ratio for NHS Health Check invitation changed to 0.73 [95% CI: 0.58 – 0.84]. When conducting an unmatched analysis using MICE, the hazard ratio stayed at 0.47 [95%CI: 0.46 – 0.48]. See Table 6-8 the hazard ratio under different methods.

Table 6-8: Results of alternative analyses

Imputation Method	Matching Method	Cohort size	No of events	Hazard Ratio for Treatment [95% CI:]
Full Case	No Matching	Intervention: 2026 Control: 7020	1132	0.63 [0.54 – 0.73]
	Propensity Score Matching	Intervention: 2026 Control: 2026	445	0.73 [0.58 – 0.84]
Multiple Imputation using Chained Equations	No Matching	Intervention: 105382 Control: 188224	5163	0.47 [0.46 – 0.48]
	Propensity Score Matching	Intervention: 105382 Control: 105382	3688	0.46 [0.45 – 0.47]

Comparison to previous work evaluating “detection” of potentially previously undiagnosed cases of type 2 diabetes.

To try and untangle whether previous studies of the NHS Health Check were reporting higher rates in NHS Health Check attendees due to detecting previously undiagnosed cases when compared to non-attendees of the NHS Health Check (see Figure 6-2 of flow/process chart) I undertook a sensitivity analysis that did not exclude people with new records of type 2 diabetes within 90 days of start of follow-up. This approximately replicates the methods applied by Robson and colleagues outlined in Chapter 2 which estimated the odds of having a new diagnosis of type 2 diabetes after attending an NHS Health Check when compared to not attending an NHS Health Check (Robson et al., 2017). One of the major differences between Robson et al., 2017 and this PhD is the geographical location; this PhD investigated all general practices contributing to the CPRD, whilst Robson et al., 2017 conducted their analysis in deprived areas of London including City & Hackney, Newman and Tower Hamlets; therefore, the risk of self-fulfilling results is low due to the differential geographical inclusion criteria.

In this sensitivity analysis, I adapted my study to mirror Robson et al., 2017 by identifying those who had NHS Health Check activity (including declines and “did not attend”). I then identified those who were eligible for the NHS Health Check, without any recorded NHS Health Check activity and estimated a reasonable start of follow-up; and excluded those who were ineligible at that point in time. The outcome was a phenotypical recording of type 2 diabetes as I’ve consistently used. Categories for age, and ethnicity were adapted to reflect Robson et al., 2017’s analysis to compare my cohort against and to conduct logistic regression using the same categories. Imputation and matching were conducted in a similar way to Robson et al., 2017. A primary difference was that Robson et al., 2017 used the Townsend Quintile of Deprivation, whilst I only had access to the Index of Multiple Deprivation as my measure of deprivation; this is likely due to the geographical sampling

differences, that is Robson et al., 2017 was conducted in areas of London with disproportionate levels of deprivation (City & Hackney, Newman, Tower Hamlets) whilst this study used the CPRD's sample of England.

Gender distributions for control groups are similar across both studies for the control group, but not for the NHS Health Check group. Both studies show an increased NHS Health Check activity for the 60-74 age group when compared to a control group. Ethnicity and deprivation demographics were vastly different between the studies. See Table 6-9 for a full breakdown of the sociodemographic comparisons between Robson et al., 2017 and this study.

Table 6-9: Comparison of cohort breakdown between Robson et Al, 2017 and this study.

	Robson et al., 2017		This Study	
Patient Characteristics	NHS Health Check (n =85,122)	Control (n = 167,137)	NHS Health Check (n = 234,948)	Control (n = 234,948)
Sex				
Female	40592 (47.7%)	67620 (40.5%)	130805 (56%)	97877 (42%)
Male	44530 (52.3%)	99516 (59.5%)	104143 (44%)	137071 (58%)
Not specified	1 (0.0%)	1 (0.0%)	-	-
Age Bands, years				
40 - 59	75347 (88.50%)	152935 (91.50%)	173904 (74%)	197681 (84%)
60 - 74	9775 (11.5%)	14202 (8.50%)	61044 (26%)	37267 (16%)

	Robson et al., 2017		This Study	
Patient Characteristics	NHS Health Check (n =85,122)	Control (n = 167,137)	NHS Health Check (n = 234,948)	Control (n = 234,948)
Ethnicity				
White	37977 (44.60%)	69108 (41.30%)	198,750 (85%)	217,298 (92%)
Black	18229 (21.4%)	29732 (17.80%)	10,668 (4.5%)	4,862 (2.1%)
Asian	21392 (25.1%)	26168 (15.7%)	11,689 (5.0%)	5,895 (2.5%)
Other/not recorded	7524 (8.80%)	42129 (25.2%)	13,841 (5.9%)	6,893 (2.9%)
Deprivation* Quintile				
(Most affluent) 1	33 (0.00%)	81 (0.00%)	33776 (14%)	51693 (22%)
2	156 (0.20%)	381 (0.20%)	41665 (18%)	52415 (22%)
3	794 (0.90%)	1596 (1.00%)	50739 (22%)	50742 (22%)
4	14943 (17.60%)	30814 (18.40%)	53972 (23%)	44737 (19%)
(Most deprived) 5	69073 (81.10%)	133408 (79.80%)	54795 (23%)	35361 (15%)
Not recorded	123 (0.10%)	857 (0.50%)	-	-

After adjusting for sex, age band, ethnicity and deprivation quintile, I found a 35% increase in type 2 diabetes recordings in the NHS Health Check group when compared to their non-NHS Health Check counterparts (OR: 1.35,

95%CI: 1.30 to 1.40). In comparison, Robson et al., 2017 estimated that NHS Health Check attendees to have a 30% increase in new diagnoses of type 2 diabetes compared to their non-NHS Health Check counterparts (OR 1.30, 95%CI: 1.21 to 1.39)

Discussion

Key Results

In my NHS Health Check population, 1.55% (95%CI: 1.50% to 1.60%) of individuals have newly recorded type 2 diabetes during the 10-year study (January 2009 – January 2019) period with a maximum follow-up of 3547 days (9.7 years). My primary analysis provides evidence that the NHS Health Check reduces the incident cases of recorded type 2 diabetes in those between the ages of 40-74 without a prior history of cardiovascular-related diseases. Compared to the NHS Diabetes Prevention Programme, the NHS Health Checks crude 10-year study period incidence rate of type 2 diabetes being 1.55% (95%CI: 1.50% to 1.60%) compared to the NHS Diabetes Prevention Programme's crude 3-year study period incidence rate of 5.96% (95%CI; 5.55% - 6.42%); this is expected due to the different eligibility criteria for an invitation. That is, the NHS Diabetes Prevention Programme targets high-risk individuals whilst the NHS Health Check targets healthier individuals.

Despite this, they produced similar relative reduction with an invitation to the NHS Health Check demonstrating a 54% (HR: 0.46 [0.45 – 0.47]) 10-year risk reduction and this is similar to my analysis of the NHS Diabetes Prevention Programme (HR: 0.41;95%CI=0.38-0.44). The similarity could have occurred as participants of the NHS Health Check could have been referred to the NHS Diabetes Prevention Programme and that despite the NHS Diabetes Prevention Programme's lower age limit of 18, the median age of NHS Diabetes Prevention Programme's median age in invitees was 65.19 [95%CI: 65.01,65.38].

Unlike previous studies, this study attempted to understand the preventative effect of the NHS Health Check on an individual level by removing “previously undiagnosed cases” through a 90-day “new recording” exclusion. To test whether this exclusion was at least partially responsible for my results, I adapted my data to an alternative analysis and compared this to Robson et al., 2017 which did not isolate the NHS Health Check’s preventative effect. When I did not exclude cases of type 2 diabetes within 90 days of the start of follow-up, the odds of this being detected in the NHS Health Check group was 35% higher than a control group (OR: 1.35, 95%CI: 1.30 to 1.40) and is similar to findings by Robson et al., 2017 (OR 1.30, 95%CI: 1.21 to 1.39). Therefore, there is some evidence that at least in the first 90 days, that NHS Health Check related activity increases detection of type 2 diabetes and is likely due detection of previously undiagnosed cases and access to diagnostic tools.

In terms of inequities (an aim of the NHS Health Check is to reduce inequities), my results hint at a detrimental effect for those experiencing higher levels of deprivation on the incident of type 2 diabetes (H.R.: 1.14 [1.13 – 1.15]). This suggests that the improvements to the NHS Health Check could be made to help further close the inequality gap as this was one of the aims of the NHS Health Check and is in line with recommendations from previous studies identified in my systematic review in Chapter 2 (Kypridemos et al., 2018). My results also indicate that non-white participants, particularly Asian participants who were 41% more likely to develop type 2 diabetes compared to their white counterparts, are comparable to the results found in the NHS Diabetes Prevention Programme in Chapter 5.

Strengths

I used trial emulation, multiple imputation, propensity score matching, and Cox proportional hazard models to mitigate missing data, baseline differences and censorship. I also used linkage between the CPRD, HES and ONS, and as a result, this study benefited from using the largest primary care observational dataset that was further complemented through linkage. This enabled me to reduce the risk of misclassification, especially if there was an under-recording of chronic kidney disease, hypertension, heart disease, type 2 diabetes, or stroke incidence in any single dataset.

By comparing invitees against non-invitees of the NHS Health Check, I included those who either rejected or did-not-attend an NHS Health Check in the intervention group akin to an intention-to-treat analysis. This reduces biases related to health-seeking behaviour which could bias the results in either direction, firstly these individuals who attended could be considered healthier to begin with, but there may also be a higher rate of detection due to higher rates of contact with healthcare and diagnostic tools.

Limitations

One of the major challenges when evaluating the NHS Health Check is the large amounts of missing data, even more missing amounts of data compared to programmes such as the NHS Diabetes Prevention Programme. This is likely due to the eligibility criteria of the NHS Health Check which consists of “healthier” individuals, who are less likely to have covariates such as blood sugar levels measured. To mitigate this, I have conducted both full case analysis and multiple imputation, although these are both assuming that the data is not missing at random in such a population. Due to previous work demonstrating the CPRD’s representativeness, it is likely the data was to some extent missing at random. A recommendation for policy makers to tackle high levels of missingness is to incentivise general practitioners in

collecting socio-demographic and clinical data collected as part of the NHS Health Check as part of the Quality Outcome Framework. Not only would this improve data specifically for evaluation of the NHS Health Check, but this would reduce the “social determinants” of missing data and improve models currently used in general practice such as the QRisk2 score currently used as part of the NHS Health Check.

A further challenge with establishing participation in public health interventions in administrative datasets is the usage of their clinical codes, particularly at the introduction of the intervention. Unlike the NHS Diabetes Prevention Programme, the NHS Health Check is deployed in all general practises, meaning that I could not mitigate misclassification by using control participants from non-participating general practises. Therefore, I used a combination of READ codes and clinical covariate recording to establish NHS Health Check activity (including none) for each patient, rather than at the level of the practice which introduces more uncertainty around NHS Health Check activity when compared to NHS Diabetes Prevention Programme activity. Consequently, this could introduce two biases that impact the outcome in the opposite directions. Firstly, participants of the NHS Health Check are more likely (in the initial stage) to be detected for disease due to access to diagnostic testing, leading to an underestimate of the NHS Health Check if not controlled for. An alternative bias is that those who were assigned to the NHS Health Check group using a phenotypic recording based upon clinical covariate recording (as opposed to a READ code) were active health seeking participants which could bias the towards over-estimating the preventative effect of the NHS Health Check. Therefore, to reduce these biases, further clinical codes could be used to differentiate participants who are believed to be worried well in the NHS Health Check similarly to the ICD10 code Z71.1 which represents "Person with feared complaint in whom no diagnosis is made."

As I used the retrospective observational study design, certain baseline characteristics were significantly different even after matching, meaning that there could be unmeasured confounding variables. I attempted to tackle this by conducting multivariate analysis on top of propensity score matching. Chapters in the next section attempt to address limitations of this study such as the large amounts of missing data.

Related to baseline differences is the fact that despite being around for 10 years, not all eligible individuals were not invited to the NHS Health Check. This could result in residual confounding as there may have been (unmeasured) reasons for the propensity of not being invited; for example, if general practitioners did not send out invitations to those who they knew were healthy.

Despite the 10-year study period (January 2009 to January 2019), the distribution of the follow up periods were lower, with a mean of 965 days (2.6 years) of follow-up with a maximum of 3547 days (9.6 years) of follow-up in the NHS Health Check cohort. This likely reflects the limitation of administrative data, where the published average follow-up period in the CPRD is 1861 days (5.1 years) (Herrett et al., 2013).

Interpretation

Rates of type 2 diabetes in “healthy” adults between the ages of 40 to 74 are relatively low at 1.55% (95%CI: 1.50% to 1.60%) when compared to high-risk patients in Chapter 5. In the population of “healthy” adults, the evidence suggests that after “passing” the screening process of the NHS Health Check, gaining access to the appropriate treatment (including none) can reduce the risk of type 2 diabetes. With a 54% (HR: 0.46 [0.45 – 0.47]) 10-year risk reduction, my findings provide evidence that the NHS Health Check is effective in reducing middle-to-long term incidence of type 2 diabetes.

Despite demonstrating a reduction in type 2 diabetes, there is some evidence the NHS Health Check is not equally effective across sections of society. In the face of the NHS Health Check's aim to close healthcare inequities, future research and iterations to the NHS Health Check should seek to understand the barriers experienced by deprived and Asian patients who are at high risk of developing type 2 diabetes and were found to be 41% more likely to develop type 2 diabetes compared to their white counterparts in this study. Inequitable outcomes were also found for individuals experiencing deprivation.

Through the use of the target trial emulation framework, there were strict eligibility criteria leading to a total of 105,382 NHS Health Check participant individuals from an original 2,906,324 individuals. In Figure 6-3, this includes losing 100,000+ individuals due to data cleaning, primarily due to NHS Health Check activity occurring after an individual has been recorded to leave their general practice and is likely due to applying algorithms to estimate NHS Health Check activity. For example, delayed test results recorded after a patient has exited a general practice. Therefore, it is important for general practitioners and clinical coders to record NHS Health Check activity using dedicated clinical codes specifically made for the NHS Health Check. It is also important for NHS England/Digital to create and update clinical codes prior to the deployment of public health interventions for general practices to record activities appropriately.

Generalisability

Overall, my results demonstrate that access to an NHS Health Check reduces individual risk of type 2 diabetes in adults without prior cardiovascular disease [adjusted hazard ratio= 0.46, 95% CI:0.45 – 0.47] and produces results similar to other preventative programmes, such as the NHS Diabetes

Prevention Programme for adults without prior type 2 diabetes [adjusted hazard ratio=0.41;95%CI=0.38-0.44]. My previous chapters using an interrupted time series did not detect an effect of a population level reduction in type 2 diabetes. This could be because the incident rate of type 2 diabetes was low in the “healthy” population eligible for the NHS Health Check; 1.55% (95%CI: 1.50% to 1.60%) incidence up to 10-year study period. Therefore, even with 54% (HR: 0.46 [0.45 – 0.47]) reduction at the individual level against a control group, detecting changes at the population level could be difficult due to the low rates of type 2 diabetes in a “healthy” population.

In terms of social determinants of health, my chapter generalises with previous work demonstrating the barriers experienced by minority ethnic populations and groups experiencing deprivation who are disproportionately impacted by non-communicable diseases such as type 2 diabetes. Therefore, it could be reasonable for the NHS Health Check to target high risk individuals as previously suggested (Kypridemos et al., 2018).

Whilst the NHS Health Check produced a middle-to-long term reduction in the incidence of type 2 diabetes relative to a control group, its non-targeted approach may only benefit a small proportion of individuals. There is some evidence that a targeted approach is able to improve outcomes of high-risk individuals (i.e., those who need public health interventions the most); that is the NHS Diabetes Prevention programme had a 3-year incident rate of 5.96% (95%CI: 5.5% - 6.4%) compared to the NHS Health Check’s 10-year incident rate of 1.55% (95%CI: 1.50% to 1.60%) in terms of type 2 diabetes.

Therefore, future work could investigate the impact of the NHS Health Check on those at high risk of non-communicable, lifestyle modifiable cardiovascular diseases.

In terms of the economic impact of the NHS Health Check, my results show a 54% (HR: 0.46 [0.45 – 0.47]) relative risk reduction in type 2 diabetes incidence which is a significant result. However, this represents a 1.02%

absolute risk reduction (2.06% incidence rate in the control versus 1.04% in the matched intervention group) and potentially delays or prevents 1020 cases of type 2 diabetes per 100,000 adults between the ages of 40-74 without a prior case of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes. Cost effectiveness evaluations should be undertaken which consider the results in this chapter and its impact on preventing/delaying type 2 diabetes whilst not forgetting additional health economic analysis on early detection when compared to no NHS Health Check.

Chapter 7 - Using data science methods to reduce biases when using routinely collected healthcare data to evaluate the impact of the public health interventions on the incidence of type 2 diabetes

Abstract

Background and research gap: In previous chapters, I evaluated two public health interventions (the NHS Diabetes Prevention Programme and the NHS Health Check) using established epidemiological methods. However, many of these methods often perform best under certain assumptions, such as when data is normally distributed, when missingness is low and when there is a sufficient sample size. In Chapter 5, one challenge is the relatively small number of people who participated in the NHS Diabetes Prevention Programme in the CPRD dataset when compared to an externally validated dataset; this led to an imbalance between treated and untreated individuals. In Chapter 6, there was high missingness for blood glucose recordings, perhaps due to the “healthy” eligibility criteria for the NHS Health Check where such tests may have been unwarranted for “healthy” individuals. This “healthy” eligibility criteria can also skew the distribution of age as higher age is correlated with increased comorbidities. The research gaps this chapter aims to explore is the lack of analyses comparing different methods and data with different forms of bias used to examine the challenges in traditional epidemiological studies in the evaluation of the NHS Diabetes Prevention Programme and NHS Health Check. To understand this research gap, in this chapter I examine the suitability of data science approaches designed to address these limitations.

Methods:

In my previous chapters, the analysis involved four main components: identifying a target trial for emulation in observational data, imputing missing data, resampling data to reduce baseline differences and regression analysis

to understand the relationship between public health interventions and the incident of type 2 diabetes. In this chapter, each component is “replaced” with a data science alternative which aims to tackle the limitations of previously used approaches. In this chapter I use K-Nearest Neighbour and Multiple Imputation using Random Forests for imputing missing data, I use Synthetic Minority OverSampling Technique (SMOTE) for resampling data, and Survival Trees for regression modelling.

Results - NHS Diabetes Prevention Programme:

My K-Nearest Neighbours and Multiple Imputation using Random Forests implementations imputed similar baseline characteristics to an externally validated dataset that evaluated the NHS Diabetes Prevention Programme. Using SMOTE, I increased the cohort size from 11,025 (2205 intervention + 8820 propensity score-matched control) to 53,575 individuals (24,393 synthetically generated intervention patients + 29,182 control patients). Under a traditional Cox model, the significant covariates included NHS Diabetes Prevention referrals, ethnicity, and blood glucose measurements, whilst using survival trees, this was blood glucose measurements, NHS Diabetes Prevention referrals and body mass index. By using survival trees, I estimated that patients with baseline HbA_{1c} higher than 44 mmol/mol or a HbA_{1c} higher than 42 mmol/mol with a body mass index higher than 27.45 kg/m² are less likely to have newly recorded type 2 diabetes if they participated in the NHS Diabetes Prevention Programme.

Results - NHS Health Check:

Due to the large size of the NHS Health Check data set, my K's Nearest Neighbour implementation and, by extension, the Synthetic Minority Oversampling Technique algorithm could not run due to computational and memory constraints; whilst missing data was an issue with the NHS Health Check data, small sample sizes were less likely to be an issue. My Multiple imputation using random forests implementation produces a similar socio-demographic and clinical breakdown for all covariates when compared to traditional multiple imputation using chained equations except for ethnicity.

Under a traditional Cox model, the covariates which had the largest predicting ability included blood glucose measurements, gender, and NHS Health Check invitation status, whilst under survival trees, this was blood glucose measurements, body mass index and NHS Health Check invitation status. By using survival trees, I identified specific effects with patient subgroups e.g. In patients with a baseline HbA_{1c} higher than 35 mmol/mol and a BMI higher than 25 kg/m² access to the NHS Health Check reduces the risk of newly recorded type 2 diabetes compared to those without access to the NHS Health Check. For those who were invited to the NHS Health Check, patients who identified as non-White (including Asian, Black, or Mixed ethnic groups) with a baseline HbA_{1c} higher than 45 mmol/mol and body mass index higher than 25 kg/m² were most likely to have newly recorded type 2 diabetes compared to other ethnicity and body mass index combinations.

Discussion and Conclusions:

Data Science methods can be used to reduce weaknesses in established epidemiological techniques, although they may introduce further computational challenges and biases.

Introduction

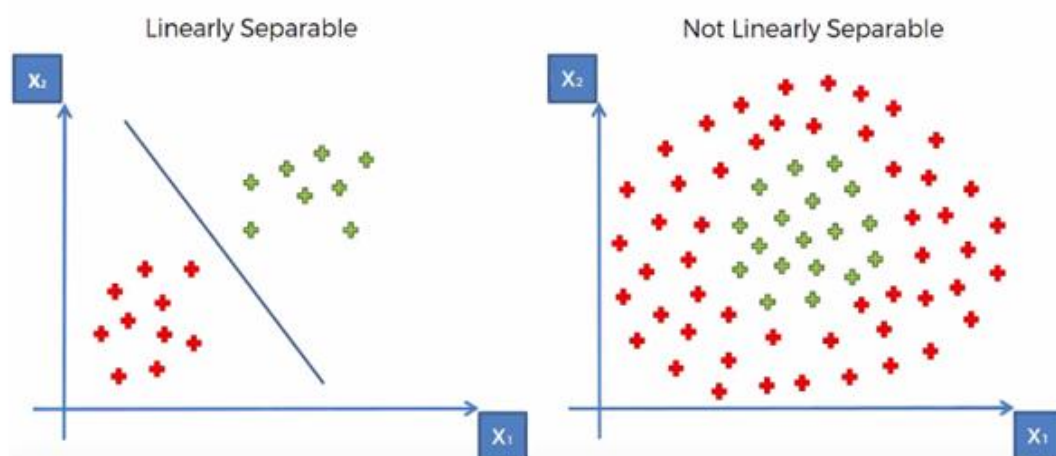
In previous chapters, I evaluated the impact of the NHS Health Check and the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes using established epidemiological methods such as target trial emulation, multiple imputation and propensity score matching. However, in these previous chapters, I identified limitations such as missing data that led to small sample sizes when undertaking a full case analysis. To overcome these issues in the earlier chapters, I used multiple imputation to estimate missing data (to avoid small sample sizes through a full case analysis and to reduce misrepresentation of those impacted by social determinants of data quality (O'Dowd, 2021)), propensity score matching to reduce baseline differences along an adjusted multivariable analysis to adjust for a variety of explanatory variables. In this chapter, I aim to introduce the limitations of traditional epidemiological methods and explore data science approaches to overcome these limitations. In Chapter 8 I will use the results of these data science approaches and triangulate them to results across all previous chapters to create an overall understanding of the impact of public health interventions on the incident of type 2 diabetes whilst taking into account the biases and strengths introduced by each study design.

Methods to reduce residuals when describing data

In Chapters 5 and 6, I found that a large amount of missing data made evaluating the NHS Health Check and NHS Diabetes Prevention Programme challenging. This was a particular problem for control participants as they did not attend their general practice leading to fewer covariates being recorded; this also impacted the recording of clinically relevant covariates such as HbA_{1c} and fasting plasma glucose as the NHS Health check was targeted at “healthy” individuals who may not have warranted a blood glucose test. This means that a large amount of data had to be imputed as a full-case analysis would have heavily reduced the sample sizes. In chapters 5 and 6, I applied Multiple Imputation using Chained Equations (MICE) as this is an established and emerging method in epidemiology as it generates multiple possible

values for a missing datapoint (Azur et al., 2011). However, the primary limitation of the default implementation of MICE is that it uses methods such as linear and logistic regression which perform best when the data is normally distributed, resulting in minimal residuals (Alexopoulos, 2010), that is the difference between the predicted outcome of a model and the actual outcome. When residuals are not minimised, linear regression may produce a less accurate result as linear regression predicts results that lie on the regression line. Logistic Regression on the other hand performs best when the data is linearly separable, that is when the data can be accurately separated using a “straight line” (Alexopoulos, 2010). See Figure 7-1 for an illustration of linear versus non-linearly separate data.

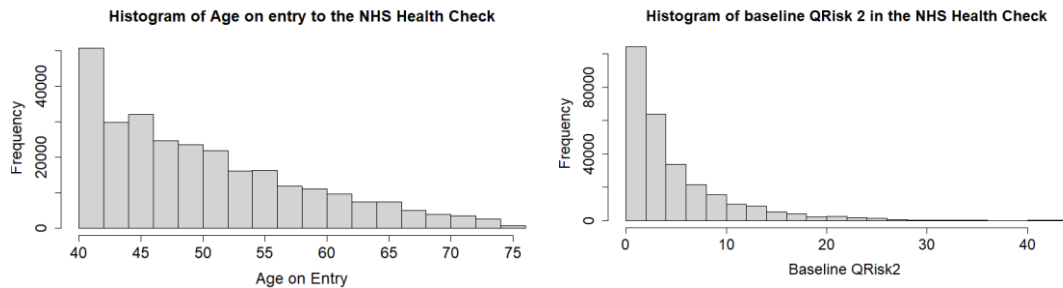
Figure 7-1: Illustration of linearly vs non-linearly separable datasets. On the left, we see a dataset that can be easily separated by a single straight line. On the right, applying the same method would produce a bad predictor. Taken from: <https://ankitnitjsr13.medium.com/math-behind-svm-kernel-trick-5a82aa04ab04>



However, the NHS Health Check and NHS Diabetes Prevention Programme data might not be normally distributed or linearly separable. For example, the distribution of age in the NHS Health Check is skewed towards the lower bound of the eligibility age and is likely due to the fact that younger individuals are less likely to have the comorbidities that eliminate individuals to be eligible for the NHS Health Check to begin with. Another example is that distribution of the Q-Risk score in the NHS Health Check could be impacted by the fact that the eligibility criteria is “healthy” individuals, thus creating a negative binomial distribution for the QRisk score. See Figure 7-2 for examples of the

distribution of age and QRisk 2 score of the NHS Health Check eligible population.

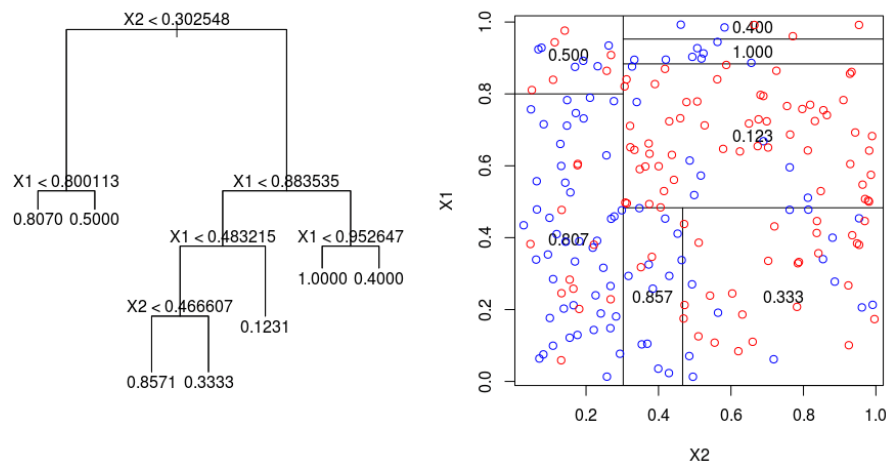
Figure 7-2: Distribution of age on entry in the NHS Health Check and QRisk2



In this chapter, I aim to apply data science methods that are less affected by assumptions in the distribution of the data with the goal of evaluating whether such methods improve the confidence of the imputed data. To evaluate the ability of these methods, I have compared the result of the imputation to that of an externally validated dataset. In this chapter, I have used the following methods: 'Multiple Imputation using Chained Equations with Random Forests' and K's Nearest Neighbors.

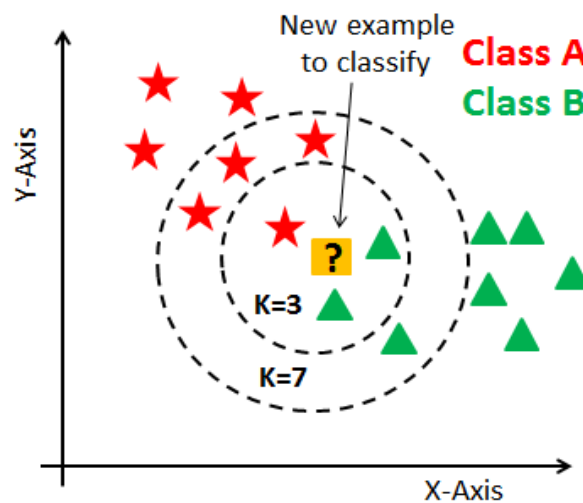
Multiple Imputation using Chained Equations with Random Forests is a variation of the established MICE algorithm for imputing, however the base model for prediction is the Random Forest instead of linear/logistic regression (Shah et al., 2014). Random Forests are based on combining models called "Decision Trees". Decision Trees avoid the non-linearly separable problem by repeatedly partitioning the data orthogonally to the various dimensions (see Figure 7-3) (Rokach and Maimon, 2008). This results in having multiple "bisectors" of the data, as compared to a single "bisector" in linear/logistic regression that aims to reduce residuals that minimises the error term across all dimensions (for example by minimising ordinary least squared). Splitting is often accomplished using the Gini Impurity score, a score used to calculate the probability of incorrectly classifying a single data point; when the probability of misclassifying is low for a subset of the data, a split is made.

Figure 7-3: Illustration of how decision trees classify data. To classify data, the decision tree repeatedly splits the data (orthogonal to the axes) to generate the decision “boundaries”. For example, the first node is at $X_2 < 0.302$, where the majority of items at this split are of class blue. Taken from: <https://bookdown.org/f100441618/bookdown-regresion/ml-tools.html>



K's Nearest Neighbors classifies and regresses data based upon the modal/mean data of the most similar data points (calculated using the smallest distance, often Euclidean or Manhattan) (Beretta and Santaniello, 2016). Conceptually, this imputes a missing datapoint by finding individuals who are similar in the non-missing measurements; K in “K’s nearest neighbour” denotes the number of neighbours to use to generate the missing datapoint and is often an odd number, usually 3 or 5. For classification, the majority class of the K’s neighbours is used. For regressing, the weighted (by closeness) mean of the closest neighbours are used. As K’s Nearest Neighbours is a non-explanatory model, it is often used for tasks such as imputing missing data and is not used to estimate the impact of an exposure on an outcome as it does not create an interpretable model. See Figure 7-4 for a graphical representation of K’s nearest neighbour.

Figure 7-4: Graphical representation of K's nearest neighbour. When $K = 3$, two of the three closest objects are of class B; leading the algorithm to select class B for the object labelled with the question mark. When $K = 7$, four of the seven objects are of class A, leading the algorithm to select class A for the object labelled with the question mark. Taken from: <https://github.com/Robots-Vision/knn-examples>



Methods for resampling patients in observational data

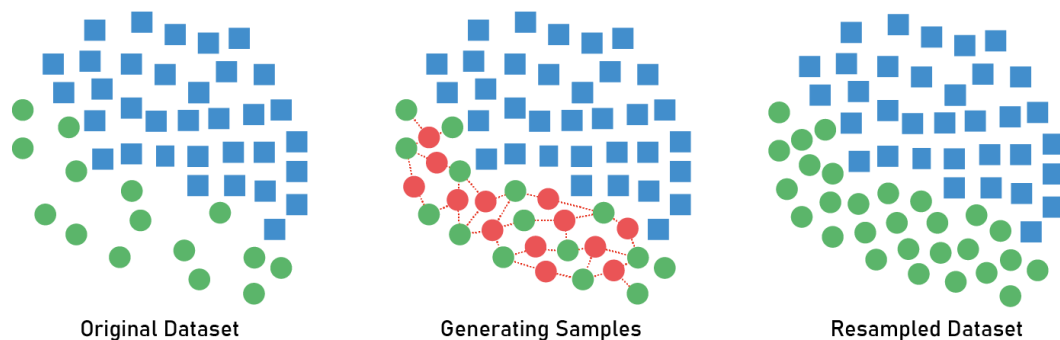
In chapters 5 and 6 I used propensity score matching to reduce differences in baseline covariates with the aim of reducing confounding by emulating the effect of randomisation in a randomised controlled trial (Austin, 2011). The limitation of this was that propensity score matching achieves this by selecting control patients (more specifically, patients from the larger group) whose baseline covariates were similar to those of the intervention patients (or generally, the smaller group). Consequently, this discarded patients whose baseline covariates were less likely to be similar to the intervention patients, causing a reduction in sample size. This is particularly true of the NHS Diabetes Prevention Programme dataset which only had 2,205 intervention patients in it resulting in a reduction of 20,362 control patients from 29,182 unmatched control patients down to 8,820 matched control patients. Whilst an unmatched analysis could solve the issue of reducing sample sizes, when the

imbalance between intervention and control is too high, algorithms used to predict can preserve high performance (e.g. accuracy) by selecting the majority group irrespective of any associations (Dubey et al., 2014). For example, given a dataset of 100 items, 90 of class positive, and 10 of class negative, by guessing positive for all 100 items, the prediction is correct 90% of the time.

In an attempt to address the limitation of small sample sizes, I aim to apply the synthetic minority over-sampling technique (SMOTE) as a sensitivity analysis to the NHS Diabetes Prevention Programme and NHS Health Check dataset. I have done this because SMOTE has the ability to preserve or improve sample sizes by generating plausible synthetic patients (Chawla et al., 2002). SMOTE repeatedly adds synthetic samples to the intervention group by sampling the "spaces" between K (usually 3 or 5) intervention samples and generating a sample-based upon the mean of these samples until a specific ratio condition is met between the intervention and control groups. Therefore, by using SMOTE, I aim to increase the number of 2,205 NHS Diabetes Prevention Programme intervention patients to match the 29,182 control patients who were eligible for the NHS Diabetes Prevention Programme but were not invited. As SMOTE does not solve the issue of baseline differences, multivariable regression methods must be applied in conjunction with SMOTE. See Figure 7-5 for a graphical example of SMOTE.

Figure 7-5: Graphical explanation of SMOTE. In this example, in the original dataset, the green class has substantially fewer readings compared to the blue class. To generate the samples, a subset of the green classes is selected, and a “synthetic” object is generated by creating the average of the selected subset. Taken from: <https://medium.com/analytics-vidhya/bank-data-smote-b5cb01a5e0a2>

Synthetic Minority Oversampling Technique



Data Science Methods for estimating the effect of an exposure on and outcome

In Chapters 5 and 6, Cox proportional hazards were used with observational data emulating a target trial to estimate the effectiveness of the NHS Diabetes Prevention Programme and NHS Health Check in preventing incident cases of type 2 diabetes. One major limitation of the Cox proportional hazard model is that it performs best when data is normally distributed as it is based upon the general linear models. Therefore, in this chapter, I applied apply survival tree analysis; in survival tree analysis, the goal is to model the time to an event using tree-based algorithms that are less reliant on the normal distribution of the data (see Chapter 7 Figure 2).

Another weakness of (semi)-parametric linear models (such as Cox Proportional hazards) is that they present the effect of an exposure on average when adjusted for a variety of covariates. Therefore, it does not consider the combination of subgroups where the NHS Diabetes Prevention Programme and NHS Health Check is a good predictor of the incidence of type 2 diabetes. A specific example of this problem can be demonstrated by

posing hypothetical questions such as “Does the NHS Health Check prevent the incidence of type 2 diabetes in males between the ages of 40-41, with a low BMI who is not deprived? “. Such information is important as it may allow public health decision-makers to identify subpopulations where the NHS Diabetes Prevention Programme or NHS Health Check are effective. In my systematic review in Chapter 2, a few studies investigate how targeted recruitment could improve the NHS Health Check, although these were analysing single dimensions such as deprivation only (Kypridemos et al., 2018, 2016). Whilst the primary goal using survival trees in this chapter is to use models that do not assume the distribution of data, this chapter will also use survival trees to explore the interactions between exposures, covariates and the incidence of type 2 diabetes. Such information could be important due to the relatively low rates of type 2 diabetes in the NHS Health Checks population of “healthy” individuals and to understand whether either programme performs differently in individuals from different ethnic backgrounds. Prior studies in translational medicine have used this technique before to understand the important interactions in understanding the incidence of chronic kidney disease (Ramezankhani et al., 2017).

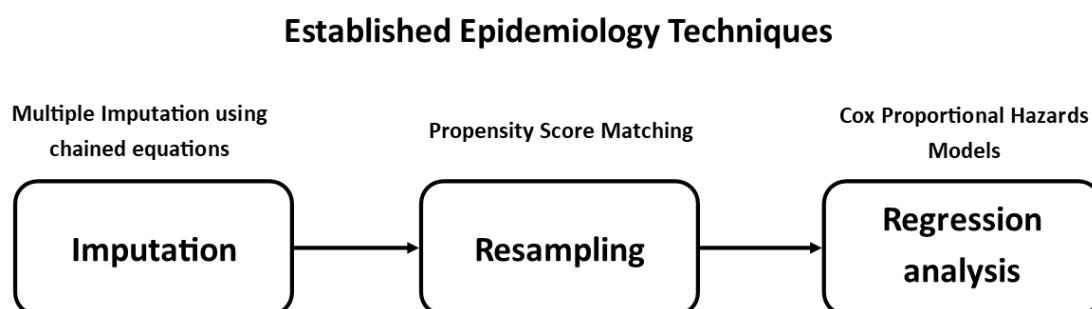
Applying data science methods to evaluate the impact of public health interventions on the incidence of type 2 diabetes

In previous chapters, after using target trial emulation to wrangle my data to replicate the data collected in a prospective trial, I imputed my data, resampled my cohort and then conducted regression analysis using MICE,

propensity score matching and Cox Proportional Hazard models (Chapter 7 Figure 6).

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Figure 7-6: Analytical pipeline used in previous chapters.



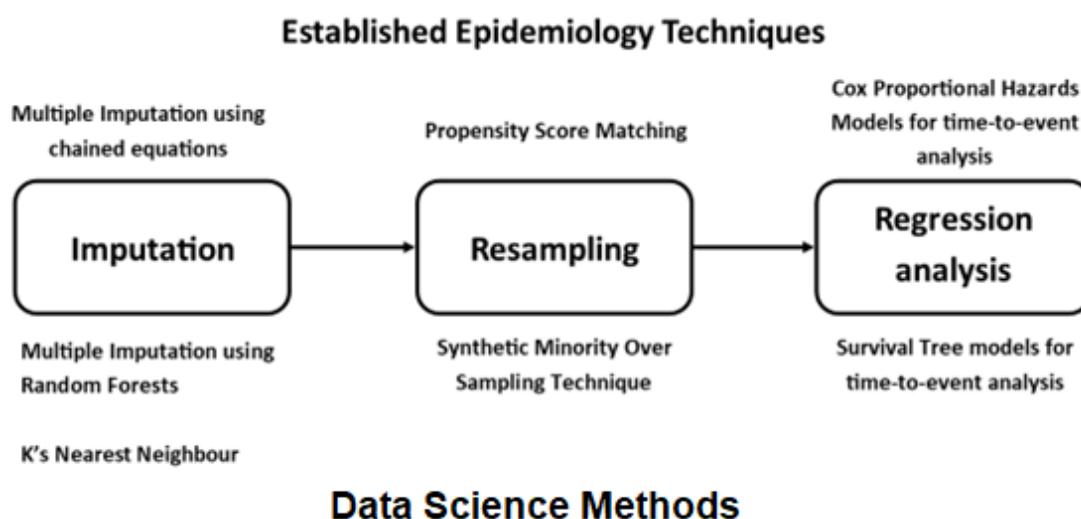
In this chapter, to tackle the missingness of covariates in the NHS Health Check and Diabetes Prevention Programme data, I applied multiple imputation using chained equations with random forests and K's Nearest Neighbours and compare the imputed datasets against those created in Chapter 5 and 6 using traditional multiple imputation using chained equations (based on linear/logistic regression). To establish the capabilities of the imputation methods, I will then compare each imputed dataset's cohort breakdown to an externally validated cohort breakdown for the NHS Diabetes Prevention Programme (Valabhji et al., 2020).

After imputation, I resampled the patients by applying the Synthetic Minority Over Sampling Technique to the NHS Health Check and Diabetes Prevention Programme data. I then compare the cohort's covariate distribution to those established in Chapters 5 and 6 which were produced using propensity score matching.

After matching and resampling, to estimate the effect of public health interventions on incidence of type 2 diabetes, I applied survival analysis using decision trees to the NHS Health Check and Diabetes Prevention Programme data and compare this to the results generated in chapters 5 and 6 which were generated using multivariable Cox proportional hazard models. See

Figure 7-7 for a graphical representation of the analytical pipeline using established epidemiological and data science techniques.

Figure 7-7: Comparison of Established Epidemiological Technique and Data Science Techniques in the public health evaluation “pipeline”.



Therefore, the aim of this chapter is using data science methods with observational data as sensitivity analyses to my previous chapters to estimate the impact of the NHS Health Check and NHS Diabetes Prevention programme on the incidence of type 2 diabetes; this chapter also aims to understand the strengths and weaknesses of these data science methods in such evaluations of a public health intervention on and outcome. The objectives for this chapter include:

- Imputing the missing NHS Diabetes Prevention Programme data using multiple imputation chained equations with random forest imputation and KNN imputation and comparing a covariate breakdown of the datasets to externally validated datasets.
- Comparing the cohorts generated using propensity score matching and synthetic minority over-sampling technique to externally validated datasets for the NHS Diabetes Prevention Programme
- Using decision trees to conduct survival analysis and comparing the results of the survival tree to those of the covariates generated by Cox

Proportional hazard models for both the NHS Diabetes Prevention Programme and the NHS Health Check

Methods

To understand whether data science methods can be used to tackle epidemiological questions, I replicated the study design, data resources, study population, primary outcomes, interventions, control populations, sample sizes from Chapter 5 for the NHS Diabetes Prevention Programme and Chapter 6 for the NHS Health Check.

To recap in brief, the CPRD dataset (linked to HES and ONS) was used to conduct two retrospective observational cohort studies using the target trial emulation framework. For each programme, the phenotyping algorithms in Chapter 4 were applied to define eligible populations (i.e., those of age, without prior disease) who were then followed up until the first recording of type 2 diabetes.

Analysis

I completed all analyses using R studio software and reported according to the REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement. To account for censorship and the binary outcome of the incident of type 2 diabetes, a time-to-event analysis was conducted. For traditional epidemiological models, a multivariable Cox proportional hazards model was used, whilst for data science methods, decision trees to create multivariable survival trees were explored. The entry time and follow-up period are the same in Chapter 5 for the NHS Diabetes Prevention Programme, and Chapter 6 for the NHS Health Check.

Covariates

To keep the analyses consistent with Chapters 5 and 6, the same covariates are used in this chapter. In brief, to evaluate the NHS Health Check/Diabetes Prevention impact on patients from a variety of backgrounds, demographics, socio-economic and clinically relevant covariates were used.

Mitigating limitations

To reduce biases due to the observational study design, I identified and addressed such biases through careful study design using traditional epidemiological techniques and modern data science techniques. Based upon weaknesses of observational studies (Hammer, Prel & Blettner, 2009), I concentrated on tackling missing data and imbalance data.

Missing data

In the NHS Health Check evaluation missingness is high and could be driven by the “healthy” eligibility criteria where blood glucose measurements may not be warranted.

To tackle missing data using emerging data science techniques, two methods were used in contrast to traditional epidemiological methods. The first method used was K's Nearest Neighbours, which imputes using missing data based upon the closest record(s) which contain the value to be imputed. In this chapter, 5 neighbours were used to impute missing data with higher weighting being given to "closer" neighbours as measured using the Euclidean distance (Beretta and Santaniello, 2016). The second data science method used for imputation was a variation of MICE using a multiple of decision trees, each dealing with a single covariate, known as random forests. A full description of MICE-RF can be found in (Shah et al., 2014).

The following covariates were used in all imputation models, all of which were established using the closest recording before each individual's (estimated) entry date within 5-years: age at the beginning of follow up, gender, ethnicity, index of multiple deprivation, body mass index, glycated haemoglobin, fasting glucose plasma, diastolic blood pressure, systolic blood pressure, serum creatinine, alcohol status, smoking status and disease status (i.e. a type 2 diabetes diagnosis). For MICE-RF ten alternative datasets were generated whilst K's Nearest Neighbors only produced one dataset. After imputation, resampling was conducted on the cohort prior to conducting a multivariable time-to-event analysis. For imputation models which produced multiple alternative datasets (MICE and MICE-RF), Cox proportional hazards were pooled using a fixed-effect meta-analysis.

Resampling comparison groups

One primary bias that could occur in observational data is imbalance data; where one group has a significantly higher proportion of data points in one group compared to others. This occurred in the NHS Diabetes Prevention Programme data due to the gradual introduction of the NHS Diabetes Prevention Programme to general practices in England. To tackle imbalance data using data science methods, this chapter uses SMOTE to generate synthetic but realistic data driven instances of the NHS Diabetes Prevention programme participants to match the eligible but non-invitees of the NHS Diabetes Prevention Programme. This reduces the biases introduced in regression analysis where models are likely to predict for the majority class (Dubey et al., 2014). Therefore, the use of SMOTE in this chapter is to test the robustness of the results in Chapter 5 and Chapter 6 which was conducted using propensity score matching and Cox Proportional Hazards models.

Ethics and approvals

Approval for this study was granted as part of an application to the CPRD's Independent Scientific Advisory Committee: protocol 18_179. Data extractions were completed by the CALIBER team under NHS research ethics approval (09/H0810/16) and ECC approval (ECC 2-06(b)/2009 CALIBER dataset).

Information governance

All analyses were completed on the UCL data safe-haven. The pseudonymised dataset will be securely destroyed after four years in the first occurrence in line with the latest Independent Scientific Advisory Committee's guidance. In line with CPRD policy, I did not report any data with a cell containing <5 events and where necessary I will protect these counts with secondary suppression.

Results – NHS Diabetes Prevention Programme

Numbers Analysed

In total, I had 31,387 individuals eligible for the NHS Diabetes Prevention

programme, of whom, 2,205 were referred to the NHS Diabetes Prevention Programme; whilst 29,182 were not. See Chapter 5 for details of the cohort derivation.

Population and Characteristics

Of the 2,205 NHS Diabetes Prevention Programme referred individuals, 172 provided data for all variables, and 1,486 of the 29,182 control individuals. See Chapter 5 for more details of the population and characteristics.

Comparing Imputed Cohorts from MICE, MICE-RF and K's Nearest Neighbor Imputation

When imputing using MICE, MICE-RF and KNN, all algorithms produced similar values and are comparable to the established NHS Diabetes Prevention Programme population (Valabhji et al., 2020). All algorithms produced cohorts with a higher proportion of those aged 75 or over when compared to Valabhji et al., (25% versus Valabhji et al., 2020's 19%). In terms of ethnicity, all algorithms produced a higher proportion of Asian patients, with MICE-RF producing the closest result compared to Valabhji et al., 2020. All methods also produced a higher proportion of White patients, with MICE producing the closest proportion compared to Valabhji et al., 2020. Whilst all algorithms produced a higher proportion of deprived patients, MICE-RF produced the closest proportion for all deprivation groups when compared to Valabhji et al., 2020. For weight-related measures (mean weight and BMI), MICE produced the closest results compared to Valabhji et al., 2020. For baseline HbA_{1c}, MICE-RF produced the closest mean HbA_{1c} compared to Valabhji et al., 2020. See Table 7-1 for a breakdown of the imputed cohort breakdown and comparison.

Table 7-1: Comparison of imputation models against an externally established dataset. Bold highlights represent the closest value to Valibhji et al., 2020's dataset; this was calculated using the values with the lowest difference with Valibhji et al., 2020's values.

	Valabhji et al., 2020				MICE		MICE –RF		KNN	
	Referred to NHS DPP		Referred and attended an initial assessment		Referred to NHS DPP		Referred to NHS DPP		Referred to NHS DPP	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Overall	324,699	100	152,294	100	2,205	100	2,205	100	2192	100
Sex										
Male	147,890	46	68,780	45	1,066	48	1,066	48	1052	48
Female	172,252	53	82,637	54	1,139	52	1,139	52	1140	52
Age band (years)										
<40	17,797	5	5,818	4	88	4	88	4	88	4
40–44	15,811	5	5,593	4	110	5	88	4	88	4
45–49	22,604	7	8,449	6	132	6	154	7	153	7
50–54	32,021	10	12,735	8	176	8	132	6	132	6
55–59	37,938	12	16,647	11	243	11	265	12	285	13
60–64	40,880	13	19,656	13	265	12	221	10	219	10
65–69	46,787	14	25,481	17	287	13	353	16	351	16
70–74	48,106	15	26,616	17	353	16	353	16	329	15
≥75	62,641	19	31,281	21	551	25	551	25	548	25
Unknown	114	0	18	0		—		—		—
Mean age	62	—	64	—	65	—	65	—	65	—
SD age	13.4	—	12.4	—	13.7	—	13.7	—	13.7	—
Ethnicity										
Asian	—	—	17,364	11	397	18	331	15	395	18
Black	—	—	9,567	6	132	6	110	5	88	4
Mixed	—	—	2,539	2	22	1	22	1	22	1
Other	—	—	1,432	1	66	3	44	2	44	2

	Valabhji et al., 2020				MICE		MICE –RF		KNN	
	Referred to NHS DPP		Referred and attended an initial assessment		Referred to NHS DPP		Referred to NHS DPP		Referred to NHS DPP	
White	—	—	105,315	69	1588	72	1698	77	1644	75
Unknown	—	—	16,077	11	—	—	—	—	—	—
Deprivation quintile										
IMD 1 (most deprived)	68,616	21	29,388	19	706	32	639	29	701	32
IMD 2	65,469	20	29,604	19	485	22	485	22	570	26
IMD 3	62,733	19	30,141	20	441	20	419	19	373	17
IMD 4	61,798	19	30,446	20	331	15	353	16	329	15
IMD 5 (least deprived)	65,108	20	32,247	21	243	11	309	14	219	10
BMI grouping at I.A.										
Underweight/healthy	—	—	22,953	15	507	23	529	24	504	23
Overweight	—	—	50,850	33	772	35	772	35	877	40
Obese	—	—	67,390	44	926	42	904	41	811	37
Unknown	—	—	11,101	7	—	—	—	—	—	—
Mean (kg/m ²)	—	—	30.3	—	29.59	—	29.53	—	29.38	—
S.D.	—	—	6.1	—	6.4	—	6.3	—	6.1	—
Mean HbA _{1c}	—	—	41.8*	—	43.2	—	43.0	—	43.1	—

Sampling Techniques Compared

After applying imputation (MICE), two techniques were applied to resample the data to avoid the imbalance between the 2,205 intervention patients versus 29,182 control patients. After applying propensity score matching on the control group, 8,820 patients were selected, and baseline covariates were converging towards the intervention group. After applying the synthetic minority oversampling technique to the intervention group, 22,188 synthetic patients were generated, however, baseline covariates were less likely to mirror the unmatched control counterparts. See Table 7-2 for a breakdown and comparison of MICE + Propensity Score Matching and MICE + SMOTE.

Table 7-2: Comparison of Multiple Imputation using Chained Equations + Resampling techniques, broken down by healthcare and socio-demographic covariates.

	MICE			
Covariate	Intervention	SMOTE Intervention	Unmatched Control	Propensity Score Matched Control
Total	2,205	24,393	29,182	8,820
Gender				
Male	1,065 (48.32%)	11870 (48.66%)	15,073 (51.65%)	1,066 (48.35%)
Female	1,140 (51.68%)	12523 (51.34%)	14,109 (48.35%)	1,139 (51.65%)
Mean Age	65.19 [65.01,65.38]	65.24 [65.20,65.31]	64.02 [63.96, 64.08]	65.34 [65.25, 65.44]
Mean BMI	29.59 [29.51, 29.67]	29.48 [29.46,29.50]	29.53 [29.50,29.55]	29.63 [29.58, 29.66]
Mean HbA _{1c}	43 [43,43]	43 [43,43]	41 [41, 41]	43 [43, 43]
Mean FPG	5.6 [5.6, 5.6]	5.6 [5.6,5.6]	5.6[5.6, 5.6]	5.6 [5.6, 5.6]
Ethnicity				

	MICE			
Covariate	Intervention	SMOTE Intervention	Unmatched Control	Propensity Score Matched Control
White	1,591 (72.17%)	16,153 (66.22%)	23,894 (81.88%)	6,571 (74.50%)
Black	131 (5.96%)	1,817 (7.45%)	1,833 (6.28%)	561 (6.36%)
Asian	393 (18.05%)	2,996 (12.16%)	2,629 (9.01%)	1,363 (15.45%)
Mixed	24 (1.11%)	1,515 (6.21%)	344 (1.18%)	101 (1.15%)
Other	60 (2.73%)	1,942 (7.96%)	482 (1.65%)	224 (2.54%)
Index of Multiple Deprivation				
(Most Deprived)1	698 (31.64%)	6,139 (25.17%)	5,831 (19.98%)	2,430 (27.55%)
2	495 (22.44%)	6,889 (28.24%)	5,886 (20.17%)	2,104 (23.86%)
3	436 (19.76%)	5,874 (24.08%)	6,674 (22.87%)	1,976 (22.40%)
4	331 (15.03%)	3,813 (15.63%)	6,166 (21.13%)	1,456 (16.51%)
(Least Deprived)5	245 (11.13%)	1,678 (6.88%)	4,625 (15.85%)	854 (9.68%)
Drinking Status				
Non-Drinker	1,323 (60.01%)	12,518 (51.32%)	12,507 (42.86%)	4,974 (56.39%)
Ex Drinker	117 (5.29%)	5,184 (21.25%)	2,539 (8.70%)	736 (8.35%)

	MICE			
Covariate	Intervention	SMOTE Intervention	Unmatched Control	Propensity Score Matched Control
Occasional Drinker	665 (30.16%)	5,881 (24.11%)	11,962 (40.99%)	2,784 (31.56%)
Current Drinker	73 (3.30%)	683 (2.8%)	1,331 (4.56%)	224 (2.54%)
Excess Drinker	26 (1.19%)	122 (0.5%)	797 (2.73%)	98 (1.11%)
Binge Drinker	NA	5 (0.02%)	47 (0.16%)	NA
Smoking Status				
Non-Smoker	1,152 (52.24%)	11,426 (46.84%)	14,512 (49.73%)	4,320 (48.98%)
Ex-Smoker	577 (26.17%)	7,296 (29.91%)	9,324 (31.95%)	2,767 (31.37%)
Ex or current smoker	8 (0.35%)	2,412 (9.89%)	76 (0.26%)	25 (0.28%)
Current Smoker	468 (21.24%)	3259 (13.36%)	5,270 (18.06%)	1,708 (19.37%)

Outcomes and Estimations

Multiple imputation using Chained Equations + Synthetic Minority Over Sampling Technique

Of 53,574 individuals (24,393 synthetically generated intervention patients + 29,182 control patients) who were identified after imputation and oversampling the intervention group, 4.13% (n = 2,216) developed type 2 diabetes within 2.5 years of initiating the NHS Diabetes Prevention Programme. Of the 24,393 intervention patients, 3.99% (n = 976) developed diabetes within two and a half years of initiating the NHS Diabetes Prevention Programme. Of the 29,182 control (matched) patients, 4.25% (n = 1240) developed diabetes by two and a half years of initiating the NHS Diabetes Prevention Programme. Between the imputed control group and the imputed oversampled intervention group, there was an overlap in the 95% confidence interval for the recording of type 2 diabetes during follow-up, 4.02%-4.49% versus 3.76%-4.25% respectively. See Table 7-3 for the unadjusted incidence of type 2 diabetes in the imputed and synthetically generated cohort.

Table 7-3: Unadjusted type 2 diabetes incidence rates for control and intervention groups between June 2016 and January 2019. Results are for MICE + Synthetic Minority Sampling Technique

		Imputed Control (N = 29,182)	Imputed Oversampled Intervention (N = 24,393)	Total (N = 53,574)
Outcome	No Type 2 Diabetes during follow up	27,942 95.75% 95%CI: 95.51 – 95.98	23,417 96.01% 95%CI: 95.75 – 96.24	51,359 95.86% 95%CI: 95.69 – 96.03
	Type 2 Diabetes during follow up	1,240 4.25% 95%CI: 4.02 – 4.49	976 3.99% 95%CI: 3.76 – 4.25	2,216 4.13% 95%CI: 3.97 – 4.31

Adjusted Results

Cox Proportional Hazards

After imputation, propensity score matching and adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, IMD, baseline alcohol intake, baseline smoking consumption, baseline BMI, and age on entry, the hazard ratio for a referral to the NHS Diabetes Prevention Programme demonstrated that referred patients were 59% (H.R.: 0.41 [95% CI: 0.38 – 0.44]) less likely to develop type 2 diabetes compared to the imputed and matched control group. See Chapter 5 for further details.

When substituting propensity score matching for synthetic minority oversampling, the adjusted hazard ratio for the primary exposure, that access to the NHS Diabetes Prevention Programme stayed within margin (HR: 0.43 [95% CI: 0.41 – 0.44]). The only covariates whose 95% confidence interval were not overlapping when comparing SMOTE to propensity score matching were baseline smoking status and index of multiple deprivation.

Results are presented as propensity score matching vs SMOTE to demonstrate the difference in the regression results when using differential resampling methods. See Table 7-4 for a full breakdown of the hazard ratios for each covariate.

Table 7-4: Covariates and their adjusted hazard ratio. H.R. = 1.00 (i.e., no effect). $HR < 1$ = protective to type 2 diabetes recording during follow-up. $HR > 1$ = more likely to have newly recorded type 2 diabetes during follow-up. See Table 7.2 for cohort breakdown.

Covariate	Adjusted Hazard Ratio for MICE + Propensity Score Matching [95% CI:]	Adjusted Hazard Ratio for MICE + Synthetic Minority Over Sampling [95% CI:]
NHS DPP referral		
Not referred (reference)	1.00 [Ref]	1.00 [Ref]
Referred	0.41 [0.38, 0.44]	0.43 [0.41 – 0.44]
Ethnicity		
Asian (ref)	1.00 [Ref]	1.00 [Ref]
Other	0.50 [0.44 – 0.72]	0.54 [0.51 – 0.59]
White	0.56 [0.52 – 0.60]	0.59 [0.56 – 0.62]
Mixed	0.57 [0.44 – 0.72]	0.74 [0.68 – 0.76]
Black	0.68 [0.62 – 0.76]	0.72 [0.67 – 0.76]
Blood Glucose measures		
Fasting Plasma Glucose*	1.38 [1.32 – 1.45]	1.34 [1.30 – 1.38]
Baseline HbA _{1c} *	1.33 [1.31 – 1.35]	1.31 [1.29 – 1.31]
Gender		
Male (reference)	1.00 [Ref]	1.00 [Ref]
Female	0.82 [0.78 – 0.87]	0.76 [0.73 – 0.78]
Baseline smoking status	1.02 [1.00 – 1.04]	0.96 [0.95 – 0.97]
Index of Multiple Deprivation	1.04 [1.02 – 1.06]	1.08 [1.07 – 1.09]
Baseline Body Mass Index	1.02 [1.02 – 1.02]	1.02 [1.01 – 1.02]
Baseline alcohol status	0.99 [0.97 – 1.02]	0.97 [0.96 – 0.97]
Age on entry	1.00 [1.00 – 1.00]	1.00 [1.00 – 1.00]

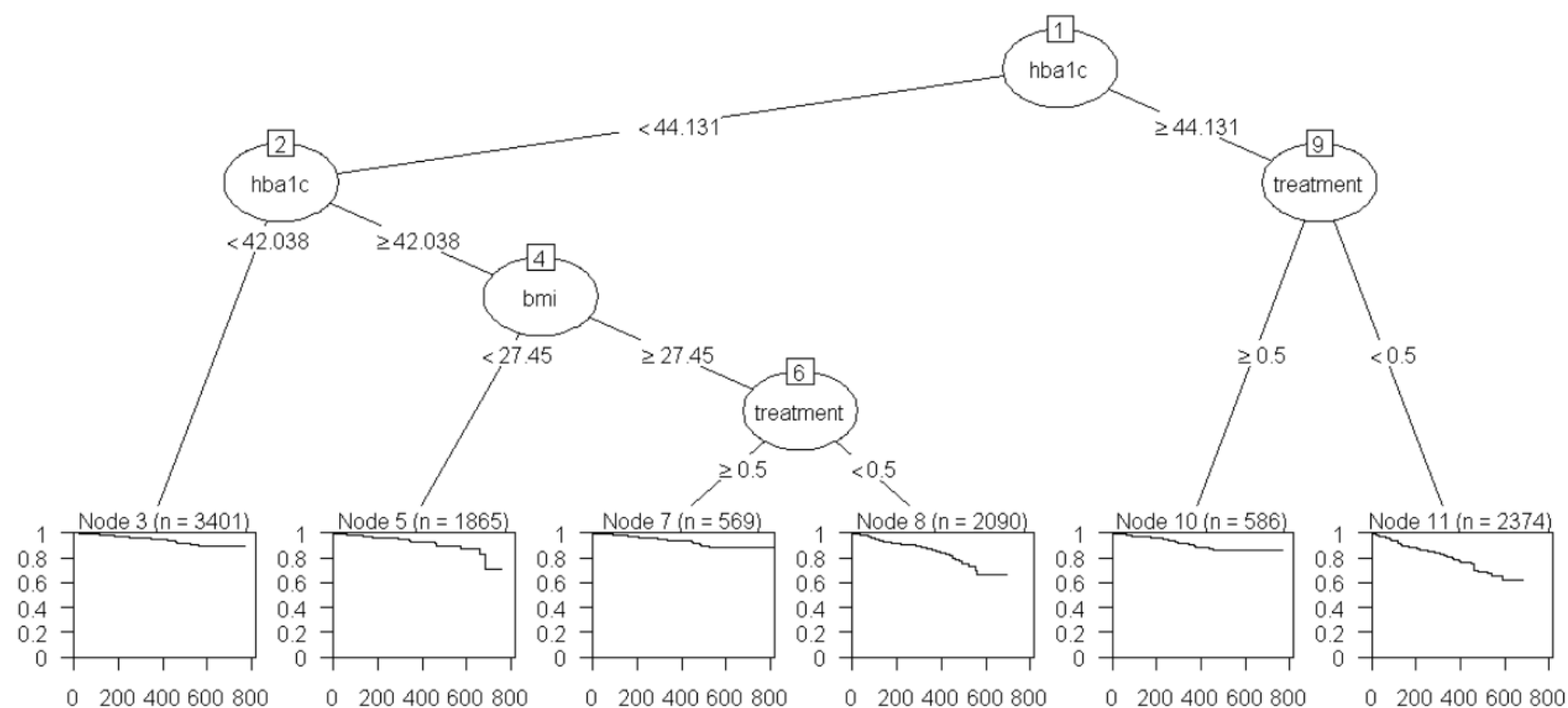
Data Science multivariate subgroup analysis

When predicting the time-to-event for type 2 diabetes with NHS Diabetes Prevention Programme invitation status and adjusting for ethnicity, gender, baseline HbA_{1c}, IMD, baseline alcohol intake, baseline smoking consumption, baseline BMI, and age on entry, the survival tree selected baseline HbA_{1c}, NHS Diabetes Prevention Programme invitation and baseline BMI as the most prominent predictors of type 2 diabetes status within the study period; this is because gender, IMD, baseline alcohol intake, baseline smoking consumption and age on entry did not have an effect on the risk of misclassification.

The two scenarios where the NHS Diabetes Prevention Programme demonstrate an impact is where the baseline HbA_{1c} is more than 44.13 mmol/mol (node 9 in Figure 7-8) or when the baseline HbA_{1c} is more than 42.038 mmol/mol and the baseline BMI is more than 27.45 kg/m² (node 6 in figure 7-8).

See Figure 7-8 for the multivariate subgroup Kaplan-Meier curve.

Figure 7-8: Survival Tree Diagram to evaluate the impact of the NHS Diabetes Prevention Programme on the incidence of Type 2 diabetes recording within the 2.5 years study period. In each node the x-axis represents the follow-up time, whilst the y-axis represents the proportion risk free.



Results- NHS Health Check

Please refer to Chapter 6 for the numbers analysed and the population and characteristics.

Comparing various imputation and matching methods

Due to the large size of the cohort, K's Nearest Neighbour imputation did not run on the NHS Health Check Cohort when using the same computer (UCL Data Safe Haven's configuration as of 2019) set up as the traditional epidemiology study; this is because K's Nearest Neighbour's simultaneously compares all individuals with all other individuals in the dataset; the warning produced stated memory limitations. In Chapter 5, this consisted of a possible 293,606 individuals (105,382 intervention participants + 188,224 unmatched participants); therefore, for each individual, they are compared against 293,605 individuals to find 5 nearest individuals to impute data from. This would create $293,606^2$ comparison operations and 293606 versions of the data to compare against (one dataset per individual). As of December 2023, the UCL Data Safe Haven's virtual machine instance specifications consist of an 8-core Intel Xeon 6240 central processing unit with 64GB of RAM; a similar error was produced in 2023 as in 2019. As SMOTE uses KNN as part of its process, this did not run either due to the size of the NHS Health Check cohort.

As part of the inclusion criteria removes patients who have type 2 diabetes, hypertension, chronic kidney disease on entry by imputed covariate reading (i.e., by imputed baseline HbA_{1c}, fasting plasma glucose, serum creatinine or blood pressure), MICE-RF generated more intervention patients at 110,474 compared to traditional MICE's 105,382 intervention patients. This is similar to the unmatched control group 'here MICE-RF generated more control patients at 213,741 patients instead of MICE's 188,224 control patients. When broken down by covariates, MICE-RF produced similar results to MICE for all covariates except for ethnicity. MICE-RF produces less patients for all ethnicities proportionally except for the "other ethnicity". See Table 7-5 for a covariate breakdown of the cohort.

Table 7-5: Distribution of sociodemographic and clinical of the cohort by imputation status, matching status, trial-arm and covariates. Values in square brackets denote 95% confidence interval.

	Multiple Imputation using Chained Equations			Multiple Imputation using Chained Equations with Random Forests		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
Total	n = 105,382	n = 188, 224	n = 105,382	n = 110,474	n = 213,741	n = 110,474
Gender						
Male	59.76% (n = 62976)	58.29% (n = 109716)	59.72% (n = 62934)	58.82% (n = 64981)	60.04% (n = 128330)	59.76% (66019)
Female	40.24% (n = 42406)	41.71% (n = 78508)	40.28% (n = 42448)	41.18% (n = 45593)	39.96% (n = 85441)	40.24% (44455)
Mean Age [95% CI]	50.44 [50.42 – 50.46]	50.71 [50.69 – 50.72]	50.41 [50.39 – 50.43]	50.44 [50.43 – 50.45]	50.66	50.44 [50.44 – 50.45]
Mean BMI [95% CI]	26.65 [26.61 – 26.69]	26.55 [26.52 – 26.58]	26.65 [26.61 – 26.69]	26.55 [26.54 – 26.56]	26.68 [26.67 -26.69]	26.66 [26.64 – 26.67]
Mean HbA _{1c} [95% CI]	36.7 [36.72 – 36.74]	36.93 [36.92 – 36.93]	36.7 [36.72 – 36.73]	36.85 [36.85 – 36.85]	36.61 [36.70 – 36.71]	36.68 [36.68 – 36.69]
Mean FPG	4.94	4.97	4.94	4.95	4.93	4.93

	Multiple Imputation using Chained Equations			Multiple Imputation using Chained Equations with Random Forests		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
[95% CI]	[4.94 – 4.94]	[4.97 – 4.97]	[4.94 – 4.94]	[4.95 – 4.95]	[4.93 – 4.93]	[4.93 – 4.93]
Mean Serum Creatinine [95% CI]	53.23 [53.22 – 53.25]	52.97 [52.96 – 52.99]	53.27 [53.26 -53.29]	54.21 [54.21 – 54.21]	54.23 [54.23 – 54.23]	54.23 [54.23 – 54.24]
Mean Qrisk [95% CI]	5.28 [5.27 – 5.29]	5.11 [5.10 – 5.12]	5.25 [5.24 – 5.26]	5.36 [5.36 – 5.36]	5.31 [5.31 – 5.32]	5.30 [5.30 – 5.30]
Mean Dias BP [95% CI]	75.78 [75.77 – 75.79]	75.76 [75.75 – 75.77]	75.78 [75.77 – 75.79]	75.72 [75.72 – 75.73]	75.77 [75.77 – 76.78]	75.77 [75.76 – 75.77]
Mean Sys BP [95% CI]	122.54 [122.52 – 122.56]	122.59 [122.58 – 122.61]	122.53 [122.51 – 122.55]	122.66 [122.65 – 122.66]	122.64 [122.64 – 122.65]	122.63 [122.63 – 122.63]
Ethnicity						
White	80.43% (n = 84,759)	80.46% (n = 151445)	80.37% (n = 84696)	70.68% (n = 78083)	72.01 % (n = 153915)	72.24% (n = 79806)
Black	5.97% (n = 6291)	5.71% (n = 10748)	6.00% (n = 6323)	1.92% (n = 2121)	2.63% (n = 5621)	2.58% (n = 2850)
Asian	8.61% (n = 9073)	8.89% (n = 16752)	8.62% (n = 9084)	3.05% (n = 3369)	3.82% (n = 8165)	3.78% (n = 4176)

	Multiple Imputation using Chained Equations			Multiple Imputation using Chained Equations with Random Forests		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
Mixed	1.76% (n = 1855)	1.61% (n = 3030)	1.75% (n = 1844)	0.55% (n = 608)	0.76% (n = 1625)	0.75% (n = 829)
Other	3.24% (n = 3404)	3.32% (n = 6249)	3.26% (n = 3435)	23.8% (n = 26293)	20.78% (n = 44415)	20.66% (n = 22813)
Index of Multiple Deprivation						
(Least Deprived) 1	18.25% (n = 19232)	20.31% (n = 38228)	17.88% (n = 18843)	19.26% (n = 21276)	19.45% (n = 41573)	19.22% (n = 21233)
2	19.75% (n = 20813)	21.21% (n = 39922)	19.92% (n = 20992)	21.22% (n = 23443)	20.52% (n = 43860)	20.64% (n = 22802)
3	21.38% (n = 22531)	21.54% (n = 40525)	21.57% (n = 22731)	22.52% (n = 24879)	21.42% (n = 45783)	21.52% (n = 23774)
4	20.96% (n = 22088)	19.72% (n = 37118)	21.06% (n = 22193)	19.73% (n = 21797)	20.02% (n = 42791)	20.33% (n = 22459)
(Most Deprived) 5	19.67% (n = 20718)	17.23% (n = 32431)	19.57% (n = 20623)	17.27% (n = 19079)	18.59% (n = 39734)	18.28% (n = 20206)
Drinking Status						
Non-Drinker	41.8%	45.07%	41.66%	44.59%	42.77%	42.78%

	Multiple Imputation using Chained Equations			Multiple Imputation using Chained Equations with Random Forests		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
	(n = 44050)	(n = 84814)	(n = 43902)	(n = 49261)	(n = 91417)	(n = 47261)
Ex Drinker	5.46% (n = 5754)	5.28% (n = 9938)	5.19% (n = 5469)	5.42% (n = 5988)	5.57% (n = 11905)	5.34% (n = 5899)
Occasional Drinker	40.58% (n = 42753)	39.30% (n = 73972)	41.26% (n = 43481)	39.55% (n = 43692)	40.29% (n = 86116)	40.52% (n = 44764)
Current Drinker	7.87% (n = 8294)	6.90% (n = 12987)	7.75% (n = 8176)	6.97% (n = 7700)	7.46% (n = 15945)	7.49% (n = 8275)
Excess Drinker	4.01% (n = 4226)	3.23% (n = 6080)	3.85% (n = 4057)	3.25% (n = 3590)	3.68% (n = 7866)	3.62% (n = 3999)
Binge Drinker	0.28% (n = 295)	0.23% (n = 433)	0.29% (n = 306)			
Smoking Status						
Non-Smoker	47.33% (n = 49877)	48.18% (n = 90668)	47.41% (n = 49962)	47.83% (n = 52840)	47.29% (n = 101078)	47.29% (n = 52243)
Ex-Smoker	19.89% (n = 20960)	19.74% (n = 37155)	19.76% (n = 20823)	20.09% (n = 22194)	19.98% (n = 42706)	20.12% (n = 22227)
Ex or current smoker	0.1%	0.07%	0.07%	0.07%	0.09%	0.08%

	Multiple Imputation using Chained Equations			Multiple Imputation using Chained Equations with Random Forests		
Covariate	Intervention	Unmatched Control	Matched Control	Intervention	Unmatched Control	Matched Control
	(n = 106)	(n = 132)	(n = 74)	(n = 77)	(n = 192)	(n = 89)
Current Smoker	32.69% (n = 34439)	32.02% (n = 60269)	32.76% (n = 34523)	32.00% (n = 35363)	32.64% (n = 69765)	32.51% (n = 35915)

Outcomes and Estimations

Traditional Cox Proportional Hazards with MICE-RF and PSM

After adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, IMD, baseline alcohol intake, baseline smoking consumption, baseline BMI, age on entry, baseline blood pressure, and serum creatinine, the hazard ratio for a referral to the NHS Health Check was 59% (H.R.: 0.41 [95% CI: 0.51 – 0.52]) less likely to develop type 2 diabetes compared to the imputed and matched control group. Differences between the hazard ratios existed in Ethnicity (Other, Black) where under MICE-RF, they are protective characteristics compared to the Asian ethnicity (HR for Ethnicity Other 0.48 [95%CI: 0.47-0.49] and HR for Ethnicity Black 0.78 [0.77 – 0.80]); this was the opposite direction under traditional MICE. See Table 7-6 for a breakdown of the hazard ratios when comparing MICE and MICE-RF when using Cox PH models.

Table 7-6: Covariates and their adjusted hazard ratio. H.R.= 1.00 (i.e., no effect). HR < 1 = protective to type 2 diabetes recording during follow up. HR > 1 = more likely to have a phenotypical recording of type 2 diabetes during follow up

Covariate	Adjusted Hazard Ratio using MICE and PSM [95% CI:]	Adjusted Hazard Ratio using MICE-RF and PSM [95% CI:]
NHS Health Check		
Not invited (reference)	1.00 [Ref]	1.00 [Ref]
Invited	0.46 [0.45 - 0.47]	0.51 [0.51 - 0.52]
Blood Glucose Measures		
Fasting Plasma Glucose	4.95 [4.86 – 5.04]	5.15 [5.12 - 5.18]
HbA _{1c}	1.22 [1.22 – 1.23]	1.31 [1.31 - 1.31]
Age on Entry	0.93 [0.93 – 0.93]	0.94 [0.94 - 0.94]
Gender		
Male (reference)	1.00 [Ref]	1.00 [Ref]
Female	1.68 [1.64 – 1.72]	1.64 [1.62 - 1.65]
ccc		
Asian (reference)	1.00 [Ref]	1.00 [Ref]
Black	1.01 [0.97 – 1.05]	0.78 [0.77 - 0.80]
Mixed	1.12 [1.04 – 1.20]	0.92 [0.88 - 0.95]
Other	1.25 [1.19 – 1.32]	0.48 [0.47 - 0.49]
White	0.59 [0.58 – 0.61]	0.46 [0.45 - 0.47]
Blood Pressure		
Systolic Blood Pressure	1.00 [1.00 – 1.00]	1.01 [1.01 - 1.01]
Diastolic Blood Pressure	1.00 [1.00 – 1.00]	1.00 [0.99 - 1.00]
Serum Creatinine	1.00 [1.00 – 1.00]	0.99 [0.99 - 0.99]
Body Mass Index	1.00 [1.00 – 1.00]	1.00 [1.00 - 1.00]
Q-Risk	1.12 [1.11 – 1.12]	1.09 [1.09 - 1.09]

Covariate	Adjusted Hazard Ratio using MICE and PSM [95% CI:]	Adjusted Hazard Ratio using MICE-RF and PSM [95% CI:]
IMD2015 - 5	1.14 [1.13 – 1.15]	1.07 [1.06 - 1.07]
Smoking	0.90 [0.90 – 0.91]	0.95 [0.95 -0.96]
Alcohol Consumption	0.98 [0.97 – 0.99]	0.96 [0.96 - 0.97]

Data Science multivariable subgroup analysis

When predicting the time-to-event for type 2 diabetes with NHS Health Check invitation status and adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, IMD, baseline alcohol intake, baseline smoking consumption, baseline BMI, age on entry, baseline blood pressure, and serum creatinine, the factors which predict the most variation include blood glucose measures, body mass index and an NHS Health Check invitation. See Figure 7-9 for the whole survival tree; due to the size of the survival tree, a link to view and zoom this online can be in the following URL:

https://www.dropbox.com/s/7hahsq6hksib8r5/nhshc_random_forest_remove_grisk-remove-fgp.jpeg

The survival tree algorithm produced two scenarios where the NHS Health Check invitation was a predictor in the incidence of type 2 diabetes using tree-based algorithms. These scenarios were generated based upon a gini-index as opposed to significance testing

- The first scenario shows that the NHS Health Check increases the event-free rates if the patient's HbA_{1c} is at least 35.25 mmol/mol with a BMI of at least 24.55 kg/m². For those who had reduced access to the NHS Health Check who have a HbA_{1c} reading of 35.25 mmol/mol or higher with a BMI of at least 24.55 kg/m², predictors include baseline serum creatinine. See Figure 7-10
- The second scenario is when the patient's HbA_{1c} level is at least 40.492mmol/mol with a BMI higher than 24.55 kg/m². Under this scenario, patients who were invited to the NHS Health Check have decreased event free rates if they were non-White (specifically Asian, Black, or Mixed) with a baseline HbA_{1c} level higher than 44.63mmol/mol. See Figure 7-11

Figure 7-9: Survival Tree Diagram for the NHS Health Check. Access to the image can be found here, where it is zoomable: https://www.dropbox.com/s/7hahsq6hksib8r5/nhshc_random_forest_remove_qrisk-remove-fgp.jpeg

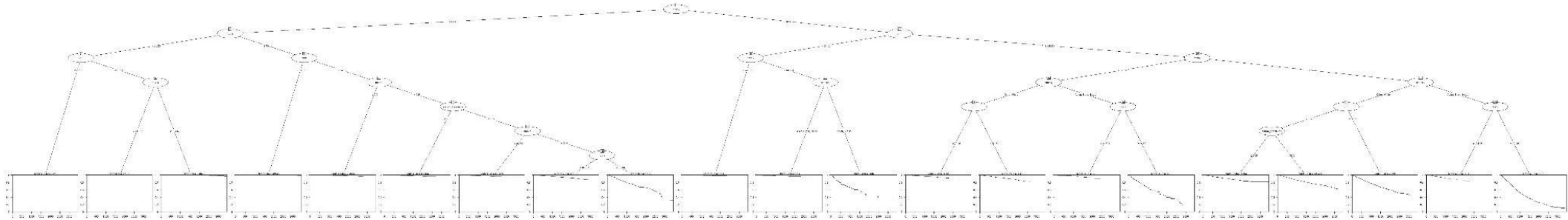


Figure 7-10: The prior nodes in this tree included a having a HbA1c of at least 35.25 mmol/mol with a BMI of at least 24.55 kg/m2. In this tree, those who participants in the NHS Health Check had longer disease-free time compared to those who did not participate in the NHS Health Check. For those who did not participate in the NHS Health Check, survival time is predicted by serum creatinine and HbA1c.

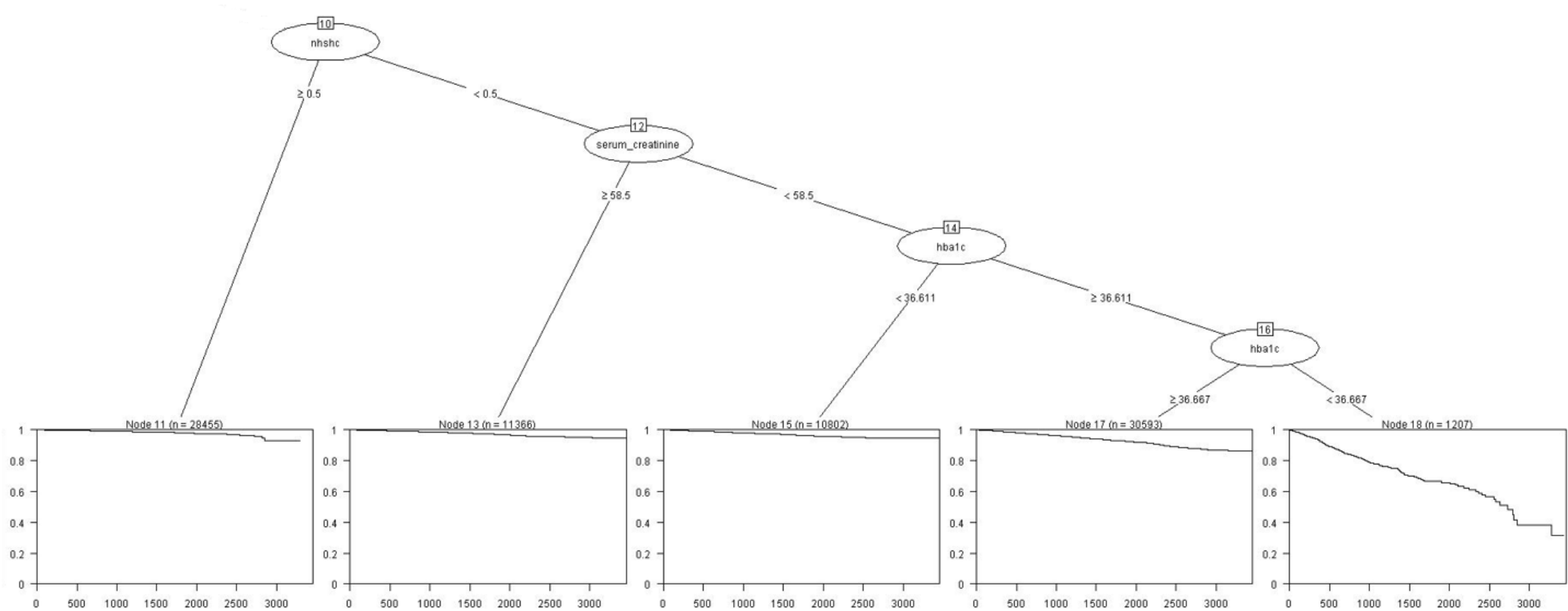
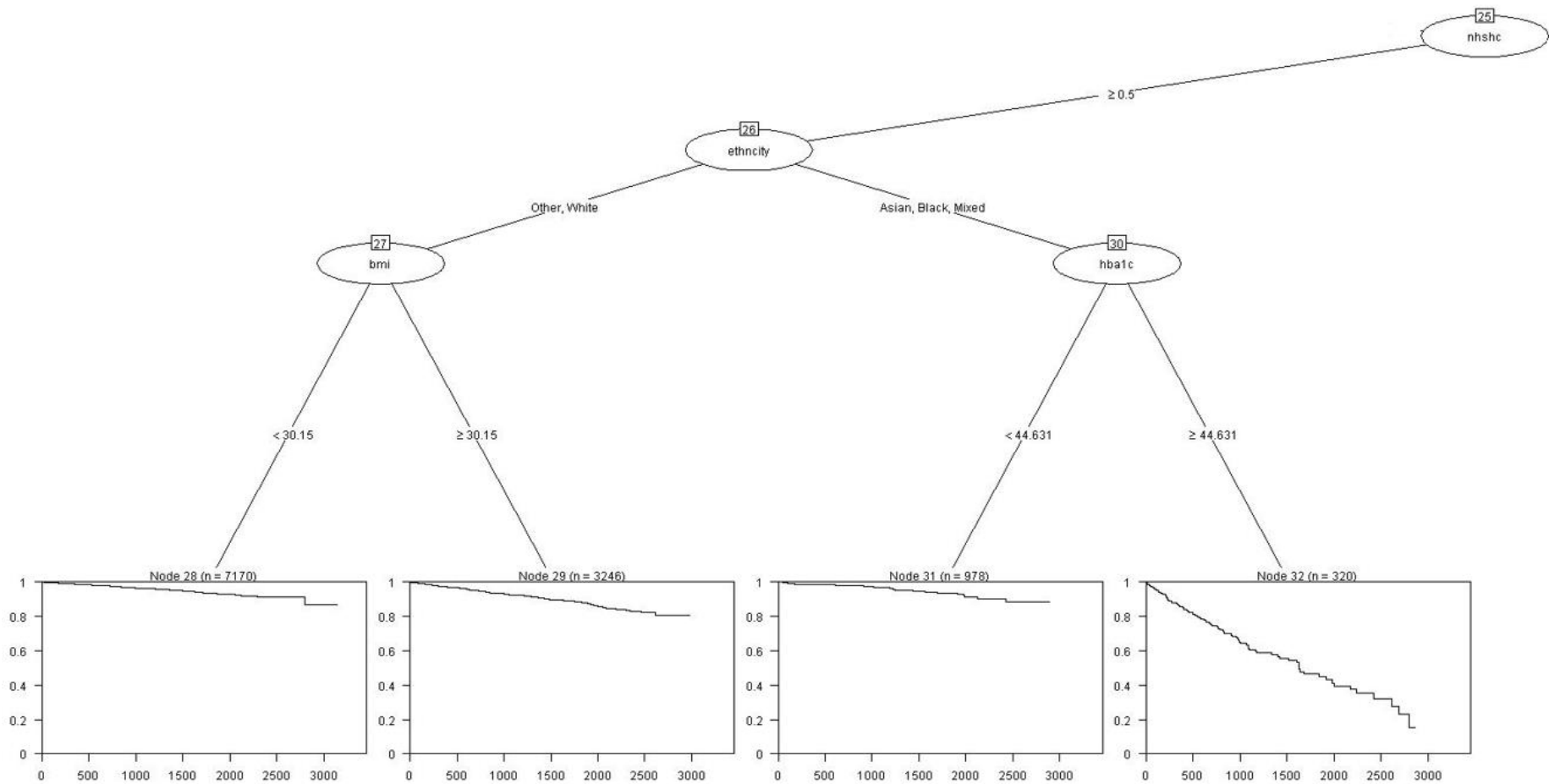


Figure 7-11: To be a part of this subtree, patients needed a HbA1c of more than 40.492mmol/mol with a BMI higher than 24.55 kg/m2. In this tree, those who participated in the NHS Health Check had differential outcomes based upon ethnicity, BMI and HbA1c.



Discussion

In this chapter, I applied data science methods as sensitivity analyses to test the robustness of the results in Chapters 5 and Chapter 6. In Chapters 5 and 6, I used Multiple Imputation using Chained Equations to impute missing data that work best when the data is normally distributed; in this chapter, I used K's Nearest Neighbour Imputation and MICE with Random Forest to impute data and both these data science methods do not assume the distribution of covariates which is important as the risk of eligibility reduces with age. Furthermore, in this chapter I've applied the Synthetic Minority Over Sampling Technique to sample patients instead of propensity score matching used in chapters 5 and 6; in contrast to reducing the number of patients analysed, the use of SMOTE acts as a sensitivity analysis by generating realistic synthetic patients given existing distributions within the data. Finally, this chapter applies Survival Tree methods to model time-to-event data in contrast to Cox Proportional Hazards models used in chapters 5 and 6; by using Survival trees, this chapter finds important interactions terms in determining the incidence of recorded diabetes whilst chapters 5 and 6 only produced coefficients without interactions.

In this chapter, I have shown that methods such as KNN and MICE-RF produce similar baseline characteristics to those of MICE, and in turn, of *Valibhji et al., 2020*'s validated cohort. Whilst no imputation method produced the exact distribution of *Valibhji et al., 2020*'s validated cohort, MICE-RF produced the closest breakdown to Valabhji et al., 2020 for IMD, whilst MICE was better at predicting weight distributions. Whilst I performed KNN on the same computer as MICE and MICE-RF, KNN

failed to impute the NHS Health Check cohort due to its relatively large size.

When using MICE vs MICE-RF on the NHS Health Check cohort, MICE-RF produced a slightly more conservative reduction of 49% (adjusted HR: 0.51 [95%CI: 0.51 - 0.52]) compared to MICE's 54% reduction (adjusted HR: 0.46, [95% CI:0.45 – 0.47) when estimating the hazard ratio of incident type 2 diabetes. The conservative nature this estimate created by MICE-RF is potentially due to the differences in ethnic breakdown (which themselves, also produce different hazard ratios when compared to using standard MICE). This is likely due to MICE-RF's higher proportion of predicting patients as belong to "Other" ethnicities when compared to MICE. Due to these high rates of "Other" ethnic patients (20%+) in the NHS Health Check cohort, the results should be interpreted cautiously, including the hazard ratios produced for the hazard ratios related to ethnicity.

In terms of data resampling, by using SMOTE, I was able to analyse larger cohort sizes and reduce dataset imbalance for the NHS Diabetes Prevention Programme. One of the challenges in the previous chapters was that the NHS Diabetes Prevention Programme was only trialled in a portion of general practises, and only some of those general practises had provided data to the CPRD data set, leading to a relatively small sample of 2,205 intervention patients when compared to *Valibhji et al., 2020*'s sample of 152,294 who attended the NHS Diabetes Prevention Programme. By using SMOTE, I was able to increase this 2,205-intervention sample to 24,393 intervention synthetic patients and preserve the size of the control group when compared to using

propensity score matching. Overall, the impact of changing from propensity score matching to SMOTE produced no change to the adjusted hazard ratio (0.41 [95%CI: 0.38 - 0.44] for propensity score matching to 0.43 [95%CI: 0.41 - 0.44] for SMOTE for the NHS Diabetes Prevention Programme). This provides more confidence in the underlying data of the previous chapter as an extra sensitivity analysis for the NHS Diabetes Prevention Programme.

Previously I've used established Cox proportional hazards to explain the overall effect of the NHS Health Check and NHS Diabetes Prevention Programme when adjusted for a variety of covariates. Whilst this shows the NHS Health Check and NHS Diabetes Prevention Programme's average effect when considering other covariates, it does not consider the complex interaction of a patient's socio demographic and clinical characteristics. By using survival trees in this chapter, I was able to understand the role the NHS Health Check and NHS Diabetes Prevention Programme play in the intersectionality of sociodemographic and clinical backgrounds of patients. For the NHS Health Check, whilst traditional Cox Proportional Hazards models estimate that blood glucose, NHS Health Check invitation status and gender are the top predictors on the incidence of type 2 diabetes, survival trees estimated that blood sugar measures, body mass index and an NHS Health Check invitation were the best risk predictors. Through survival trees, I found evidence that participants of the NHS Health Check can have different outcomes based upon ethnicity, suggesting that improvements can be made to increase health equity; although such results should be interpreted with caution with future work to be undertaken to understand stratified impact of public health interventions in identified groups. For

the NHS Diabetes Prevention Programme, traditional Cox Proportional Hazard models estimate that NHS Diabetes Prevention invitation status, ethnicity and baseline blood sugar measurements are top predictors on the incidence of type 2 diabetes, whilst survival trees used baseline blood glucose measurements, invitation status and body mass index as it's predicting variables on the incidence of type 2 diabetes. Surprisingly, body mass index was not shown as an important predictor using Cox Proportional Hazard models whilst this was considered important when interacted with baseline blood glucose measures when using survival tree analysis. I postulate this is because matching was used, which reduces variation in Cox Proportional Hazard models whilst survival tree analysis found specific interactions that predict the outcome. Cox Proportional Hazard models would require interaction terms to be pre-specified.

Strengths

In this chapter, I have shown that KNN and MICE-RF have produced a similar baseline sociodemographic and clinical breakdown compared to a validated external dataset for all covariates apart from deprivation (extreme quintiles), ethnicity (White and Asian), age (proportion of over 75 years old) and the under-weight/healthy categories. One major strength of using SMOTE matching is improving sample sizes for small datasets such as the NHS Diabetes Prevention Programme. For the NHS Diabetes Prevention Programme, SMOTE created 24,393 intervention individuals instead of 2,205 individuals under a standard epidemiological analysis. SMOTE also preserved the 29,182 control individuals instead of under-sampling them to match the intervention group, allowing models to consider patients from a wider variety of

backgrounds. Finally, by using survival trees, I was able to identify subgroups based upon a combination of covariates that may benefit from access to public health interventions in the prevention of type 2 diabetes, whereas this is traditionally done using a single covariate (e.g., by gender or age group).

Limitations

One major limitation I found by applying these data science methods is that they can be limited by computational capacity. This occurred when I tried to apply methods based upon K's Nearest Neighbors on the larger NHS Health Check dataset. Not only did this impact my attempt of imputing data, but this also impacted my attempt to oversampling the data. Whilst re-sampling may not have impacted the NHS Health Check Data (as I had 105,382 intervention patients against 188,224 control patients), this may not be applicable for other datasets. At the time of conducting this PhD, a more powerful computer may not be cost effective in solving this issue due to the large number of comparison operations and memory storage required to conduct K's Nearest Neighbour analysis on the NHS Health Check Data; in 2023 (nearly 3 cycles of Moore's law, i.e. 8 times more powerful processing power), the same problem still occurs.

Even when I could apply KNN based algorithms such as SMOTE, I found that baseline differences were significantly different between control and intervention groups, although this did not drastically change the multivariate Cox proportional hazard ratios (primarily due to multivariable adjustment).

A further challenge with using SMOTE is that whilst it preserves (or even increases sample size calculations from 2205 intervention patients to 24,393 synthetic patients), it does so by generating synthetic, hypothetical patients; this contrasts with propensity score matching, which reduces sample sizes whilst using existing real patients (from 29182 controls to 8820 matched controls). Consequently, using SMOTE alone would be questionable due to its use of artificial patients based upon observed and measured data. Therefore, in this PhD, the use of SMOTE was used to test the robustness of the results produced in Chapter 5 and was internally validated against an established epidemiological method, propensity score matching.

Finally, whilst survival trees are capable of conducting automated interactive sub-group analysis, decision trees are not able to state whether each covariate crosses the null hypothesis when conducting an equivalent hypothesis test. Therefore, interpretation of the results contains less confidence compared to (semi-)parametric based methods such as Cox proportional hazards. Furthermore, the library for creating survival tree's (partykit) does not provide the ability to add features which are important in epidemiological research such as creating cumulative incidence curves or creating tables at risk.

Interpretation

This chapter provides evidence that alternative data science methods can be used to address weaknesses in traditional observational studies. Both MICE-RF and KNN can produce similar results to traditional MICE and can be used as alternatives to traditional MICE. SMOTE can be

used to increase and preserve sample sizes in studies that have small samples. Using survival trees can complement Cox proportional hazard models by creating automated sub-group analysis.

Generalisability

Modern data science methods produced similar methods for imputing missing covariate data when compared to established epidemiological methods for NHS Diabetes Prevention Programme CPRD sample data; both methods were externally validated against a population level dataset and had a similar distribution in measured covariates.

The results from the data science methods agree with the traditional Cox Proportional Hazard models that access to the NHS Diabetes Prevention Programme/NHS Health Check is associated with the incidence of type 2 diabetes. Traditional Cox Proportional Hazard models and modern data science methods also choose baseline blood glucose measurements as good predictors on the 2.5 (NHS Diabetes Prevention Programme)/ 10 (NHS Health Check) year risk of developing the incidence of type 2 diabetes. For the NHS Health Check, both traditional methods and modern data science methods found that Black and Asian participants experienced worse type 2 diabetes healthcare outcomes compared to their White counterparts.

Chapter 8 - Using triangulation to understand the biases from a range of study designs evaluating the impact of public health interventions on the incidence of type 2 diabetes

Abstract

Introduction: In previous chapters, I evaluated the impact of public health interventions on rates of type 2 diabetes using a range of different data sources (e.g., primary care records, secondary care records), methods and study designs (e.g., systematic reviews, interrupted time series, two retrospective cohort studies, and two data science alternatives), each with different assumptions and biases. Different data, analytical units, methods, study designs and assumptions have an impact on the impact of public health intervention's direction of effect on rates of type 2 diabetes. Each study's results were viewed in isolation and in this chapter, I use triangulation to explore each study's biases and summarise the direction of the effect of public health interventions on the incidence of type 2 diabetes.

Method: I applied an established triangulation framework to understand the differences between each study and more importantly, the biases in the data and methods used and how this might affect the direction of the results when compared to a randomised controlled trial. I then presented the results in reference to the triangulation framework taking into consideration the biases and methods.

Results –

When analysing the NHS Health Check using systematic reviews, I found that estimates are biased towards an underestimation of the reduction in type 2 diabetes incidence as new diagnoses may also include previously

undiagnosed prevalent cases. When analysing at the population level using a time series analysis, I found estimates are potentially biased towards an underestimation (when compared to a randomised controlled trial) of its impact due to the low type 2 diabetes incidence rates in this “healthy” population or a low attendance rate of the NHS Health Check. At the individual level, when analysing the NHS Health Check using the outcome of prevalent cases of type 2 diabetes, previously undiagnosed cases are more likely detected compared to non-attendees of the NHS Health Check, which would lead to an overestimate of the effectiveness of the intervention. When removing previously undiagnosed cases by using incidence of type 2 diabetes as the primary outcome, my estimates of NHS Health Check demonstrate a relative preventative effect for those who were offered access to the NHS Health Check when compared to a usual care group and my results were comparable to randomised controlled trials evaluating other public health interventions. When using data science methods to understand if access to the NHS Health Check is a good predictor on the incidence of type 2 diabetes, I found that patients who had access to the NHS Health Check who were recorded as non-White (specifically Asian, Black or Mixed) with a baseline HbA_{1c} higher than 45 mmol/mol and BMI higher than 25 kg/m² were most likely to develop type 2 diabetes compared to other ethnicity and BMI combinations.

For the NHS Diabetes Prevention Programme, all applied methods demonstrated a reduction in type 2 diabetes incidence in high-risk individuals compared to controls and is expected based upon results from similar programmes elsewhere in high income countries. Using traditional epidemiological techniques, I found an invitation to the NHS Diabetes Prevention Programme produced a 59% reduction in type 2 diabetes incidence rates [adjusted hazard ratio=0.41;95%CI=0.38-0.44] and my results were comparable to randomised controlled trials. Using data science methods, I found that patients with baseline HbA_{1c} higher than 44 mmol/mol

or a HbA_{1c} higher than 42 mmol/mol with a BMI higher than 27.45 kg/m² are less likely to develop type 2 diabetes if they participated in the NHS Diabetes Prevention Programme.

Discussion and Conclusions:

Using systematic reviews and interrupted time series I did not detect a preventative effect of public health interventions on the incidence of type 2 diabetes and this is expected as they do not evaluate the same effect measure as a randomised controlled trial. Without using target trial emulation, my observational study produced similar results to prior studies which evaluated “new diagnoses” of type 2 diabetes. Using target trial emulation with the same observational study dataset produced similar results to randomised controlled trials which evaluated public health intervention on the incidence of type 2 diabetes. Using data science identified subgroups where the NHS Health Check is effective and where they could be improved based upon sociodemographic and clinical characteristics and add to prior literature on the inequities involved in the NHS Health Check. With all the evidence taken into consideration and their biases, the NHS Health Check and Diabetes Prevention Programme can demonstrate individual level reductions on the incidence of type 2 diabetes, although this may not reflect in detectability at the population level.

Introduction

Studies evaluating the preventative effect of interventions on the incidence of a disease often suffer from a wide variety of biases and challenges. This can usually range from uncontrolled confounders in observational studies to low sample sizes and limited study periods in prospective controlled trials. Whilst combining studies through meta-analyses and assessing the risk of bias in studies can improve the quality of evidence, this can only be achieved if all studies to be meta-analysed are comparable, for example through equivalent RCTs. Unfortunately, meta-analyses examining the effectiveness of NHS Health Check or the NHS Diabetes Prevention Programme in preventing the incidence of type 2 diabetes are not possible due to the heterogeneity in included populations, interventions, comparison, and outcomes of included studies. In the case of systematic review in Chapter 2, the primary reason for not conducting a meta-analysis was due to differences in populations (individual versus general practice level) and different outcomes (change in risk, change in prevalence, new diagnoses previously unrecorded and incidence).

An alternative approach to “combining” various studies instead of meta-analysing data is triangulation. Triangulation aims to strengthen causal inferences by integrating results from several different approaches where each approach has different key sources of potential biases (Lawlor et al., 2017). This differs from meta-analyses, as meta-analyses quantitatively combine the results from similar approaches, with differences often arising in the different geographical location of the meta-analysed cohorts (although other differences are often meta-analysed). In meta-analyses the primary goal is to combine results and reduce random error, but this already assumes that there are minimal biases across comparable studies. In triangulation studies on the other hand, various approaches (at least 2) are used to answer studies which aim to answer similar clinical questions which were evaluated using different methods

and different sources of biases (particularly due to the study design). Whilst comparable outcomes (e.g. odds ratios, hazard ratios) can be “pooled” in a triangulation study, with such analyses providing a: “qualitative assessment of the strength of evidence regarding causality” (Lawlor et al., 2017).

In this chapter, I take advantage of the range of data sources, and study designs used throughout the thesis (including meta-analyses, interrupted time series, retrospective propensity score-matched observational studies, and public health data science approaches to observational studies) in order to evaluate the causal evidence for the NHS Health Check and Diabetes Prevention Programme in reducing incident type 2 diabetes. See Table 8-1 for a list of study designs that were used in this PhD thesis in the evaluation of each public health intervention. The aim of this chapter is to investigate the evidence produced in previous chapters through triangulation. The objectives of this chapter are to:

- Understand the studies in the previous chapters by breaking them down into the components set out in the framework set out by Lawlor, Tilling and Smith (Lawlor et al., 2017).
- Understand the biases, strengths, and weaknesses of each study design.
- Summarise the direction of effect (e.g., reduces type 2 diabetes, no effect, increases type 2 diabetes) of each study design on type 2 diabetes outcomes.
- Summarise the different approaches to estimating the effect of public health interventions on type 2 diabetes.

Table 8-1: List of studies designs applied to each programme.

Study Design	NHS Health Check	NHS Diabetes Prevention Programme
-Systematic review	✓	X
-Interrupted time series	✓	X
-Propensity score matched population level observational cohort study	✓	✓
-Data science approaches to population level observational cohort studies	✓	✓

The triangulation framework

The methods of this chapter follows the framework as described in by Lawlor (Lawlor et al., 2017) which sets out the 5 following criteria for triangulation:

Criterion 1: results from at least two, but ideally more, different approaches, with differing and unrelated key sources of potential biases are compared.

Criterion 2: The different approaches address the same underlying causal question.

Criterion 3: For each approach, the duration and timing of the exposure that it assesses is taken into account when comparing results.

Criterion 4: For each approach, the key sources of bias are explicitly acknowledged when comparing results.

Criterion 5: For each approach, the expected direction of all key sources of potential bias are made explicit where this is feasible, and ideally within the set of approaches being compared there are approaches with potential biases that are in the opposite direction.

Applying the Triangulation framework to the NHS Health Check

See Table 8-2 for the key sources of biases and the expected direction of the key sources of potential biases with a brief breakdown of the 5 criteria below:

Criterion 1: For the NHS Health Check, I conducted 4 studies using 4 different approaches including systematic reviews, interrupted time series, retrospective observational propensity-matched cohort studies, and data science-based observational cohort studies. Summaries, assumptions, and sources of biases for each approach are described in Chapter 8 Table 2.

Criterion 2: All 4 studies aimed to evaluate the effect of the NHS Health Check on rates of type 2 diabetes, although it is noted that the systematic review and interrupted time series analysis included other additional healthcare outcomes.

Criterion 3: Due to the pre-specified nature of the NHS Health Check, the duration of the intervention is similar across all studies, however as the NHS Check's role is to refer patients (who are in need) to other NHS public health interventions, the timing of receiving the NHS Health Check may change support received by patients. For example, those who received the NHS Health Check after 2016 in specific geographical areas had access to the NHS Diabetes Prevention Programme.

Criterion 4: For the systematic review, the primary bias is that most studies did not consider removing prevalent cases on entry. For the interrupted time series study, the primary bias is that it requires a large number of people to have partaken in the NHS Health Check for there to be a detectable effect. The primary bias for the retrospective observational studies is uncontrolled and unmeasured confounding covariates which are likely to be associated with the intervention (i.e., there is more missing data in the control group).

Criterion 5: For the systematic review, my evaluation finds that the bias (reporting of previously undiagnosed cases) would increase the rates of newly diagnosed type 2 diabetes cases (compared to a randomised controlled trial where prevalent cases are excluded on entry). For the interrupted time series, there is evidence that the bias (relatively low uptake rate in healthy individuals) would either provide the same or a lower effect when compared to a similar randomised controlled trial. For the observational studies, the primary sources of bias (confounding) were controlled for using a variety of methods including propensity score matching and multivariate adjustment. Studies have found that methods for controlling for confounding using propensity score matching were more likely to overestimate the effect of intervention as compared to their randomised controlled trial counterparts, although estimates were not generally found to be statistically significantly different (Dahabreh et al., 2012).

When evaluating the effect of study type on rates of type 2 diabetes, I found that the systematic review's result, the same or higher rates of type 2 diabetes in those who attended, was likely due to bias that understates the preventative effect of public health interventions on the prevention of incident type 2 diabetes. This may have been primarily driven by the NHS Health Check's ability to identify previously undiagnosed cases which were not accounted for in the systematic reviews of the NHS Health Check. This is

because an alternative healthcare outcome for the NHS Health Check is the reduction in complications of diabetes (more specifically cardiovascular disease) through early detection, monitoring and disease control.

When using an interrupted time series analysis to evaluate the effect of the NHS Health Check on hospital admissions on type 2 diabetes admission rates, the results of no change in the rates of change in the growth of diabetes between 2003 and 2017 is an underestimate of the preventative effect of the NHS Health Check on incident type 2 diabetes. This is primarily due to the requirement of the interrupted time series analysis where a large enough proportion of patients in the hospital episode statistics data would have had to take part in the NHS Health check for there to be a detectable change in admission rates for diabetes. Biases also exist as rates of type 2 diabetes in “healthy” individuals; from Chapter 6, I found that rates were relatively low in the (up to) 10-years of follow up, at 1.04% (95%CI: 0.98% - 1.11%); therefore, detections at a population level may be difficult.

When analysing the effects of the NHS Health Check as a public health intervention using primary care datasets (linked to secondary care and office of national statistics death records), on the outcome of newly diagnosed type 2 diabetes in those without diabetes on entry, the result (a reduction in type 2 diabetes incidence in NHS Health Check invitees) reflected the direction estimated by the triangulation framework. That is, analysing adults without type 2 diabetes on entry, and using propensity score matching, I would expect that an invitation to the NHS Health Check would either have no effect or a preventative effect. When taking into consideration the study design, and follow up, the NHS Health Check provides a reasonable estimate when compared to the randomised controlled trials that evaluated different types of diabetes prevention programmes on the outcome of the incident of type 2 diabetes. See Figure 8-1 for a graphical representation of time-to-event triangulation with randomised controlled trials. In summary, the Diabetes

Prevention Programme, 2003 study produced a hazard ratio of 0.42 [95CI: 0.34 -0.51] at a 3-year follow-up period whilst my estimate of the NHS Diabetes Prevention Programme produced an estimated hazard ratio of 0.41 [95%CI=0.38-0.44]. The NHS Health Check produced an estimated hazard ratio of 0.46 [95% CI:0.45 – 0.47] at up to 10-years whilst the Ilanne-Parikka *et al.*, 2013 study produced a 13-year estimate of 0.614 [95% CI 0.48 - 0.79] and the updated Diabetes Prevention Programme study in 2015 produced a 15-year hazard ratio of 0.73[95% CI 0.65-0.83]. Therefore, as a function of follow-up time, we expect effects of such public health interventions to reduce with both my studies (of the NHS Health Check and the NHS Diabetes Prevention Programme) following the trends of their randomised controlled trial counterparts.

When analysing the effect of the NHS Health Check as a public health intervention using data science methods, the outcome of reduction in newly diagnosed type 2 diabetes without diabetes on entry overestimates the preventative effect of the NHS Health Check on type 2 diabetes outcomes. That is, data science methods could overestimate the preventative effect of the NHS Health Check when compared to a randomised controlled trial. This is likely driven by the fact that survival trees isolate the scenarios where the NHS Health Check is associated with a new diagnosis of type 2 diabetes in those who did not have type 2 diabetes on entry.

Figure 8-1: Plot depicting the NHS Health Check and Diabetes Prevention Programme in comparison to non-NHS diabetes prevention programmes which use a time-to-event analysis when taking into consideration time since the start of follow-up. In this graph, the x-axis denotes study duration whilst the y-axis denotes the natural log of hazard ratio.

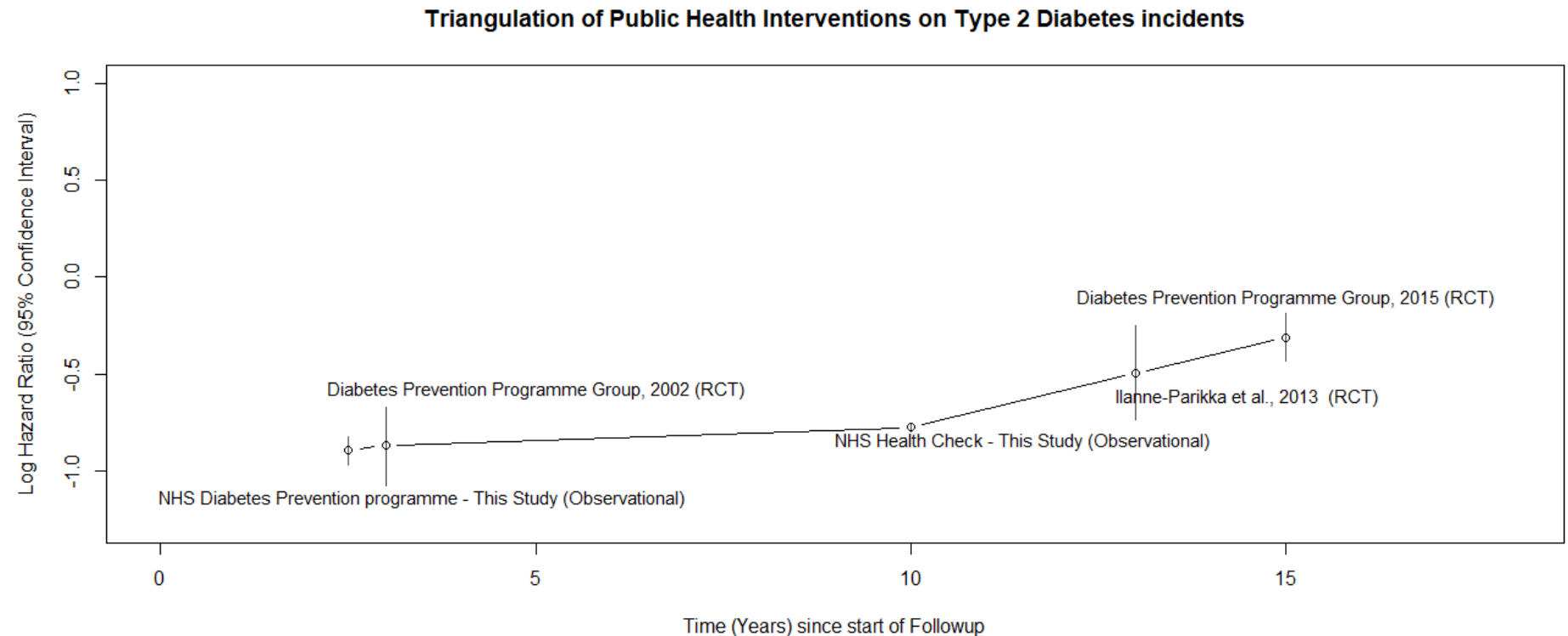


Table 8-2: Key sources of biases in different aetiological epidemiology approaches for the NHS Health Check

Approach	Description of study	The assumption for this study	General Key source of bias (Criterion 4)	Direction sources of bias have on the result (Criterion 5)
Systematic Review (Chapter 2)	Systematic review on the NHS Health Check to establish its impact on cardiovascular events, diabetes, stroke and chronic kidney disease.	Studies which were included are comparable. The NHS Health Check has not changed its intervention since the introduction. Studies that were included are of high quality.	Included studies primarily review the NHS Health Check as a screening programme which can pick up previously unrecorded cases	Taking part in the NHS Health Check, participants would have undergone more screening (such as blood glucose tests, blood pressure measuring equipment, etc) through their general practitioner. This would lead to a higher rate of detection of such diseases shortly after the initial NHS Health Check consultation compared to those who were not invited but were eligible. In Chapter 2, Robson et al 2017, Chang et al 2016, who found a 30% increase in detection rates of type 2 diabetes when comparing attendees against non-attendees. This was confirmed in Chapter 6.
Univariable interrupted time series (Chapter 3)	Interrupted time-series analysis conducted between 2003 to 2017 and mirrored the eligibility of the NHS Health Check that estimated monthly national hospital admissions trends for cardiovascular disease before and after the introduction of the NHS Health Check.	That the NHS Health Check is effective in reducing the risk of cardiovascular disease There was no change in clinical coding practices.	Study assumes there are no other co-interventions that may have impacted the outcome and may have been “confounded” by other unaccounted interventions. Study design does not follow traditional methods for calculating causal inferences. This is because interrupted time series’ causal inferences are based upon the impact of an intervention on rates in the population over a period. If the intervention is not given to a high enough proportion of the population, then detecting the impact of the intervention can be difficult. Another bias with the interrupted time series study design is the impact of temporal variability due to clinical coding. An example of this includes financial incentives in primary care for treating type 2 diabetes in the primary care setting may result in a drop of type 2 diabetes admissions in the secondary care setting.	If successful co-interventions existed, then an interrupted time series <u>may overestimate the effect of the NHS Health Check on type 2 diabetes rates by erroneously attributing</u> the reduction to the NHS Health Check. Compared to an RCT, interrupted time series is more likely to <u>underestimate the impact of the intervention on eligible individuals</u>. In Chapter 6, NHS Health Check eligible patients (after screening) were not likely to develop type 2 diabetes 1.04% (95%CI: 0.98% - 1.11%). Even if a drop at the population level, it could only be a small absolute reduction. Even if the NHS Health Check was successful at the individually, we need a large proportion of individuals to partake in the NHS Health Check to detect a population level drop; as per Chapter 1, this is currently at 20% of the eligible population. For temporal variability (i.e. Clinical coding changes), it is <u>difficult to estimate the direction of bias</u> such an event could have on the estimation of the NHS Health Check on type 2 diabetes rates. This is because these coding practices are time-varying; that is they often change to reflect diagnoses of concern at that point in time.

Approach	Description of study	The assumption for this study	General Key source of bias (Criterion 4)	Direction sources of bias have on the result (Criterion 5)
Multivariable retrospective observational propensity-matched cohort studies (Chapter 6)	Retrospective observational cohort study for the period January 2009 to January 2019 comparing rates of new type 2 diabetes diagnoses among eligible adults who were referred to the NHS Health Check with rates for propensity score-matched controls who were eligible for the NHS Health Check but were not invited. Eligibility for the NHS Health Check was defined as being between 40-74 on entry without a previous recording of chronic kidney disease, diabetes, heart disease, hypertension, or stroke on entry. Imputation was conducted using multiple imputation using chained equations with time to the first record of type 2 diabetes was modelled using Cox regression with age, alcohol intake, body mass index, serum creatinine, ethnicity, sex, HbA1c, index of multiple deprivations and smoking status included as covariates.	That I carefully chose the covariates to avoid unmeasured confounders That propensity score matching reduced differences in baseline differences between intervention and control groups, leading to a reduction in the risk of confounding by indication. That imputed values using multiple imputation are less biased when compared to a completed case analysis. That removing those who have a record for type 2 diabetes within 90 days of their start of follow-up were removing prevalent cases.	Unmeasured confounding, for example, disproportionate amounts of missing data in the control arm. Such confounders are less likely to exist in randomised controlled trials due to the randomised nature. An example of this in observational study is confounding by indication where those who were assigned treatment were more likely to develop the disease. Datasets which are used in observational studies were primarily designed for administrative purposes (and not for research), leading to high amounts of missing data. Missingness was more likely for control groups due to non-attendance (also a consequence of confounding by indication) Access to the NHS Health Check has been shown to demonstrate an initial increase in type 2 diabetes diagnoses due to access to diagnostic tools (for example, blood tests)	Studies have demonstrated that the use of propensity score matching may overestimate the impact of an intervention on an outcome (Dahabreh et al., 2012) when compared to RCTs, although rarely statistically significant. As ethnicity is a social determinant of data quality in cardiovascular disease risk outcomes (Collins and Altman, 2010), without the use of multiple imputation, populations were found to be more likely to be White, who are often at lower risks of cardiovascular disease compared to minority ethnic counterparts therefore a full case analysis may underestimate the impact of the NHS Health Check on type 2 diabetes as it could reduce the population to those who are less likely to develop the outcome. Whereas multiple imputation has been shown to generate a less biased estimate in the population due to its ability to include minority ethnic individuals in analysis. Emulating a removal of prevalent cases in the NHS Health Check is likely to produce a more appropriate estimate. Whilst this also brings up the risk of health seeking behaviour, we controlled for this by 1) analysing invitees instead of attendees leading to point 2) where studies have shown uptake is low at 20%. It is difficult to understand how unmeasured confounding impacts the direction and biases in this evaluation.

Approach	Description of study	The assumption for this study	General Key source of bias (Criterion 4)	Direction sources of bias have on the result (Criterion 5)
Multivariate data science approaches to retrospective observational cohort studies (Chapter 7)	A retrospective observational cohort study was conducted using linked electronic healthcare records between January 2009 to January 2019. New rates of type 2 diabetes diagnoses were compared among eligible adults referred to the NHS Health Check with rates for those who were not referred. Eligibility for the NHS Health Check was defined as being between 40-74 on entry without a previous diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke. Those who had a prior diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke were excluded on entry, akin to a randomised controlled trial. Imputation was conducted using multiple imputation using random forests whilst Survival trees were used to estimate the time to the first record of type 2 diabetes.	That I carefully chose the covariates to avoid unmeasured confounders That propensity score matching reduced differences in baseline differences, leading to a reduction in the risk of confounding by indication. That by using multiple imputation, that the imputed values are representative of the real population	The analytical method (survival trees) aim to find scenarios (interactions) where the NHS Health Check is a good predictor on the outcome of the incident of type 2 diabetes. The primary limitation with observational studies is that there are unmeasured confounding variables as in the above example. Missingness was more likely for control groups as they were less likely to go to the general practice (also a consequence of confounding by indication)	The sub-group analysis nature of the <u>survival tree method means that it could overestimate the preventative effect</u> by isolating the NHS Health Check variable to only situations where it is a good predictor of the incident of type 2 diabetes. This therefore ignores patients for whom the NHS Health Check is not effective at all, even though they are eligible for the NHS Health Check. For example, for healthy individuals for whom the NHS Health Check may not impact their health due to their healthy status. Similarly to the study above, the use of imputation creates a <u>better estimate</u> by including those who are more likely to develop type 2 diabetes even if they do have missing baseline data. As stated above, this study could be impacted by unmeasured confounding, whose direction of bias is difficult to measure.

Applying the Triangulation Framework to the NHS Diabetes Prevention Programme

I have applied the triangulation framework to studies which analysed the NHS Diabetes Prevention Programme as follows:

Criterion 1: For the NHS Diabetes Prevention Programme, I conducted 2 studies using 2 different approaches including a retrospective observational propensity score matching study, and data science based observational cohort study. The primary assumption for both studies is that I adjusted for confounding variables and that this reduced the risk due to confounding.

Criterion 2: Both studies aimed to evaluate the preventative effect of the NHS Diabetes Prevention programme on the incidence of type 2 diabetes.

Criterion 3: The specification for the NHS Diabetes Prevention Programme includes a duration of 16 hours of face-to-face interactions of 13 sessions within 36 weeks; this was the same for both studies; both studies had the same follow-up period of 2.5 years between 2016 to 2019.

Criterion 4: The major biases for the retrospective observational studies conducted are uncontrolled and unmeasured confounding covariates.

Criterion 5: For the traditional observational cohort study, I used propensity score matching to reduce the effects of confounding by indication; however, studies have demonstrated that propensity score matching may overestimate the impact of the intervention when compared to a comparable randomised controlled trial (Dahabreh et al., 2012). For the data science-based observational study, I used

multivariate survival trees which may overestimate the effectiveness of the NHS Diabetes Prevention Programme as survival trees isolate the scenarios where the NHS Diabetes Prevention Programme is a good predictor of the incidence of type 2 diabetes.

When analysing the effects of the NHS Diabetes Prevention Programme using primary care datasets (linked to secondary care and office of national statistics death records), the outcome (reduction in newly diagnosed type 2 diabetes in those without diabetes on entry) reflected the direction estimated by the triangulation framework where propensity score matching is likely to generate either the same or a preventative effect when compared to a randomised controlled trial. See Table 3 for the key resources of biases for this study design and

When analysing the effects of the NHS Diabetes Prevention Programme using data science methods, the outcome (reduction in newly diagnosed type 2 diabetes without diabetes on entry) reflected the predicted outcome in the triangulation framework (overestimation of the treatment effect as compared to a randomised controlled trial). This is likely driven by the fact that survival trees isolate the scenarios where the NHS Diabetes Prevention Programme is associated with a new diagnosis of type 2 diabetes in those who did not have type 2 diabetes on entry

Table 8-3: Key sources of biases in different aetiological epidemiology approaches for estimating the effectiveness of the NHS Diabetes Prevention Programme

Approach	Description of study	The assumption for this study	General Key source of bias when compared to a randomised controlled trial	Direction sources of bias has on result
Multivariable retrospective observational propensity-matched cohort studies (Chapter 5)	Retrospective observational cohort study between June 2016 to January 2019. I compared rates of new type 2 diabetes diagnoses among eligible adults who were referred to the NHS Diabetes Prevention Programme rates for controls who were eligible for the NHS Diabetes Prevention Programme but were not invited. Adults with pre-existing type 2 diabetes were excluded. Time to the first record of type 2 diabetes was modelled using Cox regression.	That I carefully chose the covariates to avoid unmeasured confounders. That propensity score matching reduced differences in baseline demographic, leading to a reduction in the risk of confounding by indication. That by using multiple imputation, the imputed values are representative of the target population. Removal of cases within 90 days since the start of follow-up is appropriate method for removing prevalent cases of type 2 diabetes.	The primary limitation with observational studies is that there are unmeasured confounding variables. Such confounders are less likely to exist in randomised controlled trials due to the randomised nature of arm-assignment. In randomised controlled trials, there are often eligibility checks which we had to emulate using clinical input. Missingness was more likely for control groups as they were less likely to go to the general practice (also a consequence of confounding by indication) and have data on confounding covariates recorded in their electronic health records.	The use of propensity score matching may <u>overestimate the impact</u> of an intervention on an outcome (Dahabreh et al., 2012). As participants of the NHS Diabetes Prevention Programme can only be referred if their general practitioner confirms a diagnosis of non-diabetic hyperglycemic (as opposed to diabetes), we expect in observational data, that there is a higher rate of type 2 diabetes diagnosis within the beginning of follow-up in the control group as they were not actively checked. By removing all cases diagnosed within the first 90 days from both intervention and control groups, we expect there to be a disproportionate amount of prevalent cases in the control group. Removing those with a phenotypical recording of type 2 diabetes within the first 90 days in the NHS Diabetes Prevention Programme, our result is likely to <u>produce a conservative estimate of the impact of public health interventions on type 2 diabetes incidents.</u> Although the use of multiple imputation gives a <u>better estimate</u> of the NHS Health Check on the incident of type diabetes by including those who are more likely to develop type 2 diabetes even if they do have missing baseline data.
Multivariable data science approaches to retrospective observational cohort studies (Chapter 7)	A retrospective observational cohort study was conducted between June 2016 to January 2019. New rates of type 2 diabetes diagnoses were compared among eligible adults referred to the NHS Diabetes Prevention Programme with rates for those who were not referred. Adults with pre-existing type 2 diabetes on entry were excluded. Imputation was conducted using multiple imputation using random forests whilst Survival trees were used to estimate the time to the first record of type 2 diabetes.	That I carefully chose the covariates to avoid unmeasured confounders. That propensity score matching reduced differences in baseline differences, leading to a reduction in the risk of confounding by indication. That by using multiple imputation, the imputed values are representative of the real population.	As previously mentioned, unmeasured confounding variables could impact such observational studies. Missingness was more likely for control groups as they were less likely to go to the general practice (also a consequence of confounding by indication)	The sub-group analysis nature of the survival tree method means that it <u>would overestimate the preventative effect by isolating the NHS Health Check variable to only situations where it is a good predictor of the incidence of type 2 diabetes.</u> he use of multiple imputation provides a <u>better estimate</u> of the NHS Health Check on the incident of type diabetes by including those who are more likely to develop type 2 diabetes even if they do have missing baseline data.

Discussion

In previous chapters, I used various methods to evaluate the effectiveness of the NHS Health Check and the NHS Diabetes Prevention Programme on rates of type 2 diabetes as outlined in the first chapter of my PhD. These methods include systematic reviews, interrupted time series, two retrospective cohort studies, and two public health data science alternatives. Each method has different underlying data, assumptions and sources of bias and this final chapter aims to collate all the results and combine them using aetiological triangulation to understand the results produced from various methods that introduce various biases. This chapter then summarises the direction of the effect of public health interventions on the incidence of type 2 diabetes through the various studies.

Key Results of triangulation

By triangulating studies which evaluate the NHS Health Check Programme and the NHS Diabetes Prevention Programme, I generated a better understanding of these programmes' effect on the different outcomes related to type 2 diabetes. When evaluating the NHS Health Check as screening programmes, there is evidence that this situation detects previously undiagnosed cases which should be removed if they are to be conceptualised in this manner. Therefore, to estimate their preventative effect on the incidence of type 2 diabetes without this removal of prevalent cases is providing a biased estimate of their effect. For example, an important goal of the NHS Health Check is to be able to detect previously undiagnosed cases of type 2 diabetes, a more appropriate outcome would include whether the NHS Health Check reduces the complications of diabetes (e.g., diabetic retinopathy, amputations related to diabetes) compared to a comparable set of previously undiagnosed diabetic patients who did not receive the NHS Health Check.

When trying to understand public health interventions as a preventative measure by removing previously undiagnosed cases on (estimated) entry, both the NHS Health Check and the NHS Diabetes Prevention Programme demonstrate a preventative effect against type 2 diabetes. This is similar to programmes worldwide (Diabetes Prevention Programme Group, 2015, 2002; Ilanne-Parikka et al., 2013) which were mentioned by teams at Public Health England (Barron et al., 2018).

One challenge when understanding the effect of public health interventions on reducing the incidence of type 2 diabetes, even if it is effective on the individual level, is whether it produces a detectable reduction of type 2 diabetes at the population level. Through the interrupted time series work in Chapter 3, I did not detect the NHS Health Check's impact on hospital admissions for type 2 diabetes. This is potentially caused by the assumptions of the interrupted time-series design, particularly that a high enough proportion of the population needed to have partaken in the intervention for there to be a detectable change in monthly admissions of type 2 diabetes. In addition, the healthy adult requirement of the NHS Health Check means that the outcome would have been hard to detect using an interrupted time series study as rates of type 2 diabetes in this group were found to be low (1.55%) in Chapter 6.

Strengths of triangulation

The detailed strengths of each study can be found in previous chapters. A primary strength of the systematic review is that it was able to understand the wide variety of measures and outcomes of the NHS Health Check on type 2 diabetes; this allowed me to understand current limitations of the literature to inform the studies in Chapters 3, 5, 6 and 7 of my PhD. Despite showing evidence of reducing cardiovascular risk, rates of previously unrecorded

cardiovascular disease, and type 2 diabetes were higher in those who had access to the NHS Health Check. Whilst this sounds conflicting; this was likely due to the ability to detect previously undiagnosed cases and understanding this fact was possible by triangulating with Chapter 6 which conducted a primary analysis that excluded those with a diagnosis shortly after NHS Health Check (or estimated control) entry and a sensitivity analysis that did not. My sensitivity analysis that replicated Robson et al, 2017 with the same underlying trends and produced the same result at Robson et al, 2017; therefore, by triangulating the results of one study type (observational cohort), I had disentangled the biases of another study type (systematic review).

Without prior studies analysing the impact of the NHS Health Check on national rates of type 2 diabetes (and other cardiovascular diseases) I undertook an interrupted time series which did not detect changes on a national level. Compared to a randomised controlled trial, I expected an interrupted time series to underestimate the impact of the NHS Health Check on rates of diseases. By triangulating this interrupted time series (Chapter 3) with an observational study (Chapter 6), I concluded that the low rates of type 2 diabetes in “healthy” adults 1.55% at the individual level would mean that detecting changes on a national level would be difficult.

By undertaking an observational study using data science methods, I found subgroups where the NHS Health Check (and Diabetes Prevention Programme) is more likely to be effective under specific subgroups of the eligible population. Such results triangulate well with our understanding of the social determinants of health and agree well with the simulation studies found in my systematic review (Chapter 2) (Collins et al., 2017) (Kypridemos et al., 2016).

In the absence of randomised controlled trials and a meta-analysis, using triangulation allowed me to understand the effect of the NHS Health Check and NHS Diabetes Prevention Programme on various outcomes and measures. By understanding the potential biases, I understand the direction in which the biases would influence the result. Triangulation allowed me to understand how to compare studies to generate an appropriate view of how each study should be interpreted, especially when the different study designs produce effects of opposing directions. Triangulation also allowed me to understand results which may seem to be conflicting.

Limitations of triangulation

The detailed limitations of each study can be found in previous chapters. Whilst triangulation aims to combine studies akin to a meta-analysis, the different outcome measures cannot generate a single point estimate. Whilst the triangulation framework helps me understand how certain biases can impact the direction of my results, it does not account for all biases. For example, changes in clinical coding practices in Chapter 3 are time-varying and can impact rates of admissions in both directions (an increase or a reduction) depending on different versions of clinical coding guidelines.

It is also hard to understand the impact of missing data; whilst previous studies have demonstrated that conducting a full case analysis can underestimate cardiovascular, the social determinants of health are often the social determinants of missing data (Collins and Altman, 2010). Whilst I used multiple imputation to reduce missingness, it is difficult to understand whether such a method would over or underestimate the impact of public health interventions on the incidence of type 2 diabetes as the use of multiple imputation simply produces a more appropriate estimate when compared to using a full case analysis.

It is also difficult to understand how biases such as unmeasured confounding can impact an observational study in terms of underestimating or overestimating the impact of an intervention (i.e. the NHS Health Check and the NHS Diabetes Prevention Programme) on an outcome (incidence of type 2 diabetes). Therefore, even if unmeasured confounding does exist in my study, I am unable to take into account how my results should be interpreted.

Finally, the target-trial emulated observational studies and the data science alternatives were modelled using an intention-to-treat analysis, that is of those who have any NHS Health Check and NHS Diabetes Prevention Programme activity. Such analyses evaluate the impact of an invitation to these programmes but do not understand the impact of completing these programmes. Whilst this does mean that my preventative estimates are conservative, this does mean I am underestimating the impact of these programmes when compared to a per-protocol analysis. For the NHS Diabetes Prevention Programme, this would include starting from an invitation, and completing all sessions and starting the follow-up after the completion of the 9-month programme. For the NHS Health Check, this includes, being invited to the NHS Check, finding no pre-existing conditions during the screening, and following the patient until they finish their prescribed treatment (for example the NHS Diabetes Prevention Programme).

Interpretation of triangulation

Access to public health interventions such as NHS Health Check and the NHS Diabetes Prevention Programme reduces individual risk of developing type 2 diabetes compared to a control group in adults without a previous case of type 2 diabetes.

Chapter 9 - Concluding Remarks, Implications and Future Work

Concluding Remarks

Combining established epidemiological and novel applications of data science methods in my thesis provide evidence to support the effectiveness of the NHS Health Check in achieving its goals of reducing the incidence of type 2 diabetes. In addition, it also facilitates detection of previously undiagnosed type 2 diabetes in those who are invited to an NHS Health Check compared to a similar group of patients who were not invited. This disentangles prior systematic review evidence on higher rates of “new detection” in attendees of a health check. However, such preventative benefits were not detectable in population level statistics, and this is likely due to the low acceptance rates of the NHS Health Check and its eligibility criteria of “healthy” individuals who had low rates of type 2 diabetes over time. The data science methods suggest patients’ subgroups including those who identified as non-White (including Asian, Black, or Mixed ethnicities) with a baseline HbA_{1c} higher than 45 mmol/mol and BMI higher than 25 kg/m² are more likely to have a recorded diagnosis of type 2 diabetes even if they’ve taken part in the NHS Health Check when compared to their White counterparts; this could be related to higher baseline risks. Future research should investigate whether the NHS Health Check can improve outcomes in such populations to understand it’s aim of being equitable; potentially using the target trial emulation framework on previously collected data. This is important as Robson et al., 2016 found that ethnic minority groups (particularly Bangladeshi patients) were more likely to attend an NHS Health Check compared to their white counterparts (Robson et al., 2016).

The NHS Diabetes Prevention results reflect those of similar interventions in the United States and in Finland which were evaluated using randomised

controlled trials, leading to promising long-term results. Even though these trials have higher eligibility thresholds compared to the NHS Diabetes Prevention Programme, for example, the USA's Disability Prevention Programme Group required an age limit of at least 25 years old and a body mass index of at least 24kg/m² and Ilanne-Parikka *et al* in Finland requiring a body mass index of at least 25kg/m² in those between the ages of 40-65, the results triangulated well with the NHS Diabetes Prevention Programme with a lower age limit of 18 years and no body mass index requirements.

The data science methods suggest that baseline body mass index could also be considered when targeting patients to be invited to the NHS Diabetes Prevention Programme. Whilst the minimum HbA_{1c} level that is required for referral to the NHS Diabetes Prevention programme is 42 mmol/mol, patients with this blood sugar level with a body mass index (BMI) higher than 27.45 kg/m² should have further attention paid to them due to the additional risk of developing type 2 diabetes compared to those with a lower body mass index.

See Table 9-1 for how the seven aims and objectives of this PhD (from Chapter 1 Table 2) were met through the variety of study designs in Chapters 2,3,5,6,7 and 8.

Table 9-1: Research Gap table from Chapter 1 and the results during the study of this PhD

#	Research Gap	PhD Objective	Method	Main findings	Chapter
1	Lack of a recent comprehensive overview of the studies which evaluate the NHS Health Check in terms of their population (inclusion/exclusion criteria), control groups, and healthcare outcomes (and how these outcomes are measured)	To establish the existing evidence-based on the effectiveness of NHS Health Check, which mediates the widespread use of statins and intensive diabetes prevention programmes on healthcare outcomes by undertaking a systematic review to identify existing evaluations.	I conducted a systematic review using PubMed and Embase via Ovid to search for articles that use the NHS Health Check to establish its impact on cardiovascular events, diabetes, stroke and chronic kidney disease. I used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart to help with the inclusion/exclusion criteria and used the Centre of Evidence-Based Medicine's guidelines to appraise the studies. I then stratified the studies disease and method (Systematic Review, RCT, Observational). Observational studies were further stratified by whether included a control group for comparison and whether they were a simulation using the data from the Health Survey for England (HSE). Meta-analyses were conducted where possible.	I found 22 studies complying with the inclusion criteria. 13 analysed cardiovascular outcomes, 4 analysed diabetic healthcare Outcomes, 3 analysed stroke, 4 analysed chronic kidney disease and 6 analysed hypertension. I could not meta-analyse the data due to differences in populations (individual level vs general practice level), comparison groups (before and after the intervention, intervention, and control groups) as well as different outcomes (change in prevalence, change in risk score). Overall, I found that whilst the NHS Health Check decreases individual risk factors for cardiovascular disease, the prevalence of cardiovascular disease is still higher amongst NHS Health Check attendees. Prevalence of diabetes, stroke and chronic kidney disease was the same or higher in NHS Health Check attendees, however, this may be related to baseline differences and detection of prevalent cases.	Chapter 2
2	Lack of evidence about the national impact of the NHS Health Check on rates of cardiovascular disease, diabetes, and chronic kidney disease at the population level in England.	To conduct a quasi-experimental interrupted time series analysis using aggregated populational level datasets to estimate the association between NHS Health Check and changes in rates of cardiovascular disease, diabetes, and chronic kidney disease since its introduction.	To conduct this study, I used hospital episode statistics between June 2003 to March 2017 with an interruption in January 2009 (introduction of NHS Health Check). I choose Hospital Episode Statistics due to its high coverage of admissions compared to primary care datasets. I then established monthly admission rates (adjusted for population size) for chronic kidney disease, heart disease, stroke and type 2 diabetes using Hospital Episode Statistics. To mirror the inclusion criteria of the NHS Health Check, I only included those between the ages of 40-74 on admission. Comparisons of rates were made before Check (June 2003 to December 2008) and after the introduction of the NHS Health Check (January 2009 to March 2017).	Between the start of the study and the introduction of the NHS Health Check (i.e. 2003 to 2009), there was a month-to-month decrease of 1.82 admissions per month per 100,000 people [95% CI: -2.14 admissions/100,000 to -1.51 admissions/100,000) for cardiovascular disease, diabetes and stroke combined. After the introduction of the NHS Health Check until the end of the study (i.e., from 2009 to 2017), there was a month-to-month decrease of 0.13 admissions per month per 100,000 people [95% CI: -0.29 admissions/100,000 to 0.03 admissions/100,000]. I found substantial changes in clinical coding for these outcomes over time, and for this reason, my evaluation demonstrated that the interpretation of these findings are limited to estimate the association between NHS Health Check and changes in rates of cardiovascular disease, diabetes and chronic kidney disease at the population level.	Chapter 3 Research Paper 1

#	Research Gap	PhD Objective	Method	Main findings	Chapter
3	Lack of evidence-based clinical code list for phenotyping the NHS Health Check population and cardiovascular, diabetic, and chronic kidney disease-based outcomes in primary care datasets. Lack of consensus on the inclusion/exclusion criteria when evaluating the NHS Health Check as a preventative programme.	To improve primary and secondary care electronic health record code lists by undertaking a systematic review to generate evidence-based code lists that can be used to identify patients that have had an NHS Health Check or have participated in the NHS Diabetes Prevention Programme and their subsequent health outcomes. To introduce a method that overcomes biases when identifying clinical codes used to extract data from administrative observational healthcare datasets. To use to improve the lack of consensus on the inclusion and exclusion criteria when evaluating the NHS Health check as a preventative intervention.	I conducted a systematic review using PubMed and Embase via Ovid to search for articles that evaluated the NHS Health Check, the NHS Diabetes Prevention Programme, and their associated healthcare outcomes (diabetes, heart disease, hypertension and stroke) using primary care datasets including the Clinical Practice Research Dataset, The Health Improvement Network and the QResearch dataset. As previous work has established that chronic kidney disease detection is unreliable using READ codes, I did not include this. The primary inclusion criteria I used included publications which specifically used the READ clinical code terminology. To overcome the issue of confidence in clinical coding, I created a map of each READ code, which maps to the various studies which used that specific code. Using this method, I was able to state exactly which READ codes the scientific community use and how confident each READ code represents a disease by counting the number of citations per code.	In total, I found 167 articles after screening a total of 13,182 articles. I found a total of 8664 READ codes, with 1770 READ codes associated with diabetes, 4019 with heart disease, 2551 for hypertension and 766 for stroke. - For heart disease, the most cited codes were “G30..15” and “G30..00” with 19 studies quoting them each. - For hypertension, the most used codes started with “G20” or “G24” and had 18 citations each. - For Stroke, the most cited codes were “G66..11” and “G667.00” with 26 citations each. - The most cited type 2 diabetes codes had 22 citations each and all started with “C10F”. - For the NHS Health Check, I found 421 unique READ codes(most of which were based upon data collected during the NHS Health Check), with the most popular codes “9mC*” having 3 citations each. - For the NHS Diabetes Prevention Programme, I found 5 READ codes , all starting with 679m*, all having 2 citations each (due to the recent deployment of the NHS Diabetes Prevention Programme).	Chapter 4
4	Lack of observational studies emulating randomised controlled trials to evaluate the preventative effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes	To conduct a trial-emulating population-based cohort study using matched primary and secondary care health records to understand the preventative effect of the NHS Health Check and NHS Diabetes Prevention Programme on the incidence of type 2 diabetes.	I conducted a retrospective observational cohort study using linked electronic health records using data from primary care (clinical practice research datalink) with secondary care (hospital episode statistics) and office of national statistics death records. To emulate a randomised controlled trial, I removed those with an exclusionary diagnosis on entry so that I could appropriately evaluate the preventative effect of the NHS Health Check and NHS Diabetes Prevention Programme. To tackle missing data, I used multiple imputation with chained equations. I then emulated randomisation using propensity score matching to generate cohorts with similar baselines. I then modelled the time to first recording of type 2 diabetes using	I found 2205 individuals who participated in the NHS Diabetes Prevention Programme and 8820 matched controls were identified. During the 2.5-year study period, 4.13% of NHS Diabetes Prevention Programme individuals had newly recorded type 2 diabetes vs 6.42% of controls. My results indicate that NHS Diabetes Prevention Programme referrals were associated with a 59% reduction in type 2 diabetes recorded incidence rates [adjusted hazard ratio=0.41;95%CI=0.38-0.44]. My results were comparable to other randomised controlled trials evaluating similar interventions worldwide.	Chapter 5
5	Lack of observational studies emulating randomised controlled trial to evaluate the preventative effect of the NHS Health Check on preventing type 2 diabetes			I found 105,382 individuals who participated in the NHS Health Check and 105,382 matched controls with a similar breakdown in age, sex, deprivation, and relevant clinical covariates were identified. During the 10-year study period, 1.04% of NHS Health Check individuals had newly	Chapter 6 Presentation 1

#	Research Gap	PhD Objective	Method	Main findings	Chapter
			multivariate Cox proportional hazards models to account for individuals from different background.	recorded type 2 diabetes vs 2.06% of controls. My results indicate that NHS Health Check referrals were associated with a 54% reduction in recorded type 2 diabetes incidence rates [adjusted hazard ratio= 0.46 95% CI:0.45 – 0.47].	
6	Lack of analyses comparing different methods and data with different forms of bias used to examine the challenges in traditional epidemiological studies in the evaluation of the NHS Diabetes Prevention Programme and NHS Health Check.	To compare data science methods used for multiple imputation, matching and multivariate time-to-event analyses to established epidemiology methods in order to examine the effect of these new methods on bias within the study designs of the evaluations of the NHS Health Check and the NHS Diabetes Programme.	Separate evaluations of the NHS Health Check and the NHS Diabetes Programme were undertaken. First, traditional Multiple Imputation using Chained Equations was compared to Multiple Imputation using Multiple Imputation using Random Forests and K's Nearest Neighbour imputation. Second, propensity Score Matching was compared to Synthetic Minority Over Sampling Technique. Finally, Cox proportional hazard models were compared against multivariate survival trees.	Results - NHS Diabetes Prevention Programme: Both K's Nearest Neighbours and Multiple Imputation using Random Forests produced similar results to Multiple Imputation using Chained Equations; all methods produced similar results to an externally validated dataset. Using SMOTE increased the cohort size from 11,025 (2205 intervention + 8820 propensity score-matched control) to 53,574 individuals (24393 synthetically generated intervention patients + 29182 control patients). Traditional epidemiological methods demonstrate that the NHS Diabetes Prevention reduces type 2 diabetes incidence rates by 59% [adjusted hazard ratio=0.41;95%CI=0.38-0.44] when adjusting for a variety of clinical and sociodemographic covariates; with NHS Diabetes Prevention Programme activity, ethnicity, baseline blood glucose measures and gender being identified as significant variables. By using survival trees with the same clinical and sociodemographic covariates, I found that patients are less likely to have recorded type 2 diabetes if they participated in the NHS Diabetes Prevention Programme with a baseline HbA_{1c} higher than 44 mmol/mol or a HbA_{1c} higher than 42mmol/mol with a BMI higher than 27.45 kg/m². Results - NHS Health Check: Due to the large size of the NHS Health Check data set, K's Nearest Neighbour and, by extension, the Synthetic Minority Oversampling Technique could not run due to memory constraints; this was not an issue with established epidemiological methods such as Multiple Imputation using Chained Equations and Propensity Score Matchings. Multiple imputation using Random Forests produces a similar breakdown for all covariates when compared to traditional Multiple Imputation using Chained Equations except for ethnicity. Using traditional Cox Proportional Hazards, NHS Health Check referrals were associated with a 54% reduction in type 2 diabetes recorded incidence rates [adjusted hazard ratio= 0.46 95% CI:0.45 – 0.47] when adjusted for a variety of sociodemographic and clinical covariates; NHS Health Check activity, blood	Chapter 7

#	Research Gap	PhD Objective	Method	Main findings	Chapter
				glucose measures, age, gender, ethnicity cardiovascular risk deprivation, smoking and alcohol status were found to be significant variables. Using the same set of sociodemographic and clinical covariates with survival trees, I found that patients are less likely to have recorded type 2 diabetes if they participated in the NHS Health Check with a baseline HbA _{1c} higher than 35mmol/mol with a BMI higher than 25kg/m ² . Patients who identify as non-White (including Asian, Black or Mixed) who were invited to the NHS Health Check with a baseline HbA _{1c} higher than 45mmol/mol and BMI higher than 25kg/m ² were most likely to have recorded type 2 diabetes compared to other ethnicity and BMI combinations.	
7	Lack of triangulated analyses comparing studies using different datasets and methods – each with different biases – in order to examine the impact of these biases on the estimates of the effectiveness of the NHS Diabetes Prevention Programme and NHS Health Check on reducing the incidence of type 2 diabetes	To triangulate the results from all evaluations undertaken in the thesis in order to evaluate the biases and challenges introduced by each study method and investigate the overall effect of the NHS Diabetes Prevention Programme and NHS Health Check on type 2 diabetes.	I applied a triangulation framework to the studies in my PhD in reference to the direction of bias in reference to a comparable randomised controlled trial	Using systematic reviews and interrupted time series, I did not detect a preventative effect of public health interventions on the incidence of type 2 diabetes and this is expected as they do not evaluate the same effect measure as a randomised controlled trial. Without using target trial emulation, my observational study produced similar results to prior studies which evaluated “new diagnoses” of type 2 diabetes. When using target trial emulation with the same observational study dataset, I produced similar results to randomised controlled trials which evaluated public health intervention on the recorded incidence of type 2 diabetes. Using data science methods, I identified subgroups where the NHS Health Check is effective and where they could be improved based upon sociodemographic and clinical characteristics and add to prior literature on the inequities involved in the NHS Health Check. With all the evidence taken into consideration and their biases, my work shows the NHS Health Check and Diabetes Prevention Programme can demonstrate individual level reductions on the recorded incidence of type 2 diabetes, although this may not reflect in detectability at the population level.	Chapter 8

Policy recommendations

This research demonstrates that the NHS Health Check and NHS Diabetes Prevention programme can reduce the incidence of type 2 diabetes under an emulated “controlled” environment. However, using a variety of methods, I found that it is difficult to detect changes at a population level, and this could be explained through the low uptake of the NHS Health Check. Therefore, policy should concentrate on increasing uptake, particularly patients who identify as non-White (including Asian, Black, or Mixed ethnicities) who have an HbA_{1c} higher than 45 mmol/mol and BMI higher than 25 kg/m²; where possible, these set of patients should be referred to the NHS Diabetes Prevention Programme due to its effectiveness. Future evaluations of such policies could be done using the same methods in PhD, including the use of the target trial emulation framework along with imputation and matching methods. In addition, if these policies were to be implemented, a further survival tree analysis should be used to understand the robustness of the results for these high-risk groups within the NHS Diabetes Prevention programme. If the groups generated in this PhD’s survival tree are robust, increased uptake would still produce similar at-risk groups except with different numbers to reflect the change in uptake. If newer groups are identified at risk, further modifications should be made as part of an interactive clinical audit to constantly improve public health interventions in preventing type 2 diabetes.

As the NHS Diabetes Prevention Programme produces promising results, policymakers should consider expanding the NHS Diabetes Prevention Programme to comparable geographical areas as those where the NHS Diabetes Prevention Programme is currently deployed. Therefore, given the internal triangulation and external validity of this PhD of the trial emulation studies, further randomised controlled trials are not likely required to evaluate the impact of public health interventions on the incidence of type 2 diabetes.

Stakeholder involvement

Unfortunately, due to my contribution to the COVID-19 pandemic public health effort, I was unable to conduct stakeholder involvement including public and patient involvement and engagement. I have been interviewed by the publication Re:Solve Global Health, an online publication aimed at healthcare stakeholders, including doctors and patients about my views on the NHS Health Check. My message to clinicians and patients is that the NHS Health Check helps uncover previously undiagnosed and “unknown” cases and provides patients access to much needed diagnostic tools. Furthermore, I would like patients to understand that patients who are identified of being high-risk (of developing type 2 diabetes) that the NHS Health Check can provide access to preventative programmes such as the NHS Diabetes Prevention Programme which can reduce or delay the progression of type 2 diabetes. My interview can be viewed here:

<https://web.archive.org/web/20230406053159/https://www.re-solveglobalhealth.com/post/should-health-checks-be-mandated-for-all>

Furthermore, during my PhD, I have been contacted by policy and evaluation stakeholders at Public Health England (now, the Office for Health Improvement and Disparities') about the imputation of the NHS Health Check data. A draft of the data science chapter (Chapter 7) of my PhD was provided to Public Health England to demonstrate the options for imputing missing data.

Novel method applications in my PhD

During my PhD I have applied a variety of novel applications of data science methods in evaluating public health interventions using observational data. Future studies should consider using such methods to strengthen their findings.

In Chapter 4, I introduced a simple method for understanding how popular a specific READ code is in understanding its use in the current literature. Whilst using systematic reviews to generate code lists is not new, studies rarely analyse how many times specific READ codes are used to identify disease populations. Such methods are important as they help researchers provide a quantitative measure in the selection of their clinical codes when conducting an observational study.

In Chapters 5 and 6, I've pioneered a method for estimating an appropriate start of follow-up for those who did not initiate treatment. The primary advantage this introduces is that it allows similar individuals to have similar follow-up periods, and this is important in a time-to-event analysis as those who have longer follow-up are more likely to experience the event (in this case incident type 2 diabetes) due to the cumulative effect of the hazard function. This contrasts other methods such as randomly picking an index date (and checking eligibility) as this produces follow-up times closer to the mean follow-up time; whilst matching similar control individuals on an intervention participant's index date does not control for follow-up time.

In Chapter 7, I've introduced a variety of data science methods to complement established epidemiological methods as part of my analysis. First, I've introduced methods for imputation such as Multiple Imputation using Random Forests and K's Nearest Neighbour imputation. Both imputation methods were able to produce similar results to a population-level dataset but do not require assumptions of the distribution of the underlying data when compared to Multiple Imputation using Chained Equations. Secondly, I've used the synthetic minority over-sampling technique (SMOTE) when evaluating the NHS Diabetes Prevention Programme to "preserve" sample sizes. Such sampling methods are important, particularly when observational datasets record a small sample of the whole population. Finally, I've applied survival tree analysis to understand the subgroups where 1)

public health interventions are effective and 2) situations where there are differential outcomes based upon socio-demographic or clinical characteristics of patients partaking in public health interventions. By understanding these subgroups, we can 1) target groups which are likely to benefit from such interventions and 2) improve the current intervention for individuals who do not benefit as much as others.

Future recommendations for research

One of the main aims of this PhD is to pragmatically emulate a randomised controlled trial through trial emulation using observational data; this includes using strict inclusion and exclusion criteria based upon an (estimated) entry date. Whilst this process emulates an “eligibility” screening process in a randomised controlled trial, this is used by the NHS Health Check as a screening process to identify previously unrecorded cases of chronic kidney disease, heart disease, hypertension, stroke and type 2 diabetes. As stated in previous chapters, this “screening” process can bias the analysis as previously undiagnosed cases of type 2 diabetes can falsely be attributed as an incident case of type 2 diabetes. To tackle this issue, future work can pragmatically evaluate the NHS Health Check by including healthcare outcomes such as the complications attributed to type 2 diabetes, such as diabetic retinopathy or amputations related to type 2 diabetes. Therefore, this would change the research question from “Does the NHS Health Check prevent the incidence of type 2 diabetes in eligible adults without type 2 diabetes on entry?” to “Does the NHS Health Check reduce the progression and complications of type 2 diabetes?”. Under the later analysis, the aim is to understand whether the NHS Health Check’s ability to identify previously undiagnosed cases of type 2 diabetes allows better control of the disease compared to those are diagnosed later (or not at all).

Due to the recent deployment of the NHS Diabetes Prevention Programme, when the data is available, this analysis should be updated in a similar

manner to the Diabetes Prevention Programme Group study, 2002/2015 in the United States who updated their 2.5-year analysis at 15 years. At the time of concluding this PhD, the NHS Diabetes Prevention Programme has been deployed for 7 years, therefore an updated analysis could be conducted soon, although data availability is often lagged, and NHS Diabetes Prevention Programme activity may have been reduced during the COVID-19 pandemic.

Whilst the NHS Diabetes Prevention Programme specifically targets type 2 diabetes as the healthcare outcome, future research could consider evaluating other healthcare outcomes, primarily those covered by the NHS Health Check: chronic kidney disease, hypertension, heart disease and stroke. This is because such diseases are often seen as preventable through lifestyle changes and the programme offered by the NHS Diabetes Prevention Programme do enable such changes.

In addition to the recommendations in terms of the research on public health interventions on type 2 diabetic outcomes; there are further research recommendations that are produced out of this PhD:

Firstly, as mentioned in Chapter 2, systematic reviews which have analysed “health checks” in general included “health checks” prior to the introduction of modern interventions such as statins and the NHS Diabetes Prevention Programme. Therefore, systematic reviews should be updated to consider “health checks” abilities to mediate access to such modern preventative interventions.

Secondly, from Chapter 3, one of the major limitations was changes in clinical coding in secondary care (Hospital Episode Statistics). Whilst I found a solution for phenotyping diabetes in HES (by combining ICD10 codes for type 1 and type 2 diabetes), research should be conducted to generate phenotypes to consistently identify hypertension and chronic kidney disease in Hospital Episode Statistics over time.

Thirdly, after my Master of Philosophy to Doctor of Philosophy upgrade, my examiners suggest that my work should examine a narrower range of outcomes related to type 2 diabetes and use this as a framework for analysis. As the NHS Health Check and the NHS Diabetes Prevention Programme concentrate on “lifestyle” related interventions, future research should understand the impact of these public health interventions on other outcomes such as chronic kidney disease, heart disease, hypertension, and stroke. This reflects the recommendations above.

Fourthly, with development of the NHS Diabetes Prevention Programme, methods from Chapter 4 should be reapplied and updated to understand any new clinical codes associated with NHS Diabetes Prevention Programme activity. This maybe important due to any clinical codes that were introduced during the COVID-19 pandemic for the online stream of the NHS Diabetes Prevention Programme.

Furthermore, future work that evaluates public health interventions using observational data should consider using the framework set out by this PhD. That is 1) analysing the data on a national level to understand population level effects, 2) using trial emulation to reduce confounding when using observational to understand individual effects and 3) use triangulation to create an overall picture of the impact of such interventions when considering biases introduced by various study designs.

Finally, during this PhD, methods were validated primarily through external validation by comparing cohort distributions and triangulating results against other sources, for example by comparing my NHS Diabetes Prevention Programme cohort against publications and comparing my NHS Health Check’s ability to find new diagnoses against prior work without applying a target trial emulation framework.

Whilst external validation produces one form of reassurance of the results, this PhD did not conduct much internal validation. Therefore, future work evaluating the NHS Health Check and NHS Diabetes Prevention Programme should test and validate the suitability of methods used, for example by testing the proportional hazards assumptions when using Cox Regression by evaluating Schoenfeld residuals. As my PhD did not conduct such internal validity checks, future work could evaluate whether there were better models which describe the data and produce more confident results for policy makers to interpret.

Chapter 10 References

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Chapter 11 Appendices

Appendices for Chapter 2

Appendix 2.1 – Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist for Chapter 2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n7
For more information, visit: <http://www.prisma-statement.org/>

Section and Topic	#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Systematic review of the studies which evaluate the NHS Health Checks on cardiovascular disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes.
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklisdt.	Introduction and research gap: Prior to this PhD research, the last systematic review examining the evidence of the effectiveness of the general health checks in adults was conducted in 2012, with results covering health checks implemented up until 1999. This is before the widespread use of modern interventions such as statins and intensive diabetes prevention programmes and before the NHS Health Check itself. Therefore, there is a lack of a recent comprehensive overview of the studies which evaluate the NHS Health Check in terms of their population (inclusion/exclusion criteria), control groups, and healthcare outcomes (and how these outcomes are measured). This chapter aims to systematically review the literature specifically on the NHS Health Checks to update previous systematic review of health checks to inform the latter chapters of this PhD. The objective of this chapter is to evaluate whether and how the NHS Health Check impacts rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes or changes in measurable cardiovascular risk and health-style related outcomes such as QRisk-2 cardiovascular score and body mass index. Method: A systematic search was conducted on PubMed and Embase via Ovid for studies examining the NHS Health Check to establish its impact on cardiovascular events, diabetes, hypertension, stroke, and chronic kidney disease on 28th October 2018. The <i>Population</i> of interest was NHS Health Check eligible patients and practices with the <i>Intervention</i> consisted of the NHS Health Check. <i>Comparisons</i> were made before/after the NHS Health Check and between eligible invitees and eligible non-invitees. The <i>Outcomes</i> included cardiovascular disease, chronic kidney disease, hypertension, stroke, and type 2 diabetes. The inclusion criteria were English language studies that specifically examined the impact of the NHS Health Check on the above healthcare outcomes. Studies that evaluated uptake of the NHS Health Check, or other health checks were excluded (such as those outside of England). Studies before the introduction of the NHS Health Check (2009) were not included. Qualitative studies, comments, editorials, or responses were excluded. Included studies were appraised using the Centre of Evidence-based Medicine guidelines. Studies were stratified by disease and design (systematic review, randomised controlled trial and observational). Observational studies were stratified by whether included a control group for comparison. Meta-analyses were conducted where possible. Results: Nineteen studies were included from, a total of 6,759 articles. Thirteen studies with cardiovascular outcomes were included, four with diabetic healthcare outcomes, three for stroke-based outcomes, four analysed chronic kidney disease and six analysed hypertension. Due to heterogeneous outcome measures, a meta-analysis was not possible. When compared with both pre-NHS Health Check and a control group, the NHS Health Check decreases individual risk factors for cardiovascular disease (e.g., body mass index). New diagnoses of cardiovascular disease are higher amongst NHS Health Check invitees when compared to non-invitees. Newly unrecorded diagnoses of diabetes, stroke and chronic kidney disease was the same or higher in NHS Health Check invitees compared to non-invitees, however, this may be related to baseline socio-demographic and clinical differences in the active participants of the NHS Health Check leading to detection of previously undiagnosed cases. Discussion and Conclusion: The literature surrounding the NHS Health Check does not explain whether attending an NHS Health Check can reduce the risk of developing diabetes, heart disease, hypertension, stroke, or chronic kidney disease in individuals who have not experienced these diseases prior to follow-up. Further studies should disaggregate the difference between detecting undiagnosed cases on entry and incident cases of diabetes, heart disease, hypertension, stroke, or chronic kidney disease after receiving the interventions.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Current debate surrounding the effectiveness of the NHS Health Check is primarily based on evidence produced in 2012 by Krogsbøll et al., 2012 (Krogsbøll et al., 2012) which is a systematic review consisting of 16 studies evaluating “general health checks” between 1963 and 1999. Krogsbøll et al., 2012 concluded that they could not find “an effect on clinical events or other measures of morbidity”. However, none of these studies specifically analysed the NHS Health Check (as this was introduced in 2009) and none of these studies included modern, current interventions; a weakness which was stated by (Krogsbøll et al., 2012) themselves
Objectives	4	Provide an explicit statement of the objective(s)	The aim of this systematic review was to summarise the impact of the NHS Health Check on health outcomes and the quality of the evidence evaluating the NHS Health Check. This systematic review achieves this by analysing the effect of the NHS Health Checks on:

Section and Topic	#	Checklist item	Location where item is reported
		or question(s) the review addresses.	- Rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes at both a patient and practice level - Changes in cardiovascular risk at a patient and population level - Changes in other health-style related outcomes such as a change in weight and body mass index
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	The inclusion criteria I used consisted of studies that were randomised controlled trials, observational, and simulation studies that were written in English. These studies had to compare the impact of the NHS Health Check on incidence, prevalence or change-in-risk for cardiovascular disease, type 2 diabetes, chronic kidney disease, hypertension or stroke. As the NHS Health Check is specific to England, I excluded studies that were set outside of England; this excluded other general health checks from around the world. Since the NHS Health Check was introduced in 2009, studies before the 1st of January 2009 were not included. Qualitative studies, comments, editorials, or responses were excluded. Studies that quantitatively analysed the uptake of the NHS Health Check and invitation methods were also excluded as they did not evaluate the effectiveness of the NHS Health Check on health outcomes.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	The search strategy was conducted using PubMed and Embase (via Ovid) on the 28 th of October 2018. The references of each paper found on PubMed and Embase were reviewed for additional sources as recommended by the Centre for Evidence-Based Medicine (CEBM).
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	MESH terms used to conduct the search included the following terms: “NHS”, “National Health* Service”, “Health Check” (See Appendix 2.2 for detailed search strings). Duplicates were eliminated by using Microsoft Excel 2010 through title and author fields.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	I had conducted the search alone; however, soon after completing this chapter, a similar systematic review that evaluated the NHS Health Check was published with similar studies (Martin et al., 2018). From Martin et al., 2018, I had added any further studies that were not found in my search; furthermore, as Martin et al., 2018 was asking the same research request as this chapter, I also included their interpretation as external validation. The inclusion criteria I used consisted of studies that were randomised controlled trials, observational, and simulation studies that were written in English. These studies had to compare the impact of the NHS Health Check on incidence, prevalence or change-in-risk for cardiovascular disease, type 2 diabetes, chronic kidney disease, hypertension or stroke. As the NHS Health Check is specific to England, I excluded studies that were set outside of England; this excluded other general health checks from around the world. Since the NHS Health Check was introduced in 2009, studies before the 1st of January 2009 were not included. Qualitative studies, comments, editorials, or responses were excluded. Studies that quantitatively analysed the uptake of the NHS Health Check and invitation methods were also excluded as they did not evaluate the effectiveness of the NHS Health Check on health outcomes.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the	I had independently conducted the data collection of the data items. Each study that met the inclusion criteria had the following data items manually extracted into a matrix using Microsoft Excel 2010: - Study Design: Systematic Review, Controlled Study, Observational Study, Simulation Study - Healthcare Outcome: Chronic Kidney Disease, Cardiovascular Disease, Hypertension, Stroke, Type 2 diabetes or Other - Measure: Changes in Prevalence, Changes in Incidence, Changes in risk - Analytical Unit: Individual level, General Practice Level - Comparison Group: True or False

Section and Topic	#	Checklist item	Location where item is reported
		process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	To assess the risk of methodological and reporting, I used the centre of evidence-based medicine's (CEBM) appraisal tool. Using the CEBM appraisal tool, I extracted the following data items in addition to those in the Data Collection and Data Item section: • Was the assignment of the patients to treatment randomised? • Were the groups similar at the start of the trial? • Aside from the allocation of treatment, were groups treated equally? • Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised? • Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received? • How large was the treatment effect? • How precise was the estimate of the treatment effect? • Will the results help me in caring for my patients (External Validity)
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	As the goal of this systematic review is to understand the impact of the NHS Health Check on improved healthcare outcomes, all effect measures were considered. A-priori, this included: odds ratios, hazard ratios, incident rate ratios, means-difference, difference-in-difference measures. Other effect measures were used if found.

Section and Topic	#	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Descriptive tables were used to categorise studies by the study design (systematic review, controlled trial, observational studies, simulation studies), the healthcare outcome(s), measures (prevalence, incidence, other), analytical unit (individual, general practice) and whether the study used a control group. Synthesis was stratified by disease group (Chronic Kidney Disease, Cardiovascular Disease, Hypertension, Stroke, Type 2 diabetes or Other). (Micro-)Simulation studies were not used as part of the quantitative synthesis as they did not reflect real-world results. Outcomes considered for the meta-analysis included odds ratios, hazard ratios, quality-adjusted life years, and mean differences for each health outcome. For studies evaluating binary outcomes such as incidence, a confusion matrix was used to convert values to odds ratios for the meta-analysis. For secondary outcomes evaluating differences in distributions, the effect size was calculated using Cohen's D (differences in means divided by pooled standard deviation) to establish the mean difference. Studies were weighted based upon the inverse of their variability and to calculate heterogeneity, the I ² score was used. Further subgroup analyses were conducted where possible, through age, index of multiple deprivation and gender. A separate synthesis was conducted for microsimulation studies as these did not use real world data and their effects were estimated using data found in pre-existing studies.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of	Nineteen articles met the inclusion criteria from an original 6,850 papers identified. After removing duplicates, 6,054 articles were eligible to be screened by title. 120 articles were left after a title screen; 5934 articles were removed as they included either chronic kidney disease, cardiovascular disease, hypertension, stroke, or type 2 diabetes in the title but did not mention a “health check”. 29 titles were left after an abstract screen; 91 studies were primarily excluded because they were either commentaries, editorials or studies evaluating the uptake of the NHS Health Check, after a full screen, 19 studies met the inclusion criteria. See Figure 2-1 for a graphical presentation of the PRISMA filter diagram.

Section and Topic	#	Checklist item	Location where item is reported
		studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Study Design Of the 19 studies included, there was one systematic review that was Martin et al. 2018 and three prospective controlled studies were included 1) Cochrane et al. 2012; 2) Caley et al. 2014; 3) Greaves et al. 2015. Furthermore, eleven of the studies using observational data including: 1) Hinde et al. 2016; 2) Robson et al. 2017; 3) Chang et al. 2016; 4) Forster et al. 2016; 5) Forster et al. 2015; 6) Butterworth et al. 2015; 7) Artac et al. 2013; 8) Robson et al. 2016; 9) Lambert 2016; 10) Carter et al. 2016 and 11) Syed et al. 2012 Four studies used observational data but were not pragmatic as they were microsimulations, these included: 1) Kypridemos et al. 2018; 2) Mytton et al. 2018; 3) Collins et al. 2017 and 4) Kypridemos et al. 2016. Health outcomes Seven studies analysed results related to chronic kidney disease, including: 1) Martin et al., 2018; 2) Caley et al. 2014; 3) Robson et al. 2017; 4) Chang et al. 2016; 5) Robson et al. 2016; 6) Carter et al. 2016 and 7) Kypridemos et al. 2018. Eight studies analysed heart disease related outcomes, including: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Caley et al. 2014; 4) Chang et al. 2016; 5) Syed et al. 2012; 6) Mytton et al. 2018; 7) Collins et al. 2017 and 8) Kypridemos et al. 2016. Nine studies analysed results related to hypertension: 1) Martin et al. 2018; 2) Caley et al. 2014; 3) Robson et al. 2017; 4) Chang et al. 2016; 5) Forster et al. 2016; 6) Forster et al. 2015; 7) Robson et al. 2016; 8) Lambert 2016 and 9) Carter et al. 2016. Four studies analysed outcomes related to stroke, including: 1) Martin et al. 2018; 2) Syed et al. 2012; 3) Mytton et al. 2018 and 4) Collins et al. 2017. Six studies analysed outcomes related to type 2 diabetes, including: 1) Martin et al. 2018; 2) Caley et al. 2014; 3) Robson et al. 2017; 4) Chang et al. 2016; 5) Robson et al. 2016 and 6) Carter et al. 2016. Measure Five studies analysed results that measured prevalence and newly recorded diagnoses, including: 1) Martin et al. 2018; 2) Caley et al. 2014; 4) Chang et al. 2016 and 5) Carter et al. 2016. Four studies analysed results that measured previously unrecorded diagnoses, including: 1) Martin et al. 2018; 2) Robson et al. 2017; 3) Robson et al. 2016 and 4) Lambert 2016. Thirteen studies analysed other forms of measures such as change in risk. These studies included: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Greaves et al. 2015; 4) Hinde et al. 2016; 5) Chang et al. 2016; 7) Forster et al. 2016; 8) Forster et al. 2015; 8) Butterworth et al. 2015; 9) Artac et al. 2013; 10) Kypridemos et al. 2018; 11) Mytton et al. 2018; 12) Collins et al., 2017) and 13) Kypridemos et al. 2016. Analytical Unit Sixteen studies analysed the individual as the analytical unit of analysis, including: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Greaves et al. 2015; 4) Hinde et al. 2016; 5) Robson et al. 2017; 6) Chang et al. 2016; 7) Forster et al. 2016; 8) Forster et al. 2015; 9) Butterworth et al. 2015; 10) Artac et al. 2013; 10) Robson et al. 2016; 11) Carter et al. 2016; 12) Syed et al. 2012; 13) Kypridemos et al. 2018; 14) Mytton et al. 2018); 15) Collins et al. 2017 and 16) Kypridemos et al. 2016.

Section and Topic	#	Checklist item	Location where item is reported
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Five studies included results derived from using the general practice as the analytical unit of analysis: 1) Martin et al. 2018; 2) Caley et al. 2014; 4) Forster et al. 2016 and 5) Lambert 2016.
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Comparison Group Seven studies included analysis that had a comparison group, these studies were: 1) Martin et al. 2018; 2) Cochrane et al. 2012; 3) Caley et al. 2014; 4) Greaves et al. 2015; 5) Hinde et al. 2016; 6) Robson et al. 2017 and 7) Chang et al., 2016. Four following studies used a counterfactual framework for analysis; that is estimating the outcomes for the same individual under different treatment groups (including none), individuals were their own comparisons for the following studies: 1) Kypridemos et al. 2018; 2) Mytton et al. 2018; 3) Collins et al. 2017 and 4) Kypridemos et al. 2016. Seven studies did not include a comparison group: 1) Forster et al. 2016; 2) Forster et al. 2015; 3) Butterworth et al. 2015; 4) Artac et al. 2013; 4) Robson et al. 2016; 5) Lambert 2016; 6) Carter et al. 2016 and 7) Syed et al. 2012.
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	There were no double blinded randomised controlled studies analysing the NHS Health Check; this is primarily due to the NHS Health Check's active participation nature. See Table 2-2 for a summary of the risk of bias, reporting bias and certainty of evidence. Randomised Assignment Only two studies out of 19 randomly assign treatment of the NHS Health Check due to their prospective nature, with Greaves <i>et al.</i> 2015 assigning on a patient level whilst Cochrane <i>et al.</i> 2012 assigned treatment on a general practice level. To emulate the impact of randomisation such as equal baselines, four following observational studies applied matching methods, including: 1) Robson et al 2017; 2) Chang et al 2016 and 3) Forster et al. 2015,2016. For simulation studies, the following studies used a counterfactual outcomes framework: 1) Kypridemos <i>et al.</i> 2018; 2) Mytton <i>et al.</i> 2018; 3) Collins <i>et al.</i> 2017 and 4) Hinde <i>et al.</i> 2017 where potential outcomes were estimated for the same cohort under different treatment groups; therefore, each individual was assigned to all treatments. Assessment for Similar Baseline between intervention and control groups in studies From prospective studies, Greaves <i>et al.</i> 2015 which randomised treatment on a patient level found similar baselines whilst Cochrane <i>et al.</i> 2012 found no significant differences at baseline except for weight, BMI, and pulse rate. Caley et al. 2014 found that general practices 's offering the NHS Health check were comparable in terms of size, average patient age, gender split when compared to general practices not providing the NHS Health Check; however, practices offering the NHS Health Check were more deprived. For observational studies, Robson <i>et al.</i>, 2017 found that attendees were older than non-attendees, and more likely to be from more deprived quintiles or from South Asian ethnic groups. Chang <i>et al.</i>, 2016 found that Health Check attendees were older (mean age 53.5 v. 50.1), more likely to be women (52.6% v. 50.0%) and more likely to be from a white ethnic minority. (Forster <i>et al.</i>, 2016) and (Forster <i>et al.</i>, 2015) which used the same dataset found that baselines were similar amongst attendees and non-attendees. As Kypridemos et al. 2018; Mytton et al. 2018; Collins et al. 2017; and Kypridemos et al. 2016 used a counterfactual framework, individuals were compared against themselves, therefore baselines were similar for these studies. Treatment Equality Measuring treatment equality for the NHS Health Check is difficult; this is because the NHS Health Check helps mediate a variety of treatments for attendees. For those who are found to have a previously undocumented diagnosis of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes, the NHS Health Check makes referrals to the patient's general practitioner for usual care for these diseases. For patients at risk of developing at least one of aforementioned diseases, patients are then referred to preventative programmes such as the NHS Diabetes Prevention Programme. Missing Data or Loss to Follow-up Reporting of loss to follow-up was dependent on study design, and of the studies identified, loss to follow-up was reported in studies which used a before and after or difference-in-difference design. This is likely because these methodologies follow-up individuals at multiple timepoints.

Section and Topic	#	Checklist item	Location where item is reported
			Three studies reported loss to follow-up: Forster et al., 2016 and Forster et al., 2015 reported loss to follow up at 8%, and Greaves et al., 2015 reported loss to follow-up at less than 20%. Missing data was reported by two studies: Chang et al., 2016 with 20% of attendees having missing ethnicity data, whilst 40% of non-attendees had missing ethnicity data; Cochrane et al., 2012 reporting that 19% of patients had missing data. Blinding Due to the active participation required to 1) to provide the NHS Health Check, 2) (being) invite(d) to the NHS Health Check, 3) attending the NHS Health Check, and 4) potentially, being referred to either usual care or a prevention clinic, blinding is not applicable with the NHS Health Check.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Heart Disease related outcomes Thirteen studies analysed heart disease-based outcomes with one randomised controlled trial analysing the impact of the NHS Health Check against a modified version of the NHS Health Check (See Table 2-1). Of the three studies evaluating heart disease which involved a control group (see Table 2-1) all were comparing different outcomes or populations, with Cochrane et al., 2012 evaluating NHS Health Check against a modified version of the NHS Health Check, Caley et al., 2014 evaluated CVD risk between GP's offering the NHS Health Check and those GPs who did not, and Chang et al., 2016 evaluating cardiovascular disease risk between attendees and non-attendees from across a selection of general practices. Therefore, due to the differences in comparison groups and health outcomes, a meta-analysis was deemed inappropriate to evaluate the NHS Health Check 's effectiveness on heart disease. Martin et al. 2018, (systematic review) found through their evidence synthesis, that NHS Health Check attendance provided "small increases in disease detection above routine care" with a "small decrease in modelled CVD risk". No point estimate was provided as the studies were not meta-analysable. Cochrane et al., 2012 and Chang et al., 2016 concur that the NHS Health Check reduced cardiovascular disease risk using both the 10-year-Framingham Score and the QRisk2 Score by 3.5% (p-value < 0.001) and 0.21% (95% CI: -0.24%, -0.19%) respectively amongst attendees. Caley et al., 2014 established that GPs who provided the NHS Health Check and those that did not both were associated with a 0.1% reduction in the prevalence of heart disease (p-value = 0.639). Syed et al., 2012 estimated that the NHS Health Check prevents 63 chronic heart disease diagnoses, 90 myocardial infarctions over a period of 5 years in but did not include a comparison group.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Type 2 Diabetes related outcomes Six studies analysed diabetic healthcare outcomes (see Table 2-1). The studies involving a control group (see Table 2-1) could not be combined into a meta-analysis as Caley <i>et al.</i>, 2014 evaluated diabetes prevalence on a practice level, Robson <i>et al.</i>, 2017 evaluated new diabetes diagnoses on a patient level, and Chang <i>et al.</i>, 2016 presented their results using a difference-in-difference analysis. Martin et al., 2018 (systematic review) found that the rates of diagnoses of type 2 diabetes were either the same on a general practice level or higher on an individual level. No point estimate was provided as the studies were not meta-analysable. Three observational studies demonstrated the same or higher rates of the diagnoses of diabetes in NHS Health Check GP attendees using different methods. Caley <i>et al.</i>, 2014 showed no significant difference in the prevalence of type 2 diabetes in practices that undertook a health check (0.4% reduction after NHS Health Check) compared to those that did not (0.37% reduction after NHS Health Check) with a p-value of 0.74. Chang <i>et al.</i>, 2016 demonstrated a 31% increase in the prevalence of diagnosed diabetes in those who attended health checks compared to those who did not (Difference in difference = 1.31, 95% CI = 1.17 to 1.45). Robson <i>et al.</i>, 2017 also demonstrated a 30% increase in the incidence of diagnosed diabetes in those who attended the health checks compared to those who did not (OR = 1.30, 95%CI = 1.21 to 1.39, p-value <0.001). Robson et al., 2016 found that out of 1000 NHS Health checks, there would be 9 new diagnoses of type 2 diabetes; there was no control group to compare against. Carter et al., 2016 found that over a period of 5 years, 6% of attendees had a new diagnosis of type 2 diabetes; no control group was provided. Stroke related outcomes Two studies analysed stroke (see Table 2-1) with one study including a comparison group. Martin et al., 2018 synthesised that rates of stroke were lower in the NHS Health Check group but did not provide a point estimate as the studies were not meta-analysable.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	

Section and Topic	#	Checklist item	Location where item is reported
			Chang <i>et al.</i>, 2016 demonstrated limited evidence using observational data when comparing the NHS Health Check 's impact on the incidence of stroke after comparing attendees against non-attendees (Difference-in-difference = -0.03, 95% CI = -0.05 to -0.01, p > 0.05). Chronic Kidney Disease Six studies analysed chronic kidney disease (see Table 2-1). The studies which involved a comparison group could not be meta-analysed as Caley <i>et al.</i>, 2014 evaluated chronic kidney disease prevalence on a practice level, Chang <i>et al.</i>, 2016 analysed individual prevalence, whilst Robson <i>et al.</i>, 2017 evaluated chronic kidney disease new diagnoses at a patient level. Martin <i>et al.</i>, 2018 (systematic review) found that the rates of diagnoses of chronic kidney disease were the same higher among NHS Health Check attendees compared to non-attendees but did not provide a point estimate as the studies were not meta-analysable. Caley <i>et al.</i>, 2014, estimated that the NHS Health Check has no impact on the prevalence of chronic kidney disease on a practice level with a reduction of 0.60% in NHS Health Check practices and 0.38% reduction in non-NHS Health Check practices (p-value = 0.54). On a patient level, Robson <i>et al.</i>, 2017 established that the first diagnosis of chronic kidney disease was higher in the matched group which had an NHS Health Check compared to those who did not (OR = 1.83, 95% CI = 1.52 to 2.21). Chang <i>et al.</i>, 2016 demonstrated that the NHS Health Check participants had a higher prevalence of chronic kidney disease with 0.17% (95% CI 0.11% to 0.23%, p < 0.05) higher prevalence compared to those who did not attend a health check. Robson <i>et al.</i>, 2016 estimated that 4 out of 1000 NHS Health Checks would result in a new diagnosis of chronic kidney disease; no comparison groups were provided. Carter <i>et al.</i>, 2016 estimated that 1.64% of health checks would result in a diagnosis of chronic kidney disease in Leicester. Hypertensive Related Outcomes Nine studies analysed Hypertension with three studies including a control group (see Table 2-1). As Caley <i>et al.</i>, 2014 analysed the NHS Health Check on a general practice level, Forster <i>et al.</i>, 2016 analysed the NHS Health Check on a patient level and Chang <i>et al.</i>, 2016 presented their results prior to matching, a meta-analysis was deemed inappropriate due to the different comparison groups. Martin <i>et al.</i>, 2018 (systematic review) found that the rates of diagnoses of hypertension were the same or higher among NHS Health Check attendees at the individual level but not at the general practice level but did not provide a point estimate as studies could not be meta-analysed. Caley <i>et al.</i>, 2014 suggests there is no difference in hypertension prevalence on a practice level as practices that implemented the NHS Health Check saw an increase of 0.46%, whilst those that did not saw an increase of 0.30% with a p-value of 0.54. Forster <i>et al.</i>, 2016 demonstrated a statistically significant higher diagnosis rate of hypertension in men only when comparing on a patient-level (5%+, p < 0.001) to those who did not partake in an NHS Health Check. Robson <i>et al.</i>, 2017 found that those attending an NHS Health Check were more likely to be diagnosed with hypertension in a matched analysis: hypertension with an odds ratio of 1.50 (95% CI = 1.43 to 1.57). Chang <i>et al.</i>, 2016 demonstrated that participants of the NHS Health Check were more likely to have a recording of hypertension at 4.08% compared to 0.76% for those who did not participate; this generated a difference-in-difference estimator of 2.99% (2.77 to 3.21). Forster <i>et al.</i>, 2016 found that in a matched analysis, men who received the NHS Health Check were 5% more likely to be diagnosed with hypertension compared to men who did not receive the NHS Health Check (p < 0.001) Forster <i>et al.</i>, 2015 estimated (without a control group) that for every 1000 males assessed, 355 (95%CI: 340 - 369) would be newly diagnosed with hypertension and 668 (95% CI: 646 - 689) for women. Robson <i>et al.</i>, 2016 estimated that for every 27 health checks, 1 would result in a new recorded diagnosis of hypertension; no control group was provided. Lambert, 2016 estimated that new identifications of hypertension occur in one in every 10 NHS Health Checks; no control group was provided for comparison. Carter <i>et al.</i>, 2016 estimated that 19% of those who have a health check would have a new diagnosis of hypertension over a 5-year period; no control group was provided for comparison. Other healthcare-related outcomes Four studies met the secondary outcomes criteria (see Table 2-1). One systematic review was identified, Martin <i>et al.</i>, 2018. Martin <i>et al.</i>, 2018 evaluated the NHS Health Check in terms of coverage, uptake, and any health-related impact. In terms of health-related impact, Martin <i>et al.</i>, 2018 concluded that the NHS Health Check was associated with short term small increases of disease detection for cardiovascular disease, and higher rates of antihypertensive and statin prescriptions compared to no-NHS Health Check. Greaves <i>et al.</i>, 2015 propose that a variation of the NHS Health Check, known as 'Waste the Waist' estimated an average weight loss of 2.6Kg (95%CI: -4.8 to -0.3, p = 0.025) at a participant level. Hinde

Section and Topic	#	Checklist item	Location where item is reported
			et al., 2017 suggests that the NHS Health Check was associated with a reduction in mean BMI of 0.27kg/m ² (95% CI: 0.20 to 0.34) compared to no check. Syed, Talbot-Smith & Gemmell, 2012 has also estimated the NHS Health Check 's ability to prevent one case of lung cancer over a 5-year period.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Studies examining diabetic disease outcomes found evidence that health check interventions increased the diagnosis of prevalence or new type 2 diabetes diagnosis. The evidence also suggests that general practices which provide the NHS Health Check detect at least the same, and at sometimes, higher rates of previously unrecorded diagnoses of heart disease, chronic kidney disease and hypertension compared to practices that do not offer the NHS Health Check. However, it is likely that findings are a result of the NHS Health Check screening process identifying previously undiagnosed prevalent cases. Therefore, there is evidence suggesting that NHS Health Check achieves one of its goals of detecting previously undiagnosed cases of heart disease, chronic kidney disease, hypertension, and type 2 diabetes that could reduce or delay disease progression. Such results are similar to Martin et al., 2018.
	23b	Discuss any limitations of the evidence included in the review.	Existing studies were limited as they primarily evaluated the rates of detecting disease and not specifically whether the NHS Health Check reduces the incidence of chronic kidney disease, diabetes, heart disease, hypertension or stroke in “healthy” individuals without a prior disease burden. As a result of these limitations, there remains uncertainty about the strength of the evidence for the NHS Health Check to prevent cases of disease and reduce the incidence of diseases in patients without existing chronic kidney disease, diabetes, heart disease, hypertension or stroke.
	23c	Discuss any limitations of the review processes used.	One major challenge is that this study used a single reviewer for article inclusion and data extraction. Despite this, this study identified the same studies as Martin <i>et al.</i> , 2018. Similar to Martin <i>et al.</i> , 2018, no meta-analysis was conducted due to the lack of suitability of the extracted data for a meta-analysis.
	23d	Discuss implications of the results for practice, policy, and future research.	Further work should be undertaken to investigate further the evidence for effectiveness of the NHS Health Check to prevent the development of cardiovascular and diabetic disease.

Appendix 2.2 – Search Terms for the NHS Health Check

((((((((((health Check*) OR diabet* screen*) OR cardiovascular screen*) OR population screen*) OR risk factor screen*) OR opportunistic screen*) OR medical check*) OR general check*) OR periodic health exam*) OR annual exam*) OR annual review*) AND (NHS OR national health service) OR (nhshc)

Section	#	FERITS Checklist Item	In PhD Chapter
TITLE AND ABSTRACT			
Title and Abstract	1	Study design (interrupted time series) indicated in the title or the abstract. Structured abstract recommended Information on target population or study sample	Evaluating the population level impact of the NHS Health Check: a quasi-experimental interrupted time series analysis. Abstract Introduction and research gap: The NHS Health Check may be considered as a population level public health intervention which identifies and introduces high risk patients to other public health interventions; for example, statin prescriptions for individuals with high cardiovascular risk (10% QRisk), advice on weight management for overweight patients, smoking/drinking cessation assistance or a referral to the NHS Diabetes Prevention Programme for patients at high risk of developing type 2 diabetes. There is currently a lack of understanding of the NHS Health Checks influence on population level health outcomes; therefore, this chapter aims to investigate the evidence for the NHS Health Check on changes in population rates of chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes. Methods: I conducted a quasi-experimental interrupted time series analysis using the secondary care administrative data collected between June 2003 to March 2017 (latest HES build) with an interruption in 2009, when the NHS Health check was introduced. Monthly admission rates (adjusted for population size) for chronic kidney disease, heart disease, hypertension, stroke, and type 2 diabetes were estimated using Hospital Episode Statistics. To mirror the inclusion criteria of the NHS Health Check, I included individuals between the ages of 40-74 on admission. Rates of change in admission proportions were compared before and after the introduction of the NHS Health Check in 2009. Results: Between 2003 and the introduction of the NHS Health Check (2009), there was a month-to-month decrease of 1.82 admissions per month per 100,000 people [95% CI: -2.14 admissions/100,000 to -1.51 admissions/100,000] for cardiovascular disease, diabetes and stroke combined. After the introduction of the NHS Health Check in 2009 until the end of the study (2017), there was a month-to-month decrease of 0.13 admissions per month per 100,000 people [95% CI: -0.29 admissions/100,000 to 0.03 admissions/100,000]. Investigating changes in chronic kidney disease and hypertension was challenging due to varying temporal changes for these diseases during the study period. Discussion and Conclusion Using interrupted time series, I did not detect a superior change in rates of hospital admissions for cardiovascular disease, diabetes, and stroke after the introduction of the NHS Health Check when compared to pre-NHS Health Check. Such detections could be attributable to low NHS Health Check uptake introduced in Chapter 1. There were also difficulties in analysing hypertension and chronic kidney disease due to temporal variability in clinical coding for these diseases in secondary care.

Section	#	FERITS Checklist Item	In PhD Chapter
INTRODUCTION			
Background	2	Scientific background and explanation of rationale	Currently there is limited research on the effects of the NHS Health Check on healthcare outcomes, particularly rates of chronic kidney disease, heart disease, hypertension, stroke and type 2 diabetes. A great deal of existing research on the NHS Health Check has concentrated on attendance, uptake and prescribing rates (of statins and antihypertensives), with fewer studies conducted examining research on the population level health outcomes (Martin et al., 2018).
Objectives	3	Specific objectives and hypotheses	The aim of this chapter is to evaluate the effects of the NHS Health Check nationally in England. This study uses national electronic record data and a quasi-experimental interrupted time series analysis to investigate whether there were changes in yearly growth of cardiovascular disease before and after the introduction of the NHS Health Check in England. To achieve this aim, the objectives for this chapter include: Estimating monthly national hospital admissions trends per 100,000 people in the English population for cardiovascular disease before the introduction of the NHS Health Check Estimating monthly national hospital admission trends per 100,000 people in the English population for cardiovascular disease after the introduction of the NHS Health Check Comparing the change in direction and magnitude of monthly trends of cardiovascular disease trends prior to the introduction of the NHS Health Check and after the introduction of the NHS Health Check
METHODS			
Study Population	4	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	As the NHS Health Check was only offered in England, I restricted the geographical population to the English population only. Since the NHS Health Check was only offered to those between the ages of 40-74, I also applied this restriction for each admission. Due to this age restriction, and the fact that I am analysing the cardiovascular trends over time, a rolling/changing cohort was used. To account for changes in admission rates which may be caused by a change in population size, yearly population data was used as denominator data to calculate admission rates. The year population data was also a rolling number and was also restricted to those between the ages of 40 – 74 for each year between 2003 to 2017. As my dataset has “universal coverage” (Herbert et al., 2017) of NHS hospital providers in England, biases due to under-sampling were not considered to be of substantial concern.
		Methods of study population selection (such as codes or algorithms used to identify subjects from routine datasets)	The outcome of interest was monthly hospital admission rates of the diseases the NHS Health Check was designed to tackle, including heart disease, diabetes, and stroke. Therefore, in this analysis, I evaluated the chance of prevalence of heart disease, diabetes, and stroke through time. To calculate the monthly admission rates, raw numbers of admissions for a specific month were divided by the population size for the corresponding year (see analysis section). Data extraction of the outcomes was conducted by Public Health England. See Table 3-1 for ICD10 case definitions.

Section	#	FERITS Checklist Item	In PhD Chapter								
			Table 3-1: Case Definitions for cardiovascular disease, diabetes, and stroke. * Represents descendant codes <table><tr><td>Disease</td><td>Code</td></tr><tr><td>Cardiovascular Disease – Heart Failure</td><td>I50.*</td></tr><tr><td>Diabetes</td><td>E1*</td></tr><tr><td>Stroke/Cerebrovascular disease</td><td>I6*</td></tr></table>	Disease	Code	Cardiovascular Disease – Heart Failure	I50.*	Diabetes	E1*	Stroke/Cerebrovascular disease	I6*
		Disease	Code								
Cardiovascular Disease – Heart Failure	I50.*										
Diabetes	E1*										
Stroke/Cerebrovascular disease	I6*										
		Settings and locations where the data were collected	The primary unit of analysis was monthly admission rates for all hospital admissions across all hospitals in England, which provided data for that specific month.								
Study Time-period	5	Start and end dates of the data included in the study, including reasons for selecting this date range and whether this was the full dataset available or if data was restricted. (Presentation of the full time series as a web appendix recommended)	This study used data between June 2003 and March 2017. I was limited to this period because there was inconsistent use of ICD10 codes prior to 2003 (see discussion) and population data was only available until 2017.								
		Time intervals used (e.g. daily, monthly, annual) and the reason for selecting this interval	I analysed data on a month-to-month basis; monthly aggregated data were used because yearly data would not have provided enough data points whilst choosing daily samples would mean using insufficient numbers of admissions.								
		Clear definition of the pre intervention period, the intervention point (including any transition period) and the post-intervention period	I defined the pre-intervention period between June 2003 to December 2008; the intervention introduction period as January 2009, and the post-intervention period from February 2009 to March 2017. To account for the time between the introduction of the NHS Health Check and it being nationally mandated; a sensitivity analysis was conducted using a 3-year lag which allowed for a transition period during the introduction of the NHS Health Check from January 2009 to January 2012.								
Intervention	6	Details of the intervention(s) and how and when they were actually administered, specifically including:*	Intervention described in chapter 1								
		_ Why: Description of the rationale, theory, or goal of the elements essential to the intervention	The NHS Health Check was introduced in 2009 by the NHS in England to tackle the yearly growth of non-communicable health-related diseases such as diabetes as well as cardiovascular disease.								

Section	#	FERITS Checklist Item	In PhD Chapter
		_ What: Description of what was done including details of any policy changes, procedures, activities and information provided to participants	For patients who are at a high risk of developing cardiovascular disease, appropriate measures are taken to reduce their risk, for example, by prescribing statins, antihypertensive or by referring patients to other preventative care programmes provided by the NHS.
		_ Who: Who developed, implemented and/or provided the intervention	The NHS Health Check was introduced in 2009 by the NHS in England
		_ How: Description of the modes of delivery of the intervention and whether it was provided individually, in a group or to a whole population	It is delivered to individual patients through their registered general practice or alternative healthcare setting such as a local pharmacist.
		_ Where: Description of the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features	It is delivered to patients through their registered general practice or alternative healthcare setting such as a local pharmacist
		_ When: Description of when the intervention was first announced, marketed and delivered, the number of times it was delivered and the duration. Did all groups receive the intervention at the same time	The NHS Health Check was introduced in 2009
		_ Tailoring and modifications: Description of any adaptations or modifications to the intervention during the course of the study	For patients who are at a high risk of developing cardiovascular disease, appropriate measures are taken to reduce their risk, for example, by prescribing statins, antihypertensive or by referring patients to other preventative care programmes provided by the NHS. Examples of such preventative care programmes include NHS Stop smoking Service as well as introducing participants to new services such as the NHS Diabetes Prevention Programme when they were available in 2016.
		_ Adherence: Report on whether the intervention was compulsory, whether adherence was assessed and any activities to increase compliance or adherence	Initial deployment of the NHS Health Check was phased; however, since the Health and Social Care Act 2012, all local authorities were mandated to provide the NHS Health Checks. Models of the NHS Health Check were generated in 2008, with an estimated 70% attendance rate. However, studies have demonstrated uptake of the NHS Health Check is only at around 20% of the eligible population (Robson et al., 2016).
Outcomes	7	Clearly defined outcome measures	The outcome of interest was monthly hospital admission rates of the diseases the NHS Health Check was designed to tackle, including heart disease, diabetes, and stroke. Therefore, in this analysis, I evaluated the chance of prevalence of heart disease, diabetes, and stroke through time. To calculate the monthly admission rates, raw numbers of admissions for a specific month were divided by the

Section	#	FERITS Checklist Item	In PhD Chapter
			population size for the corresponding year (see analysis section). Data extraction of the outcomes were conducted by Public Health England.
		Data Source(s)	To analyse the NHS Health Check's impact in England, admitted patient care hospital records across England were examined using the Hospital Episode Statistics (HES) dataset. HES records are recorded and coded after each admission and are collected from 451 NHS hospitals providers in England on a monthly basis since 1987 to the Secondary User Service. These data are then made available for researchers to use. I used HES records for this analysis because of its high coverage of hospital admissions compared to primary care data (Denaxas et al., 2012). To generate admission rates, population size data for England were used as denominators. My population denominators were produced by the Office of National Statistics (ONS).
		Methods used to collect, process, record and extract data; any changes in data collection, processing or recording over time	Data Resource To analyse the NHS Health Check's impact in England, admitted patient care hospital records across England were examined using the Hospital Episode Statistics (HES) dataset. HES records are recorded and coded after each admission and are collected from 451 NHS hospitals providers in England on a monthly basis since 1987 to the Secondary User Service. These data are then made available for researchers to use. I used HES records for this analysis because of its high coverage of hospital admissions compared to primary care data (Denaxas et al., 2012). To generate admission rates, population size data for England were used as denominators. My population denominators were produced by the Office of National Statistics (ONS). Methods Due to historical changes in clinical definitions of cardiovascular disease, specific cardiovascular conditions could not be analysed in isolation as temporal changes in admission rates were detected. For example, studies have found that changes in clinical definitions in 2007 and ICD10 changes in 2012 caused temporal changes in admission rates for myocardial infarction and stroke (Rockenschaub et al., 2020). The temporal changes also occurred for type 2 diabetes (Figure 3-2). chronic kidney disease (Figure 3-3) and hypertension (Figure 3-4). For example, for type 2 diabetes, there was a consistent rise of admission rates between 2001 until 2012, with a sudden drop in admission in 2012; see Chapter 3 Figure 2 for a graphical representation of this. Such temporal variability was independently confirmed by two other teams in University College London.
		Information on validity and reliability of outcome measures	Due to historical changes in clinical definitions of cardiovascular disease, specific cardiovascular conditions could not be analysed in isolation as temporal changes in admission rates were caused. For example, previous studies have found that changes in clinical definitions in 2007 and ICD10 changes in 2012 caused temporal changes in admission rates for myocardial infarction and stroke (Rockenschaub et al., 2020). The temporal changes also occurred for type 2 diabetes (Figure 3-2). chronic kidney disease (Figure 3-3) and hypertension (Figure 3-4). For example, for type 2 diabetes, there was a consistent rise of admission rates between 2001 until 2012, with a sudden drop in admission in 2012;
		Information on data quality, coverage and completeness over the duration of the study	

Section	#	FERITS Checklist Item	In PhD Chapter
		period; any changes in quality, coverage or completeness over time	see Figure 3-2 for a graphical representation of this. Such temporal variability was confirmed by two other teams in University College London independently. To tackle these issues with temporal changes, non-specific diseases were evaluated (Rockenschaub et al., 2020); the groups evaluated included heart disease (ICD10 – Codes I50.*, where *represents any subsequent code), diabetes mellitus (E1*) and I6* for cerebrovascular disease. A solution for generating consistent chronic kidney disease and hypertension admission rates was not found; for example, by defining chronic kidney disease and hypertension using consistently used ICD10 subcodes had reduced the numbers evaluated. Therefore, a decision was taken to not include these outcomes using an interrupted time series design with Hospital Episode Statistics for this chapter.
History bias	8	identification of co-interventions or other concurrent events that might affect the outcome; if no such events exist, clear statement that the intervention was independent of other changes	By uncovering those who had not previously developed one of the aforementioned diseases, the NHS Health Check aims to prevent or postpone of cardiovascular disease onset through prescriptions of antihypertensives, statins and lifestyle interventions, a process that is often achieved by facilitating the referral of patients to other NHS provided public health interventions. Examples of lifestyle interventions to which patients could be referred to by the NHS Health Check include the NHS Stop Smoking Service, the NHS
		Description of design adaptations to mitigate the risk of history bias e.g: adding a control series, using multiple phases or a using a multiple baseline design	Not applicable
Unit of Analysis	9	Description of the smallest unit that is being analysed to assess intervention effects (e.g., individual, group, or community)	The primary unit of analysis was monthly admission rates for all hospital admissions across all hospitals in England, which provided data for that specific month.
Statistical Methods	10	Statistical methods used (e.g. segmented Poisson regression, ARIMA etc)	The primary method of analysis was a segmented linear regression consisting of two models with the first regression model conducted using data points from June 2003 to December 2008 and the second regression model conducted using data points from January 2009 until June 2017.
		Appropriateness of a linear model, including description of any tests for linearity and any non-linear terms included	To establish the appropriateness of the model, the coefficient of determination was used (R^2) for data points prior to the introduction of the NHS Health Check.
		Detailed description of the a priori impact model and why this was chosen, including allowance for: step or slope change effects, lagged effects, transition phase, floor, or ceiling effects. Describe why this model is	As the NHS Health Check was gradually introduced, I expected the a priori impact model would be reflected in a gradual slope change as opposed to an immediate step change. To model the NHS Health Check's gradual mandated provision, I used a 3-year lag as a part of sensitivity analysis as an alternative to the a priori impact model; a year 3-year period was chosen 2012 was when the NHS Health Check was mandated, after the 2009 introduction.

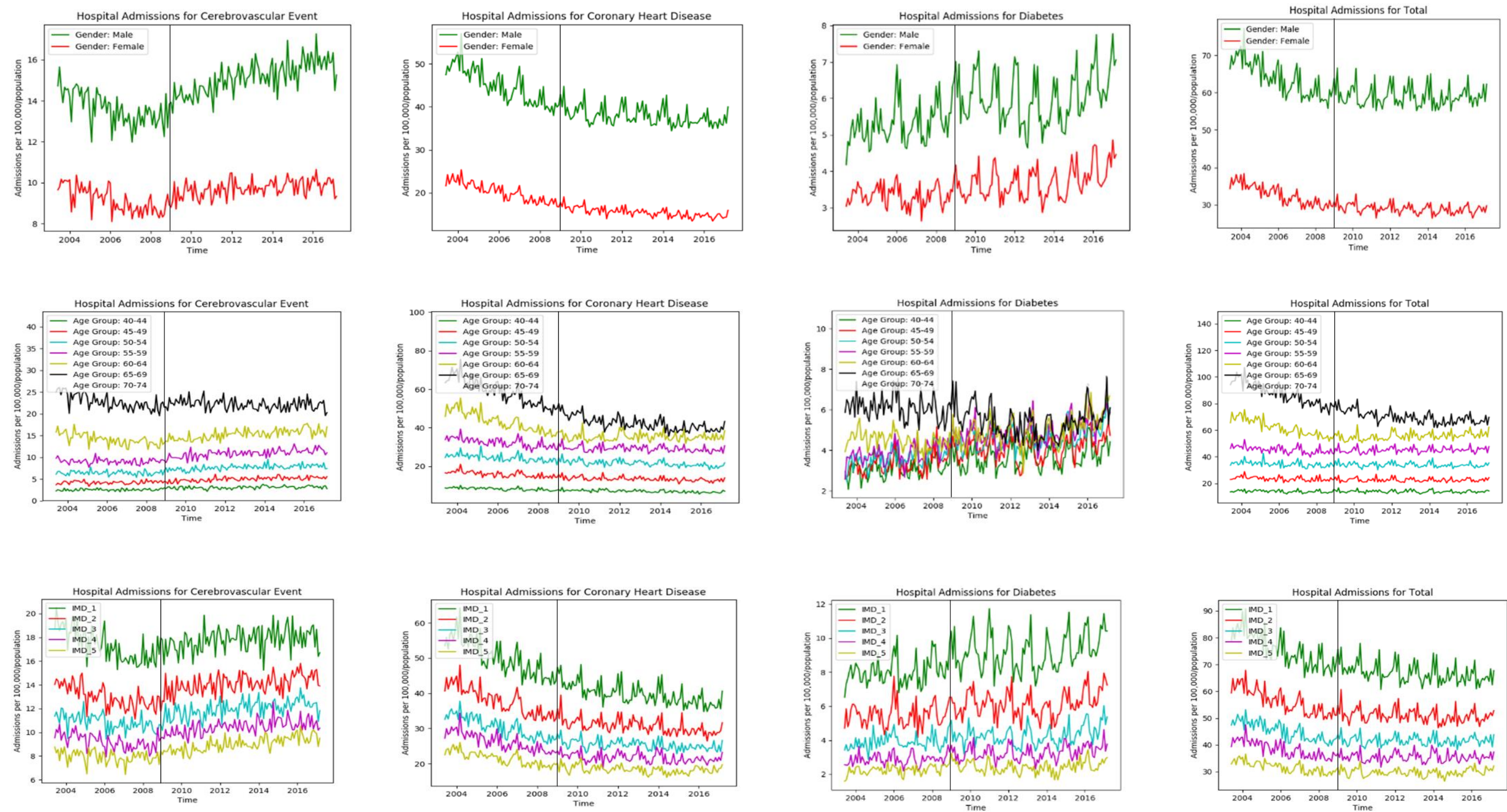
Section	#	FERITS Checklist Item	In PhD Chapter
		appropriate for the intervention and outcome under study	
		Adjustments for time varying confounders (including seasonality)	To identify the impact of seasonality and autocorrelation, that is prior trends are a good predictor of future trends, a visual analysis of an autocorrelation plot was achieved using 24-months (datapoints) worth of data as suggested to identify seasonality (Hawley et al., 2019). It is important to understand seasonality and autocorrelation as predictors of monthly rates of disease as the goal of the NHS Health Check is to change such trends. As my primary goal was to compare trend before and after the introduction of the NHS Health Check; specifically, to evaluate if the NHS Health Check decreased (or accelerated a decrease) in monthly admission rates, autocorrelation would not be problematic if the NHS Health Check significantly reduces admission rates as it would have changed the trendline instead of continuing it.
		Assessment of autocorrelation and how this was handled	To identify the impact of seasonality and autocorrelation, that is prior trends are a good predictor of future trends, a visual analysis of an autocorrelation plot was achieved using 24-months (datapoints) worth of data as suggested to identify seasonality (Hawley et al., 2019).
		Description of any stratified or subgroup analyses	Whilst multivariate analysis was not conducted, stratification was conducted by disease (cerebrovascular disease, coronary heart disease, diabetes), age group (40 – 44, 45 – 49, 50 – 54, 55 – 59, 60 – 64, 65 – 69, 70 – 74), gender (male and female) and index of multiple deprivation (1 (most deprived) – 5 (least deprived)). Admission rates for each stratum were calculated later using stratified denominators for the corresponding subgroups in the population.
		Explanation of how missing data were addressed	Results: Of the patients between the ages of 40 to 74, 86 did not have a gender reported, and there was no missing data on index of multiple deprivation. Discussion: I was unable to evaluate the impact of missing data for genders, age groups, and index of multiple deprivation data on the estimation of outcome events. This limitation exists because the reason for missingness in HES records may be different from that in the Office of National Statistics population data. Therefore, it is not possible to simply divide missing data points from HES by missing data points from the ONS particularly if the missingness is systemic (i.e., missing not at random). However, the levels of missing data were small (86 out of 1,645,644 admissions), therefore I do not believe this introduced substantial bias to the results.
		Discussion of uncertainty in the primary statistical model and description of any additional sensitivity analyses	I also conducted two sensitivity analyses. The first alternative model was used to evaluate the effect of the gradual introduction of the NHS Health Check with a 3-year lag. The second alternative model was used to evaluate the effect of resampling time points to improve the consistent use of ICD10 codes.
		Statistical software or programs used	All analysis was conducted using a combination of R version 3.6 for statistical analysis, and Python 2.7 to generate visual representations of the time-series data.

Section	#	FERITS Checklist Item	In PhD Chapter
Results			
Numbers analysed	11	Report on the number of participants (denominator) included in each analysis for each study condition throughout the study period, particularly when the denominators change for different outcomes.	Between 2003 and 2017, I found 220,027,549 hospital admissions. Of these 220,027,549 admissions, 6,665,709 were either due to cerebrovascular events, coronary heart disease or diabetes. Of these 6,665,709 admissions, 1,645,558 patients were between the ages of 40 to 74 upon each respective admission. Of the patients between the ages of 40 to 74, 86 did not have a gender reported, and there was no missing data on index of multiple deprivation. See Figure 3-6 for the study population derivation.
Population characteristics	12	Description of the baseline demographic and clinical characteristics of the intervention group and any control groups at baseline and throughout the study period (a table is recommended) Report on study group equivalence at baseline and statistical methods used to control for baseline differences. Identification of differential changes in population characteristics between study groups throughout the study period and description of statistical methods used to control for differential changes	A total of 1,645,558 admissions were evaluated between 2003 and 2017, consisting of 1,042,281 admissions for coronary heart disease, 435,095 admissions for cerebrovascular events and 168,182 admissions for diabetes. See Table 3-2 for a demographic breakdown of the sample. For all diseases, males had a higher proportion of admissions rates. For all diseases, except for diabetes, older groups had higher admissions rates. For all diseases, higher deprivation levels had higher admission rates. See Figure 3-7 for a visual breakdown of admission rates by disease, gender, age group and deprivation.
Outcomes and estimation	13	For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision. Report on both relative and absolute changes in the study outcomes following the intervention. Inclusion of null and negative findings Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	For the combined causes of cerebrovascular disease, diabetes, and heart disease, I evaluated a total of 1,645,558 admissions between 2003 and 2017. At the beginning of the study (2003), there was an average of 50.03 admissions per 100,000 people for the year 2003. At the introduction of the NHS Health Check (2009), there was an average of 46.99 admissions per 100,000 people for the year 2009. At the end of the study (2017), there was an average of 45.74 admissions per 100,000 people for the year 2017. Autocorrelation existed for approximately 14-months' worth of lag, i.e., trends tend to follow the previous 14-months; See Figure 3-8. Between the start of the study (2003) and the introduction of the NHS Health Check (2009), there was a month-to-month decrease of 1.82 admissions per month per 100,000 people [95% CI: -2.14 admissions/100,000 to -1.51 admissions/100,000]. Therefore, prior to the introduction of the NHS Health Check, there was already a month-to-month decrease in admission rates. Thus, to show an improvement, the post-NHS Health Check trend requires a faster rate of month-to-month decreases. After the introduction of the NHS Health Check until the end of the study (i.e. from 2009 to 2017), there was a month-to-month decrease of 0.13 admissions per month per 100,000 people [95% CI: -0.29 admissions/100,000 to 0.03 admissions/100,000]. As the confidence intervals were not overlapping, after the NHS Health Check, trends were considered different before the NHS Health Check. See

Section	#	FERITS Checklist Item	In PhD Chapter
		Graphical presentation of the time series for each outcome with the regression line, pre-intervention time period, intervention points and post-intervention period clearly indicated	Figure 3-9 for a visual representation of the interrupted time series for the combined admissions of cerebrovascular disease, diabetes, and heart disease.
Ancillary analyses	14		Sensitivity Analysis 1: Three Year Lag To model the impact of the gradual introduction of the NHS Health Check, a 3-year lag period was implemented which shifted the introduction of the NHS Health Check from 2009 to 2012. When implementing this 3-year lag, there was an average reduction of 2.08 monthly admissions /100,000 [95%CI: -2.44 to -1.74] between the beginning of the study and the NHS Health Check (+ 3-year lag). Between the introduction of the NHS Health Check (+ 3-year lag) until the end of the study, there was a monthly decrease of 0.68 admissions/100,000 [95%CI: -1.27 to -0.10]. Therefore, when modelling for a 3-year lag, the introduction of the NHS Health Check did not accelerate monthly decreases in admission rates. See Figure 3-16 for a visual representation of this interrupted time-series study. Sensitivity Analysis 2: Cerebrovascular Events readjustment Due to the quality of coding, there was inconsistent use of the ICD codes I6*, leading to an inconsistent trend in cerebrovascular events. See Figure 3-17 for a visual representation of this issue. Therefore, an interrupted time series analysis is less likely to be suitable for this. To tackle this issue, I resampled the time series by establishing the last data point in the time series that caused a positive correlation (Pearson's rank coefficient) between such data points and the introduction of the NHS Health Check. This was determined to be 34-months prior to the NHS Health Check (See Chapter 3 Figure 18). Therefore, the adjusted start date for the interrupted time series was March 2006. This method was used so that it maximises the number of data points before the introduction of the NHS Health Check while preserving the consistency of the ICD10 code used to establish cerebrovascular events.
Adverse events	15	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	Not Applicable
DISCUSSION			
Interpretation	16	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	Overall, the primary analysis and the sensitivity analyses suggest that there was no change in hospital admissions for coronary heart disease, stroke or diabetes associated with the introduction of NHS Health Check. Therefore, I failed to reject the null hypothesis that the NHS Health Check does not impact monthly hospital admissions for cerebrovascular disease, coronary heart disease and diabetes. This is supported by the autocorrelation graphs, which demonstrate that trends post the introduction of

Section	#	FERITS Checklist Item	In PhD Chapter
			the NHS Health Check were more likely to be influenced by pre-NHS Health Check trends up to 14 months.
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	One possible reason for such results is the mechanism and fidelity of the NHS Health Check as a prevention programme. This is because while the NHS Health Check programme is intended to be a preventative programme, it often uncovers previously undetected cases of coronary heart disease, chronic kidney disease, diabetes, and hypertension. Therefore, the prevalence of such diseases could be artificially inflated.
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	Therefore, the prevalence of such diseases could be artificially inflated. Future studies could overcome this problem by analysing incidence rates instead of admission rates; although alternative study designs should consider admission rates as the NHS Health Check also aims to reduce the severity of CVD by detecting it earlier, leading to lower long-term admission rates.
		Discussion of research, programmatic, or policy implications	This study also provides some evidence that different groups experience changes in admission rates at different levels, especially in higher deprivation groups. Therefore, future policies targeting cardiovascular health should take into consideration the social determinants of health as one of the aims of the NHS Health Check is to reduce health inequities.
Generalizability	17	Generalizability (external validity) of the findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	Based upon other studies which analysed the change in prevalence in primary care (9), this study acts as external validity by validating their results that the NHS Health Check does not seem to impact rates in the secondary care setting. Since the publication of Caley et al., Robson et al, established that attendance of the NHS Health Check is lower than initially modelled for (11); therefore, even if the NHS Health Check was effective, it is hard to detect a significant change nationally using an interrupted time series design unless uptake was higher
Overall Evidence	18	General interpretation of the results in the context of current evidence and current theory	Overall the evidence suggests that the NHS Health Check does not decrease monthly rates of admissions for cerebrovascular disease, coronary heart disease and diabetes nationally. Further analysis of the NHS Health Check should analyse the NHS Health Check as a prevention programme by evaluating the effects of the NHS Health Check on the incidence of cerebrovascular disease, coronary heart disease, diabetes, hypertension and stroke akin to a randomised controlled trial and address issues of missing data and clinical coding inconsistencies.

Appendix 3.2 – Enlarged version of Figure 11 1: Graphs depicting the admission rates per 100,000 people in the population, broken down by disease, gender, age and index of multiple deprivation. Total refers to combined cerebrovascular, coronary heart disease and diabetes.



Appendices for Chapter 4

Appendix 4.1 – Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist for Chapter 4

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Section	#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Reducing inaccuracies in identifying NHS Health Check and NHS Diabetes Prevention Programme participants in primary care records and phenotyping their cardiovascular disease, hypertension, stroke, and type 2 diabetes outcomes: a systematic review.
ABSTRACT			
Abstract	2	Identify the report as a systematic review. Provide an explicit statement of the main objective(s) or question(s) the review addresses Specify the inclusion and exclusion criteria for the review. Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. Specify the methods used to assess risk of bias in the included studies Specify the methods used to present and synthesise results. Give the total number of included studies and participants and summarise relevant characteristics of studies.	Introduction and research gap: Electronic health records can be used in conducting analyses of the NHS Health Check and the NHS Diabetes Prevention Programme. To create a structured and searchable set of records, electronic health records are dependent on clinical coding systems such as READ, International Classification of Diseases version 10 (ICD10) and Systematized Nomenclature of Medicine Clinical Terminology (SNOMED-CT) to allow researchers to extract relevant data. However, this leaves an opportunity for misclassification due to using an incorrect set of clinical codes and phenotyping algorithms. Whilst traditional studies have used two researchers (often a clinical coder and a clinician), this study explores the use of systematic reviews to create clinical code lists and phenotyping algorithms in the evaluation of the NHS Health Check and NHS Diabetes Prevention Programme. Using systematic reviews, I was able to collate the combined efforts of many research teams. Therefore, the objective of this chapter is to use systematic reviews to generate a list of phenotypes to be used in further chapters. The research gaps this chapter aims to target is the lack of systematically collected clinical code lists for phenotyping the NHS Health Check population and cardiovascular, diabetic, and chronic kidney disease-based outcomes in primary care datasets. Methods: I conducted a systematic review using PubMed and Google in search for articles and clinical code repositories which described: the NHS Health Check, the NHS Diabetes Prevention Programme, cardiovascular disease, diabetes, hypertension, and stroke phenotypes in primary care datasets such as the Clinical Practice Research Datalink, QResearch and The Health Improvement Network. I exclude other clinical coding systems such as the ICD10. I then grouped clinical codes grouped by disease and the number of references to establish how widely they have been used in the literature. Results: I screened a total of 13,182 articles, with a total of 167 articles identified that provided READ codes describing heart disease, hypertension, stroke, and type 2 diabetes. 4,018 codes describing heart disease, 2,551 codes describing hypertension, 951 codes describing stroke, 1,991 codes describing type 2 diabetes were identified. Seven articles from 1,030 were deemed eligible when searching for clinical codes and algorithms to establish participation in the NHS Health Check in primary care datasets. Four hundred twelve codes describe the NHS Health Check with “9mC” codes having the most citations with three citations each. Due to the recent deployment of the NHS Diabetes Prevention Programme, only two policy documents were reviewed. This provided 5 READ codes with two citations each. Conclusion and Discussion: This chapter produced a clinical code list to evaluate the NHS Health Check and the NHS Diabetes prevention programme using existing peer-reviewed articles and clinical coding guideline documents. Furthermore, this chapter introduces methods for quantifying often specific clinical codes are used in the peer-reviewed literature.

		Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	To overcome weaknesses in clinical coding such as variation in coding practices and errors in clinical coding, this chapter uses systematic reviews to identify and combine previously used and validated codes and to identify established phenotyping algorithms. I chose this method to identify many existing code lists that meet the requirements of this PhD. Taking this approach also has the advantage that it collates the collective efforts of multiple studies when phenotyping a given disease.
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	The aim of this study was, therefore, to identify READ codes and phenotyping algorithms previously used to identify the incidence of heart disease, hypertension, stroke and type 2 diabetes and delivery of the NHS Health Check and the NHS Diabetes Prevention Programme.
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	required for all studies using primary care datasets to analyse and identify the NHS Health Check, heart disease, diabetes, hypertension, and stroke. With input from Professor Laurie Tomlinson and their team, I've learnt that solely using READ codes to estimate chronic kidney disease would potentially underestimate the incidence of chronic kidney disease (Iwagami et al., 2017). Therefore, I did not include chronic kidney disease in my systematic review; Due to the recent deployment of the NHS Diabetes Prevention Programme (in 2016), a literature review was not conducted in the same manner as the NHS Health Check. Instead, policy documentation was reviewed to identify relevant code lists. I excluded studies that used other coding systems such as the International Classification of Diseases (ICD) and studies that used another coding system such as SNOMED-CT as these terminologies are not used in primary care datasets in England.
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	The primary search strategy was conducted using PubMed. A secondary search strategy was conducted using the first 10 pages of Google as many published studies do not publish their code lists in their paper.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	

Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Articles were imported into Microsoft Excel and then eliminated first by title, then by Abstract then by full text, including appendices and references; this was conducted by a single author as studies did not need to be weighted (i.e., missing a study is less likely to impact the result). The primary type of article included studies that used READ codes to identify the incidence of heart disease, hypertension, stroke, and type 2 diabetes. The secondary type of journal article included studies that used the CPRD/GPRD/THIN/QResearch datasets to identify the incidence of cardiovascular disease, hypertension, stroke or type 2 diabetes; this is to include any proxy measures such as HbA _{1c} , eGFR and product codes as described in Chapter 2.
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	To extract the relevant codes from the studies, the codes and their corresponding READ concepts were copied into an n*3 matrix (See Table 3 for an example). This contained the following dimensions: The study reference (Harvard), the READ Code and the READ Concept. To achieve this, each study was analysed for READ codes in the body of the study (excluding tables), the tables presented in the studies, the supplementary data (files), references and the appendixes. For codes in the body in the text or tables, I manually inserted the values into the matrix. As some authors provided their READ codes using Stata Data Files (dta format), the Haven library in R programming language (version 1.1.0) was used to convert the files to a format readable by Microsoft Excel (comma separated variables). For studies that stated they used the CPRD/THIN/QResearch database but did not provide the READ codes, I emailed the corresponding author with a request for the Codes they used.
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	

Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	I also counted the number of READ codes that were referenced by a single study; this is because I correlate the number of quotations per code with the confidence academics have when it comes to phenotyping heart disease, hypertension, stroke, and type 2 diabetes for that specific code. Therefore, using these counts, subgroup analysis could be conducted to establish the sub-set of codes that contribute the most towards identifying cases of cardiovascular disease, hypertension, stroke, and type 2 diabetes.
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	To analyse the READ codes, I counted the number of references per READ code. From this frequency, I used descriptive statistics to analyse: the average number of citations per code, codes that were cited the most, and codes that were least cited.
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of	

		statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	From 13,182 articles, 167 articles were considered eligible to identify READ codes used to identify the incidence of cardiovascular disease, hypertension, stroke or type 2 diabetes (see Figure 2). For all diseases, the most common reason for removal was the use of ICD codes instead of READ codes; this was either stated in the title or the abstract. A total of 8664 READ and product codes were found for all diseases from the eligible 167 studies. 1,770 codes were associated with diabetes, 4,019 with heart disease, 2,551 for hypertension and 766 for stroke. It should be noted that as the READ code system considers stroke a type of cardiovascular disease, many codes were classified under heart disease and stroke. See Table 5 for a summary of the most cited READ codes.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	Not applicable since this study design is about the confidence of specific READ codes and not the studies themselves.
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	

Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	A total of 8664 READ and product codes were found for all diseases from the eligible 167 studies. 1,770 codes were associated with diabetes, 4,019 with heart disease, 2,551 for hypertension and 766 for stroke. It should be noted that as the READ code system considers stroke a type of cardiovascular disease, many codes were classified under heart disease and stroke. See Table 5 for a summary of the most cited READ codes. Forty-Three articles provided READ codes for heart disease, including 23 studies identified using PubMed and 20 web pages from Google. Eight corresponding authors responded to my READ code request and provided me with the appropriate codes: (Blackburn et al., 2017; Collins and Altman, 2011; de la Iglesia et al., 2011, 2011; Johnson et al., 2016; Karch and Thomas, 2014; Langley et al., 2012; Turner et al., 2016) From all 43 sources, 9,163 codes were provided with a total of 4,018 unique READ codes to describe heart disease. 20 studies produced more than 100 READ codes describing heart disease with Taylforth, 2015, providing the most codes with 2,046. The mean number of citations per code is 1.87 (95% CI: ± 0.08). The most cited codes started with "G30" and describe variants of myocardial infarction; these had at least 19 citations each. 2914 Codes out of 4018 were only referenced once. From CALIBER's 111445 clinical codes, 188 concepts met my inclusion criteria (UCL, 2016).
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Thirty-seven articles provided READ codes describing hypertension with 24 studies identified using PubMed and 20 web pages from Google. Three corresponding authors responded to my READ code request and provided me with the appropriate codes: (Ahmed et al., 2016; Bhaskaran et al., 2012; Robson et al., 2016). From all 37 sources, 3,662 codes were provided with a total of 2,551 unique READ codes to describe Hypertension. Seven studies produced more than 100 READ codes describing Hypertension with Sinnott <i>et al.</i>, 2017 providing the most codes with 2129 codes. The mean number of citations per code is 1.42 (95% CI: ± 0.07). The most cited codes started with "G2" describing variants of Secondary Hypertension; these had at least 18 citations each (Table 11). 582 Codes out of 951 were only referenced once. From CALIBER's 111,445 clinical codes, 185 concepts met my inclusion (UCL, 2016). Following Iwagami et al., 2017 I will also use systolic and diastolic blood pressure readings on entry to complement cases of hypertension. Forty-four studies described stroke having provided 3,182 codes with a total of 951 unique READ. Twelve studies produced more than 100 READ codes describing Stroke with Zhong et al., 2018 providing the most codes with 203. The mean number of citations per code is 3.35 (95% CI: ± 0.34). The most cited codes started with "G6" and describe variants of cerebrovascular Accidents (Table 14); these had at least 26 citations each. Five hundred and eighty-two codes out of 951 were only referenced once. From CALIBER's 111,445 clinical codes, 188 concepts met my inclusion criteria for describing Stroke (UCL, 2016). Fifty-Seven sources provided READ codes for diabetes with 9,188 codes, of which 1,992 were unique. Twenty-four studies produced more than 500 READ codes describing diabetes with CALIBER providing the most codes with 693. From the 1,992 unique codes, 182 described type 1 Diabetes, 195 described type 2 diabetes and 1,615 codes were unclear. The most cited codes started with "C10F" and describe variants of type 2 diabetes; these had 25 citations each. 1,076 codes from the unsure group were cited once. Following Iwagami et al., 2017, I will also analyse glycated haemoglobin levels (HbA_{1c}) and fasting plasma glucose (FPG) to complement diagnoses of diabetes.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	This study combines the efforts of peer-reviewed articles to systematically identify heart disease, hypertension, stroke, and type 2 diabetes in primary care databases.
	23b	Discuss any limitations of the evidence included in the review.	In this chapter I have not examined the validity of the code lists identified; however, in chapters 5 and 6 which use the READ codes and algorithms, I will also present analyses that examine their validity against externally validated datasets.

	23c	Discuss any limitations of the review processes used.	Weaknesses of this study are that it only used one person to screen studies		
	23d	Discuss implications of the results for practice, policy, and future research.	Whilst this study could have been conducted by using clinical coders, clinicians and clinical expert reference groups to identify codes, Tate <i>et al.</i> , (2017) has already suggested that variation exists from different general practices, therefore, conducting this study using clinical coders, clinical and clinical expert reference groups may add to such variation as opposed to resolving it. Although I did not extract specific data on these points, it is likely that many of the studies referenced in this systematic review have used clinicians and clinical coders, therefore, this study has possibly combined the efforts of multiple clinicians and multiple clinical coders.		
OTHER INFORMATION					
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgements I thank my colleagues from University College London who provided access to the Calibre READ code dataset that greatly assisted the research, although they may not agree with all of the interpretations/conclusions of this chapter. I would also like to acknowledge the following studies that responded to my READ code request, who may not also agree with all the interpretations/conclusions of this chapter: - Collins Gitsels, Kulinskaya & Altman, 2011 - Langley et al., 2012 - Karch & Thomas, 2014 - Brudereret al., 2015 - Johnson et al., 2016 - Robson et al., 2016 - Nielen et al., 2016 - de la Iglesia et al., 2011 - Bhaskaran et al., 2012 - Yulonget al., 2015 - Turner et al., 2016 - Zghebi et al., 2016 - Vinogradovaet al., 2016 - Steel, 2016 - Gitsels, Kulinskaya & Steel, 2016 - Ahmed et al., 2016 - Datta-Nemdharryet al., 2017 - Eastwood et al., 2016 - Blackburn et al., 2017		

Appendix 4.2 – Search Strings for Chapter 4

Diabetes

("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields] OR "diabetes"[All Fields] OR "diabetes"[All Fields])

AND

(

("cprd"[All Fields] OR "Clinical Practice Research Datalink"[All Fields] OR "The Health Improvement Network"[All Fields] OR "THIN"[All Fields] OR "electronic health record"[All Fields] OR "EHR"[All Fields] OR "GPRD"[All Fields] OR "Computerized"[All Fields] OR "electronic medical record"[All Fields] OR "emr"[All Fields] OR "hospital episodes statistics"[All Fields] OR "hes"[All Fields] OR "QResearch"[All Fields] OR "computerised medical record"[All Fields])

OR

("code"[All Fields] AND ("read"[All Fields] OR "clinical"[All Fields]))

)

Cardiovascular Disease

("cardiovascular disease"[MeSH terms] OR "coronary artery disease"[All fields] OR "ischemic heart disease"[All fields] OR "angina"[All fields] OR "angina pectoris"[All fields] OR "myocardial infarction"[All fields] OR "heart attack"[All fields] OR "heart failure"[All fields] OR "congestive heart failure"[All fields] OR "hypertensive heart disease"[All fields] OR "rheumatic fever"[All fields] OR "rheumatic heart disease"[All fields] OR "cardiomyopathy"[All fields] OR "heart arrhythmia"[All fields] OR "cardiac dysrhythmia"[All fields] OR "irregular heartbeat"[All fields] OR "congenital heart defect"[All fields] OR "congenital heart anomaly"[All fields] OR "congenital heart disease"[All fields] OR "valvular heart disease"[All fields] OR "carditis"[All fields] OR "aortic aneurysm"[All fields] OR "peripheral artery disease"[All fields] OR "thrombosis"[All fields] OR "thromboembolic disease"[All fields] OR "venous thrombosis"[All fields])

AND

(

("cprd"[All Fields] OR "Clinical Practice Research Datalink"[All Fields] OR "The Health Improvement Network"[All Fields] OR "THIN"[All Fields] OR "electronic health record"[All Fields] OR "EHR"[All Fields] OR "GPRD"[All Fields] OR "Computerized"[All Fields] OR "electronic medical record"[All Fields] OR "emr"[All Fields] OR "hospital episodes statistics"[All Fields] OR "hes"[All Fields] OR "QResearch"[All Fields] OR "computerised medical record"[All Fields])

OR

("code"[All Fields] AND ("read"[All Fields] OR "clinical"[All Fields]))

)

Hypertension

("hypertension"[MeSH Terms] OR "hypertensi*"[All Fields])

AND

(

("cprd"[All Fields] OR "Clinical Practice Research Datalink"[All Fields] OR "The Health Improvement Network"[All Fields] OR "THIN"[All Fields] OR "electronic health record"[All Fields] OR "EHR"[All Fields] OR "GPRD"[All Fields] OR "Computerized"[All Fields] OR "electronic medical record"[All Fields] OR "emr"[All Fields] OR "hospital episodes statistics"[All Fields] OR "hes"[All Fields] OR "QResearch"[All Fields] OR "computerised medical record"[All Fields])

OR

("code"[All Fields] AND ("read"[All Fields] OR "clinical"[All Fields]))

)

Stroke

("stroke"[MeSH Terms] OR "stroke"[All Fields])

AND

(

("cprd"[All Fields] OR "Clinical Practice Research Datalink"[All Fields]
OR "The Health Improvement Network"[All Fields] OR "THIN"[All
Fields] OR "electronic health record"[All Fields] OR "EHR"[All Fields]
OR "GPRD"[All Fields] OR "Computerized"[All Fields] OR "electronic
medical record"[All Fields] OR "emr"[All Fields] OR "hospital episodes
statistics"[All Fields] OR "hes"[All Fields] OR "QResearch"[All Fields]
OR "computerised medical record"[All Fields])

OR

("code"[All Fields] AND ("read"[All Fields] OR "clinical"[All Fields]))

)

NHS Health Check

Search String for NHSHC for PubMed:

((((((((((Health Check*) OR diabet* screen*) cardiovascular screen*) OR population screen*) OR risk factor screen*) OR opportunistic screen*) OR medical check*) OR general check*) OR periodic health exam*) OR annual exam*) OR annual review*) AND (NHS OR National Health Service)

Search String for NHSHC for Embase:

((Health Check* or diabet* screen* or cardiovascular screen* or population screen* or risk factor screen* or opportunistic screen* or medical check* or general check* or periodic health exam* or annual exam* or annual review*) and (NHS or National Health Service)).mp. or NHSHC.af. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

NHS Diabetes Prevention Plan

Search String for NHSDPP for Pubmed:

((((diabet* check*) OR (diabet* screen*) OR (diabet* prevent*) OR (diabet* prevent* program*)) AND (NHS OR National Health* Service)) OR (NHS DPP) OR (NHSDPP) OR (NHS diabetes prevention programme)

Search String for NHSDPP for Embase:

((((diabet* check* or diabet* screen* or diabet* prevent* or diabet* prevent* program*) and (NHS or National Health* Service)) or NHS DPP).mp. or NHSDPP.af. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]

Appendices for Chapter 5

Appendix 5.1 - REporting of studies Conducted using Observational Routinely-collected Data (RECORD) checklist for Chapter 5

*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Section	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported
ABSTRACT				
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Investigating the effect of the NHS Diabetes Prevention on the prevention of type 2 diabetes in England: A population-based cohort study using linked CPRD primary care and HES secondary care health records Abstract Background and research gap: To reduce new cases of type 2 diabetes cases in England, the National Health Service (NHS) piloted the NHS Diabetes Prevention Programme. The NHS Diabetes Prevention Programme aims to prevent type 2 diabetes by providing adults at high risk with access to 13 face-to-face sessions over nine months that focus on diet and weight management. The NHS Diabetes Prevention Programme has been shown to improve intermediate outcomes for type 2 diabetes prevention, including weight loss and glycated haemoglobin (HbA_{1c}) reduction. However, there is a lack of observational studies emulating randomised controlled trials to evaluate the preventative effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes. Methods I applied target trial emulation using retrospective observational cohort data using linked electronic health records from primary (Clinical Practice Research Datalink), and secondary (Hospital Episode Statistics) care between June 2016 to January 2019. I compared rates of incident type 2 diabetes diagnoses among eligible adults who were referred to the NHS Diabetes Prevention Programme with rates for propensity score-matched (ratio of 1:4) controls who were eligible for the NHS Diabetes Prevention Programme but were not invited. Eligibility for the NHS Diabetes Prevention Programme was defined as having HbA_{1c} levels of 42-47 mmol/mol or fasting plasma glucose (FPG) levels of 5.5-6.9 mmol/L on entry. Adults with type 2 diabetes within 90 days of start of follow-up (earliest NHS DPP activity) were excluded as these were considered prevalent cases. Time to the first phenotypical recording of type 2 diabetes was modelled using Cox regression with age, alcohol intake, body mass index, ethnicity, sex, HbA_{1c}, index of multiple deprivations and smoking status included as covariates. Results I identified 2205 individuals who participated in the NHS Diabetes Prevention Programme and 8,820 matched controls of a similar age, sex, HbA_{1c} and FPG. During the 2.5-year study period, 4.13% (95%CI: 3.3% - 5.0%) of NHS Diabetes Prevention Programme individuals developed type 2 diabetes vs 6.42% (95%CI: 5.9% - 7.0%) of matched controls. My results indicate that NHS Diabetes Prevention Programme referrals were associated with a 59% reduction in type 2 diabetes incidence rates [adjusted hazard ratio=0.41;95%CI=0.38-0.44]. My findings are comparable to results produced by randomised controlled trials which evaluate similar diabetes prevention programmes worldwide. Discussion and Conclusions This study found evidence that the NHS Diabetes Prevention Programme reduced incident type 2 diabetes in high-risk groups compared to usual care. The results provide support for the effectiveness of the NHS Diabetes Prevention Programme in reducing type 2 diabetes onset and are compatible with findings for similar interventions in other settings whose effectiveness were established using randomised controlled trials.

INTRDOUCTION				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		Due to the recent phased deployment of the NHS Diabetes Prevention Programme in 2016, there is limited research with studies analysing patient uptake (Valabhji et al., 2020), and proxy measures such as weight loss and change in HbA _{1c} levels (Barron et al., 2018). Whilst randomised controlled trials evaluating similar programmes in the USA and Finland have shown a beneficial effect on the incidence of type 2 diabetes (Diabetes Prevention Programme Group, 2015, 2002)), (Ilanne-Parikka et al., 2013), there is no study that evaluates whether the NHS Diabetes Prevention Programme changes the risk of developing type 2 diabetes in high-risk adults when compared to a comparable control group in England at an individual level.
Objectives	3	State specific objectives, including any prespecified hypotheses		To achieve this aim, this chapter has the following objectives: Identify randomised controlled trials which evaluated programmes similar to the NHS Diabetes Prevention Programme to define a target randomised controlled trial which evaluates the effect of the NHS Diabetes Prevention Programme on the incidence of type 2 diabetes. Using READ codes and phenotypes identified in chapter 4 to reduce misclassification when establishing a cohort of eligible patients, their treatment status, and their healthcare outcomes. Validate the cohort identified as having NHS Diabetes Prevention Programme activity by comparing their baseline covariates to an externally validated source. Applying established epidemiological methods to reduce biases in observational studies such as missing data, misclassification, and confounding. Validate the results of this chapter by comparing the results of this observational study informed by a target trial design to randomised controlled trials which have evaluated similar interventions outside of the UK.
METHODS				
Study Design	4	Present key elements of study design early in the paper		This study used the observational, retrospective longitudinal cohort design with the “trial emulation” framework applied to reduce confounding by indication (Hernán et al., 2022).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		To analyse the NHS Diabetes Prevention Programme, the CPRD dataset was used as it is widely applied in epidemiological studies and provides approximately 4.4 million active patients from 674 general practices in England and Wales (Herrett et al., 2015). The primary clinical coding system used in the CPRD is the READ code terminology (see Chapter 4 for further details). I used CPRD extracts that were anonymised and obtained through the UCL institutional licence. To identify additional cases of type 2 diabetes not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed. The linkage period for HES data started from April 1997 until November 2018, while the linkage period for ONS death records began in January 1998 until January 2019.
Participants	6	(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or	I used the same eligibility criteria as those of the NHS Diabetes Prevention programme. I included people who were at least 18 years old on entry with a HbA _{1c} reading between 42-47 mol/mmol or an FPG reading between 5.5-7.0 mmol/L. I excluded those with a previous diagnosis of type 1 or type 2 diabetes (see primary outcomes section for how this was defined). Patients from general practices whose records were not up to standard (UTS) for one year before the introduction of the NHS Diabetes Prevention Programme were excluded.

		control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants <i>(b) Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case	algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	The primary outcome of interest was incident cases of type 2 diabetes, which were defined using the first recording of: A primary care (CPRD) diagnosis for type 2 diabetes using READ codes and medical codes. A secondary care (HES) diagnosis for type 2 diabetes using ICD10 codes. A death record (ONS) for type 2 diabetes, identified using ICD10 codes A HbA_{1c} reading of 48 mmol/L or higher from primary care records (CPRD) An FPG reading of 7 mmol/L or higher from primary care records (CPRD) Intervention Therefore, I defined the entry date (and participation in the NHS Diabetes Prevention Programme) as the first chronological READ code recording of 679m4 (NHS DPP referral), 679m0 (NHS DPP not completed), 679m1 (NHS DPP completed) and 679m2 (NHS DPP started). Patients who declined participation in the DPP (READ Code: 679m3) were included in the intervention group, akin to an intention-to-treat assignment analysis in a randomised controlled trial. Covariates To account for the NHS Diabetes Prevention Programme's impact on patients from different backgrounds, I included demographic, socio-economic and clinically relevant covariates which are collected as part of the NHS Diabetes Prevention Programme. I used the latest readings up to 5-years before each patient's (estimated) entry date. See Table 5-3 for a list of covariates used in this analysis and See Table 1-1 and Figure 1-2 to see how these are related.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement).		Data resource and Setting To analyse the NHS Diabetes Prevention Programme, the CPRD dataset was used as it is widely applied in epidemiological studies and provides approximately 4.4 million active patients from 674 general practices in England and Wales (Herrett et al., 2015). The primary clinical coding system used in the CPRD is the READ code terminology (see Chapter 4 for further details). I used CPRD extracts that were anonymised and obtained through the UCL institutional licence. To identify additional cases of type 2

		Describe comparability of assessment methods if there is more than one group		diabetes not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed. The linkage period for HES data started from April 1997 until November 2018, while the linkage period for ONS death records began in January 1998 until January 2019. Personal index of multiple deprivation data (version 2015) was also linked to primary care records to evaluate the socio-economic inequalities concerning the NHS Diabetes Prevention Programme. HES, ONS and IMD extracts were conducted by NHS Digital, who provided various “ranks” of matching success (See 5 Table 5-2 for a full breakdown of matching criteria). To enable consistent matching, the top 2 ranks were used as birthdates (to calculate age) and sex are fixed characteristics which were adjusted for as they are social determinants of health and health seeking behaviour; therefore, ranks 3 to 5 were not used in this analysis as these mismatches may lead to biases; for example, if the matched individual in HES was older, then it is expected the risk of type 2 diabetes is higher. Overall, using ranks 1 and 2, 90% of primary care records were matched to a secondary care record.
Bias	9	Describe any efforts to address potential sources of bias		Intervention I excluded patients who had a previous diagnosis of diabetes before the introduction of the NHS Diabetes Prevention programme. However, this does mean that certain patients may discover that they have a previously undiagnosed case of type 2 diabetes because of participating in the NHS Diabetes Prevention Programme. Prevalent and previously undiagnosed cases of type 2 diabetes are excluded in controlled studies (often during a screening process), which I emulated by excluding patients who had a diagnosis within 90 days of entry (See Discussion for strengths and limitations of this method). While in a prospective study, entry is primarily defined using the screening process, there is no consistently used READ code for this within CPRD. Therefore, I defined the entry date (and participation in the NHS Diabetes Prevention Programme) as the first chronological READ code recording of 679m4 (NHS DPP referral), 679m0 (NHS DPP not completed), 679m1 (NHS DPP completed) and 679m2 (NHS DPP started). Patients who declined participation in the DPP (READ Code: 679m3) were included in the intervention group, akin to an intention-to-treat analysis in a randomised controlled trial. External validity As studies have described the demographic, socio-economic and clinical characteristics of people participating in the NHS Diabetes Prevention Programme (Valabhji et al., 2020), I used this opportunity to compare my cohort to these external data. I restricted the comparisons to the covariates that both studies used to include gender, age, ethnicity, index of multiple deprivation, body mass index and baseline HbA_{1c}. (Valabhji et al., 2020) provided descriptive statistics for patients who were referred to the NHS Diabetes Prevention Programme as well as patients who were referred and attended an initial assessment. As the initial assessment recorded ethnicity and body mass index, I included both "referred" and "referred and attended an initial assessment" in my comparison of baseline descriptive statistics. Since the Diabetes Prevention Programme Group in the USA (Diabetes Prevention Programme Group, 2015, 2002) and Ilanne-Parikka <i>et al in Finland</i> (Ilanne-Parikka et al., 2013) have established the effect of similar programmes in other settings. I compared the studies using the Centre of Evidence-Based Medicine's (CEBM, 2018) evidence appraisal toolkit to compare the studies. I included both the 2002 and the 2015 study from the Diabetes Prevention Group as the follow-up time in the earlier 2002 study was similar to my analysis (3 years versus 2.5 years) and the follow-up time for the later 2015 study is similar to that of Ilanne-Parikka <i>et al.</i>, 2013 (15 years versus 13 years). I chose these studies not only because they were compared to the NHS' Diabetes Prevention Programme by Public Health England (Barron et al., 2018), but because they were conducted using gold-standard randomised controlled trials.

Study size	10	Explain how the study size was arrived at		Sample Size To understand sample sizes needed, I've compared the sample in this chapter to prior studies analysing similar interventions elsewhere in the world: Diabetes Prevention Programme Group study, 2002/2015 (USA) and Ilanne-Parikka <i>et al.</i>, 2013 (Finland). The Diabetes Prevention Programme Group study, 2002/2015 (USA) was a three armed study consisting of: 1082 placebo participants, 1073 metformin participants and 1079 Diabetes Prevention Programme participants. Ilanne-Parikka <i>et al.</i>, 2013 contained a total of 522 participants with 257 control participants and 265 participants. In this analysis, I've used all the population invited to the NHS Diabetes Prevention Programme to preserve numbers; this resulted in 2205 individuals (see results).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		Index of multiple deprivation (IMD) data was provided through linkage at the individual patient level. Ethnicity data was primarily derived from primary care records, with hospital records complementing missing ethnicity data from primary care. Ethnicity groups were grouped into the Office of National Statistics supersets (White, Black, Asian, Mixed, Other) (England and Wales Census, 2018) because certain ethnic groups, particularly "Mixed – Black and Asian" would have caused statistical disclosure issues (i.e. less than 5 individuals) leading to non-convergence in regression analysis. Alcohol and smoking status was categorised by the CALIBER team at UCL. The UCL CALIBER team's categories were used in this study due to their experience in data linkage, phenotyping and the popularity of the CALIBER resources in observational research, making categories that I used comparable to many other studies (Denaxas <i>et al.</i>, 2012). See table 3 for the categories used for alcoholic intake, IMD and smoking status. See Table 3 for the categories used for the index of multiple deprivation, alcohol and smoking status.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses		All analyses were completed in R studio software and reported according to the REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement. To account for left censorship caused by the phased introduction of the NHS Diabetes Prevention Programme, right censorship due to leaving the CPRD (through general practice transfer or death), and the interest in the first diagnosis of type 2 diabetes, I conducted a time-to-event analysis using a multivariable Cox proportional hazards model. To understand the effect of the NHS Diabetes Prevention Programme, I only considered initiators of the programme (incident users). Therefore, patients in the intervention group of the NHS Diabetes Prevention Programme were assigned an entry date equivalent to their first chronological READ code entry from 679m4 (NHS DPP referral), 679m0 (NHS DPP not completed), 679m1 (NHS DPP completed), 679m2 (NHS DPP started) and 679m3 (NHS DPP declined). Control patients were assigned an entry date using multivariable regression (See Control Population section). All patients were followed until the first chronological phenotypic recording of a diagnosis of type 2 diabetes (by READ code or ICD10), a HbA_{1c} reading of 48 mol/mol or higher, a fasting plasma glucose reading of 7 mmol/L or higher, dropout (for examples who those leave the CPRD either by changing general practice or through death) or end of study (1 January 2019). Patients were determined to have incident type 2 diabetes if they either having an ICD10 or READ recording of with type 2 diabetes (after 90 days of entry to allow for the removal of previously undiagnosed prevalent cases), had recorded a HbA_{1c} reading of 48 mmol/L or higher, a fasting plasma glucose recording of 7 mmol/L or higher, or if one of their 15 causes of death were recorded as diabetes (see primary outcomes section).

Data access and cleaning methods		..	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	To identify additional cases of type 2 diabetes not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed. The linkage period for HES data started from April 1997 until November 2018, while the linkage period for ONS death records began in January 1998 until January 2019. Personal index of multiple deprivation data (version 2015) was also linked to primary care records to evaluate the socio-economic inequalities concerning the NHS Diabetes Prevention Programme. HES, ONS and IMD extracts were conducted by NHS Digital, who provided various "ranks" of matching success (See 5 Table 5-2 for a full breakdown of matching criteria). To enable consistent matching, the top 2 ranks were used, providing 90% of the possible matches between primary and secondary care records.
RESULTS				
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	I found 465,035 individuals in the CPRD had a HbA _{1c} reading between 42-47 mmol/L or an FPG reading between 5.5-7.0 mmol/L when they were at least 18 years old in CPRD from 1987 until January 2019 (Figure 5-2). After the introduction of the NHS Diabetes Prevention Programme, only 173,593 eligible individuals continually provide data (i.e., they did not leave the CPRD dataset through general practice transfer or death). After removing individuals who had a previous diagnosis of type 2 diabetes before the introduction of the NHS Diabetes Prevention Programme, there were 111,699 individuals left. After removing the non-NHS Diabetes Prevention Programme participants from general practices which provide the NHS Diabetes Prevention Programme, there were 45,286 individuals left. Once I removed individuals who had a recording of type 2 diabetes within 90 days of their estimated entry date (i.e., likely prevalent cases), 31,387 individuals were left. Of the 31,387 individuals in the cohort, 2,205 were referred to the NHS Diabetes Prevention Programme; whilst 29,182 were not. After propensity score matching, I matched 8,820 individuals from the 29,182 control individuals as part of the matching process. See Figure 5-2 for a diagram for a graphical representation of the cohort generating process.
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (e.g., average and total amount)		Of the 2,205 NHS Diabetes Prevention Programme referred individuals, 172 were included in the full case analysis, and 1,486 of the 29,182 control individuals were included. Missingness was similar between both groups, except for HbA_{1c} and FPG, where intervention patients had a lot less missingness; this is because those in the intervention group were more likely to have these covariates measured through their participation to establish eligibility. See Table 5-5 for a breakdown of missingness by covariate. Under a full-case cohort With a full-case cohort, there were more men than women, for both the control group and the intervention group. Under the full-case cohort, certain demographic groups were unaccountable or had a few people, for example, there were no excess or binge drinkers, and there were few individuals who were of mixed ethnicity. Before matching under the full-case cohort, there were imbalances between the intervention and control group for mean HbA_{1c}, deprivation proportions, and alcohol intake proportions. After propensity score matching on the full case dataset, there were no significant differences in means or proportions

				between the intervention group and the matched control group. See Table 5-6 for a full breakdown of the cohort. Imputed Cohort After applying multiple imputation by chained equations, proportions for those analysed changed for gender, ethnicity, deprivation (least deprived), alcohol status and smoking status for the intervention group (Table 5). After applying MICE, there were more females eligible than males, with lower age, BMI, but higher FPG compared to a full case cohort. After applying MICE but before propensity score matching, there were measured baseline imbalances between the intervention and control groups in all covariates except for, BMI and, FPG, ethnicity (black and mixed-race). After applying propensity score matching on the imputed dataset, there were imbalances between the intervention and control groups only for the following covariates: Ethnicity – White and Asian, all IMD groups and alcohol status (except binge drinkers), and smoking status (except non-smoker and ex-smoker).
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures		Of 11,025 individuals (2205 intervention + 8,820 matched control) who were identified after imputation and matching, 5.96% (n = 657; 95%CI: 5.5% - 6.4%) developed diabetes within 2.5 years (Between June 2016 and January 2019) of initiating the NHS Diabetes Prevention Programme. Of the 2205 intervention patients, 4.13% (n = 91) developed diabetes within two and a half years of initiating the NHS Diabetes Prevention Programme. Of the 8,820 control (matched) patients, 6.42% (n = 566) developed diabetes within two and a half years of initiating the NHS Diabetes Prevention Programme. This created a hazard ratio of 0.64 (95%CI: 0.51 to 0.79). See Table 5-7 for a breakdown of incident of type 2 diabetes after follow-up.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		After adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, Index of multiple deprivation quintile, baseline alcohol intake, baseline smoking consumption, baseline BMI, and age on entry, the hazard ratio for a referral to the NHS Diabetes Prevention Programme demonstrated that referred patients were 59% (Hazard Ratio - HR: 0.41 [95% CI: 0.38 – 0.44]) less likely to develop type 2 diabetes compared to the imputed and matched control group. See Table 5-8 for a full breakdown of the hazard ratios for each covariate.
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and		When conducting a full case analysis, a total of 1,486 individuals provided data for the full case analysis in both the intervention and control groups. This produced a total of 74 events, less than the 423 required as

		interactions, and sensitivity analyses		part of the sample size calculations. Under a full case analysis without propensity score matching, the hazard ratio for NHS Diabetes Prevention Programme participation changed to 0.60 [95%CI: 0.32 – 1.12]. Under a full case analysis with propensity score matching, the hazard ratio for NHS Diabetes Prevention Programme participation changed to 0.59 [95% CI: 0.30 – 1.12]. When conducting an unmatched analysis using MICE, the hazard ratio for NHS Diabetes Prevention Programme referral did not change at 2 decimal places 0.41 [95%CI: 0.38 – 0.44]. See Table 6 to view the effect of imputation and matching on the hazard ratio associated with participating in the NHS Diabetes Prevention Programme. See Table 5-11 for the adjusted hazard ratio of the NHS Diabetes Prevention programme under the various sensitivity analyses.
DISCUSSION				
Key results	18	Summarise key results with reference to study objectives		My primary analysis provides evidence that the NHS Diabetes Prevention prevents incident cases of type 2 diabetes in high-risk adults with an estimated 59% (HR: 0.41 [95% CI: 0.38 – 0.44]) 2.5-year risk reduction. Unsurprisingly, those with a higher baseline fasting plasma glucose (H.R.: 1.38 [95CI: 1.32 – 1.45]) or baseline HbA_{1c} (H.R.: 1.33 [95%CI: 1.31 – 1.35]) were more likely to develop type 2 diabetes compared to those with a lower baseline blood glucose reading; although this should be read with caution as this is not the primary exposure. My cohort breakdown is consistent with previous work by Valabhji et al., 2020, a study of the NHS Diabetes Prevention's initial population, providing evidence to support the validity of the phenotypes developed in chapter 4. Furthermore, through the use of target trial emulation, guided by similar diabetes prevention programmes which were evaluated using randomised controlled trials, my point estimates for NHS Diabetes Prevention Programme participation over a control group was similar to the aforementioned trials; HR 0.41 [95%CI=0.38-0.44] for this study, 0.42 [95CI: 0.34 -0.51] for the Diabetes Prevention Group's 3 year trial and 0.614 [95% CI 0.48 - 0.79] for Ilanne-Parikka <i>et al.</i>, in (Finland).
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	My study has a smaller sample size when compared to Valabhji et al., 2020, therefore, multiple imputation played an important role in avoiding the reduction of analytical power. A challenge surrounding missing data was using the combination of HbA_{1c} and fasting plasma glucose; this is because general practitioners often used one value or the other but not both. Whilst the missingness for HbA_{1c} and fasting plasma glucose was high, the results of the imputed dataset were comparable to other external studies (Valabhji et al., 2020). Clinical coding of the NHS Diabetes Prevention Programme is relatively new due to the recent phased introduction of the intervention starting from 2016. The data I used consisted of records from 01 June 2016 to 01 January 2019 and therefore, I suspect that I may have missed a proportion of participants that recently participated in the NHS Diabetes Prevention Programme from participating general practices. To tackle this, I only used control participants from general practices who did not offer the NHS Diabetes Prevention Programme during this period; this may have resulted in a selection bias especially if the

				general practices which provide the NHS Diabetes Prevention Programme had done so due to having higher rates of type 2 diabetes. Alternatively, if practices did not record NHS Diabetes Prevention Programme activities, then my study would misclassify participants from these general practices in the control group despite having participated in the NHS Diabetes Prevention Programme, this result may conservatively estimate the impact of NHS Diabetes Prevention Programme activity on the incidence of type 2 diabetes. Despite using a target trial emulation framework, as I used the retrospective observational data, certain baseline characteristics were significantly different even after matching, suggesting that there could be unmeasured confounding variables. I attempted to tackle this by conducting multivariable analysis and externally comparing my results to validate them. When comparing my results with those of similar studies, each study defined a diagnosis of type 2 diabetes differently. Due to the retrospective nature of my study, to identify the incidence of type 2 diabetes, I used a combination of READ codes, ICD10 codes, HbA_{1c} readings and FPG readings in line with the 2010 American Diabetes Association (American Diabetes Association, 2010) criteria for diagnosing type 2 diabetes. The Diabetes Prevention Programme Group, 2002/2015 used the 1997 American Diabetes Association Criteria for diagnosing type 2 diabetes, and Ilanne-Parikka <i>et al.</i>, 2013 used the 1985 World Health Organisation criteria for diagnosing type 2 diabetes. Therefore, my study is likely to pick up more cases of type 2 diabetes compared to those only using clinical codes alone; however, these rates were similar to prior studies analysing diabetes prevention programmes worldwide using randomised controlled trials (Diabetes Prevention Programme Group, 2002/2015, Ilanne-Parikka <i>et al.</i>, 2013). To exclude previously undiagnosed cases of type 2 diabetes, I removed participants with a diagnosis of type 2 diabetes within 90 days of entry. Type 2 diabetes is an exclusion criterion for referral to the NHS Diabetes Prevention Programme, therefore individuals in the intervention group are actively assessed for type 2 diabetes by their general practitioner and can only be referred to the NHS Diabetes Prevention Programme if they have non-diabetic hyperglycaemia. For the control group who are not invited to the NHS Diabetes Prevention Programme, there is less certainty of whether a recording of type 2 diabetes shortly after the start of follow-up (i.e., up to 90 days after the start of follow up) is due to a pre-existing undiagnosed case, or truly an incident of type 2 diabetes. If people in the control arm with a recording of type 2 diabetes within 90 days of their start of follow up were included, this may overestimate the impact of

				the NHS Diabetes Prevention Programme. Therefore, my estimate of the impact of the NHS Diabetes Prevention Programme is likely to be conservative due to these features of my study design. Finally, in this analysis, by using a target trial emulation framework, I attempted to conduct an intention-to-treat analysis by emulating the treatment assignment with an NHS Diabetes Prevention Programme invitation. Consequently, this does not represent the impact of completing the NHS Diabetes Prevention Programme. Therefore, this analysis may under-estimate the impact of the NHS Diabetes Prevention Programme when compared to a per-protocol analysis.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		This analysis suggests that an invitation to the NHS Diabetes Prevention Programme may reduce short-term type 2 diabetes incidence in high-risk adults. By evaluating the preventive effect of having access to a NHS Diabetes Prevention Programme with a control group, my evaluation has demonstrated similar results to that of randomised controlled trials evaluating similar programmes worldwide at 2.5 years in the prevention of the incidence of type 2 diabetes (Diabetes Prevention Programme Group Study, 2002). It is likely that future evaluations of the NHS Diabetes Programme would converge the effect from 59% reduction at 3-years towards the 30% reduction at 15-years in line with findings from the Diabetes Prevention Programme Group Study, 2015 and Ilanne-Parikka <i>et al.</i>, 2013. With a 59% reduction in type 2 diabetes rates in patients referred to the NHS Diabetes Prevention Programme relative to eligible adults who were not referred, this study supports findings from other observational and randomised controlled trials that the NHS Diabetes Prevention Programme is effective in reducing short-term type 2 diabetes incidence in high-risk adults. As the NHS Diabetes Prevention Programme aims to close healthcare inequities, future research and iterations to the NHS Diabetes Prevention Programme could seek to understand the barriers experienced by deprived and particularly Asian patients who are at high risk of developing type 2 diabetes.
Generalisability	21	Discuss the generalisability (external validity) of the study results		Based upon studies that analyse the impact of the NHS Diabetes Prevention Programme on weight loss (Wise, 2018), my analysis contributes toward the more comprehensive evidence base to suggest a positive preventative effect of the NHS Diabetes Prevention Programme. My study generated results similar to studies based in the United States (Diabetes Prevention Programme Group, 2015). Based upon the triangulation against randomised controlled trials of similar interventions (Diabetes Prevention Programme Group, 2015 and Ilanne-Parikka <i>et al.</i>, 2013), there is confidence about the estimate of our effectiveness of the NHS Diabetes Prevention Programme. In addition to comparing the impact of the NHS Diabetes Prevention Programme on rates of type 2 diabetes, it is important to understand the eligibility of the NHS Diabetes Prevention Programme when compared to that of prior studies evaluating similar interventions (Diabetes Prevention Programme Group, 2015 and Ilanne-Parikka <i>et al.</i>, 2013), Of the various diabetes prevention programmes compared in this chapter, the NHS Diabetes Prevention Programme did not have any eligibility based upon body mass

				index, a lower age limit that is 7 years younger than the Diabetes Prevention Group in the USA and Ilanne-Parikka et al., in Finland. If the event rates of 6% within 2.5 years within the NHS Diabetes Prevention Programme is considered too low to policy makers, the eligibility criteria could be updated to include body mass index criteria and increased age eligibility similarly to studies in the United States and Finland.

Appendices for Chapter 6

Appendix 6.1 - REporting of studies Conducted using Observational Routinely collected Data (RECORD) checklist for Chapter 6

*Reference: Benchimol EI, Smeeth L, Guttman A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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Section	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported
ABSTRACT				
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Investigating the effect of the NHS Health Check on reducing incident cases of type 2 diabetes: A population-based cohort study using linked CPRD primary and HES secondary care health records in England Abstract Background and research gap: To reduce the incidence of cardiovascular disease in England, the National Health Service introduced the NHS Health Check in 2009. The NHS Health Check aims to identify those at high risk of developing preventable diseases such as chronic kidney disease, type 2 diabetes, heart disease, hypertension, and stroke. Current research suggests that rates of heart disease between invitees of cardiovascular health checks programmes similar to the NHS Health Check are comparable to patients who were not invited to take part in these programmes. Prior evaluations of the NHS Health Check have used outcomes that included prevalent, previously undiagnosed cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension and stroke which were discovered during the screening process. As a result of including prevalent and not incident cases, these existing evaluations are not examining the preventative effect of an NHS Health Check. This study aims to address this gap in the evidence base by attempting to estimate the preventative effect of the NHS Health Check by comparing the incidence of type 2 diabetes between eligible invitees and non-invitees of the NHS Health Check. Methods: I applied target trial emulation in a retrospective observational cohort study using linked electronic health records from primary (Clinical Practice Research Datalink), and secondary (Hospital Episode Statistics) care. The study time period was January 2009 to January 2019. I compared rates of incident type 2 diabetes among eligible adults who were invited to the NHS Health Check with rates for propensity score-matched controls who were eligible for the NHS Health Check but were not invited. Eligibility for the NHS Health Check was defined as being between 40-74 without a previous diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke at the start of follow-up. To emulate the NHS Health Check, I also excluded those who had a previous diagnosis of chronic kidney disease, diabetes, heart disease, hypertension, or stroke on entry, akin to a randomised controlled trial. Those with a recorded event of type 2 diabetes within 90 days of entry were also excluded as these were likely prevalent (i.e., previously undiagnosed cases) identified during the NHS Health Check. Time to the first phenotypical record of type 2 diabetes was modelled using Cox regression with age, alcohol intake, body mass index, serum creatinine, ethnicity, sex, HbA _{1c} , index of multiple deprivations and smoking status included as covariates. Results: I identified 105,382 individuals who participated in the NHS Health Check and 105,382 matched controls with a similar breakdown in age, sex, deprivation, and relevant clinical covariates. During the 10-year study period, 1.04% (95%CI: 0.98% - 1.11%) of NHS Health Check individuals developed type 2 diabetes versus 2.06% (95%CI: 1.98% - 2.15%) of usual care individuals. Individuals with an NHS Health Check referral had a 54% reduction in type 2 diabetes incidence rates

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				[adjusted hazard ratio= 0.46, 95% CI:0.45 – 0.47]. Discussion and Conclusions Rates of incident type 2 diabetes were low when compared to the NHS Diabetes Prevention Programme, which is likely due to the NHS Health Check’s invitation of “healthy” individuals, compared to the higher risk individuals invited to the NHS Diabetes Prevention Programme. I found evidence that the NHS Health Check reduces the risk of type 2 diabetes when compared to usual care. These contrasts previous findings of similar rates and is likely due to differentiating “newly recorded type 2 diabetes” as an incident case as opposed to a combination of previously undiagnosed case and incident cases.
INTRODUCTION				
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		As stated in previous chapters, the primary concern about evaluating the NHS Health Check is that previous studies have evaluated new detection, and this combines previously undiagnosed cases (important to prevent disease progression) and incident cases of type 2 diabetes. Therefore, there is limited understanding on whether the NHS Health Check reduces the incidence of disease in a disease-free population, in this case, type 2 diabetes.
Objectives	3	State specific objectives, including any prespecified hypotheses		To achieve this aim, this chapter has the following objectives: 1)To define a target trial description for the NHS Health Check in a similar manner that I had done for the NHS Diabetes Prevention Programme 2)To use READ codes and phenotypes developed in chapter 4 to reduce recording biases when establish a cohort of eligible patients, their treatment status and outcome of the incidence of type 2 diabetes. 3)Externally validate my sample by comparing to previous studies that evaluated the NHS Health Check’ ability to detect new previously unrecorded type 2 diabetes (including both previously undiagnosed cases and incident cases) 4)Understand whether the NHS Health Check could prevent incident type 2 diabetes by emulating a “screening” process for eligibility and removing those who were found to have a previously unrecorded disease on entry. 5)Apply methods to reduce other biases such as missing data and differential baseline covariates between invitees and non-invitees of the NHS Health Check
METHODS				
Study Design	4	Present key elements of study design early in the paper		This study used the observational, retrospective longitudinal cohort design with the “trial emulation” framework applied to reduce confounding by indication (Hernán et al., 2022).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		To analyse the NHS Health Check, I used the CPRD dataset. To identify additional cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension and stroke not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed (ONS death records were used for the outcome of type 2 diabetes only). See Chapter 4 for phenotyping and Chapter 5 for further details of the linkage periods and methods for the CPRD, HES and ONS datasets including which ranks of linkages were used.
Participants	6	(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.	The study period was from 1 January 2009 (introduction of the NHS Health Check) until 1 January 2019 (latest available CPRD build). I used the same eligibility criteria as the NHS Health Check, defined as those between 40 – 74 who were “healthy” which is defined as individuals without a record indicating previous diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke. The primary difference between this study and general practice is that the “healthy” eligibility criteria in general practice is applied when inviting individuals; in this study, the “healthy” eligibility criteria is applied at the start of follow up. I excluded individuals who were likely to have had pre-existing diagnoses of chronic

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		<i>Case-control study</i> - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants <i>(b) Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case	RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	kidney disease, type 2 diabetes, heart disease, hypertension or stroke during the screening process i.e. exclusion of diagnoses that were recorded within 90 days of their start of follow-up to evaluate prevention and not discovery of pre-existing conditions (See Figure 6-2).Patients from general practices whose' records were not up to standard (UTS) for one year before the introduction of the NHS Health Check were excluded (see Chapter 5 for definition of UTS)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Primary Outcome Variable The primary outcome of interest was incident cases of type 2 diabetes, which were defined using the first phenotypical recording of: 6. A primary care (CPRD) diagnosis for type 2 diabetes using READ codes and medical codes. 7. A secondary care (HES) diagnosis for type 2 diabetes using ICD10 codes. 8. A death record (ONS) for type 2 diabetes, identified using ICD10 codes. 9. A HbA_{1c} reading of 48 mmol/L or higher from primary care records (CPRD) 10. An FPG reading of 7 mmol/L or higher from primary care records (CPRD) Intervention The intervention was an invitation to the NHS Health Check. I defined the entry date (and participation in the NHS Health Check) with the first READ code recording in Table 6-2 or by using a combination of covariate readings after registering for a general practitioner, whichever was first. Patients who were invited to have an NHS Health Check but declined or did not turn up for the NHS Health Check were included in the intervention group, akin to an intention-to-treat analysis in a randomised controlled trial. To complement missing NHS Health Check READ codes, phenotyping algorithms were used to reduce misclassification. I used the Artac et al., 2013 algorithm and used a combination of blood pressure readings, body mass index records, smoking status, ethnicity, and cholesterol reading on the same day, after 3 months of registering for a general practice to denote participation in the NHS Health Check (Artac

Section	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported																																				
				et al., 2013). In these instances, I used the earliest date where all these recordings were done to use as my entry date. <i>Table 6-2: READ Codes for identifying the NHS Health Check</i> <table><tr><th>READ Code</th><th>READ Term</th></tr><tr><td>6AH..00</td><td>NHS Health Check annual review</td></tr><tr><td>6B5..00</td><td>NHS Health Check Programme</td></tr><tr><td>8Ag.0</td><td>NHS Health Check Completed</td></tr><tr><td>8Aix.00</td><td>NHS Health Check Declined</td></tr><tr><td>8Bag000</td><td>NHS Health Check completed by third party</td></tr><tr><td>8BR2.00</td><td>NHS Health Check indicated</td></tr><tr><td>9mC..00</td><td>NHS Health Check invitation</td></tr><tr><td>9mC0.00</td><td>NHS Health Check telephone invitation</td></tr><tr><td>9mC1.00</td><td>NHS Health Check invitation first letter</td></tr><tr><td>9mC2.00</td><td>NHS Health Check invitation second letter</td></tr><tr><td>9mC3.00</td><td>NHS Health Check invitation third letter</td></tr><tr><td>9mC4.00</td><td>NHS Health Check verbal invitation</td></tr><tr><td>9mc5.00</td><td>NHS Health Check invitation email</td></tr><tr><td>9mC6.00</td><td>NHS Health Check invitation SMS text message</td></tr><tr><td>9Nie.00</td><td>Did not attend NHS Health Check annual review</td></tr><tr><td>9NiS.00</td><td>Did not attend NHS Health Check</td></tr><tr><td>9Nj5.00</td><td>Failed to respond to NHS Health Check invitation</td></tr></table> Covariates To evaluate the NHS Health Check impact on patients from different backgrounds, I included demographic, socio-economic and clinically relevant covariates. I used the latest readings up to 5-years before each patient's (estimated) entry date with missing values being imputed (see Biases Missing data section). See Table 3 for a list of covariates used in this analysis.	READ Code	READ Term	6AH..00	NHS Health Check annual review	6B5..00	NHS Health Check Programme	8Ag.0	NHS Health Check Completed	8Aix.00	NHS Health Check Declined	8Bag000	NHS Health Check completed by third party	8BR2.00	NHS Health Check indicated	9mC..00	NHS Health Check invitation	9mC0.00	NHS Health Check telephone invitation	9mC1.00	NHS Health Check invitation first letter	9mC2.00	NHS Health Check invitation second letter	9mC3.00	NHS Health Check invitation third letter	9mC4.00	NHS Health Check verbal invitation	9mc5.00	NHS Health Check invitation email	9mC6.00	NHS Health Check invitation SMS text message	9Nie.00	Did not attend NHS Health Check annual review	9NiS.00	Did not attend NHS Health Check	9Nj5.00	Failed to respond to NHS Health Check invitation
READ Code	READ Term																																							
6AH..00	NHS Health Check annual review																																							
6B5..00	NHS Health Check Programme																																							
8Ag.0	NHS Health Check Completed																																							
8Aix.00	NHS Health Check Declined																																							
8Bag000	NHS Health Check completed by third party																																							
8BR2.00	NHS Health Check indicated																																							
9mC..00	NHS Health Check invitation																																							
9mC0.00	NHS Health Check telephone invitation																																							
9mC1.00	NHS Health Check invitation first letter																																							
9mC2.00	NHS Health Check invitation second letter																																							
9mC3.00	NHS Health Check invitation third letter																																							
9mC4.00	NHS Health Check verbal invitation																																							
9mc5.00	NHS Health Check invitation email																																							
9mC6.00	NHS Health Check invitation SMS text message																																							
9Nie.00	Did not attend NHS Health Check annual review																																							
9NiS.00	Did not attend NHS Health Check																																							
9Nj5.00	Failed to respond to NHS Health Check invitation																																							

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Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		To analyse the NHS Health Check, I used the CPRD dataset. To identify additional cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension and stroke not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed (ONS death records were used for the outcome of type 2 diabetes only). See Chapter 4 for phenotyping and Chapter 5 for further details of the linkage periods for the CPRD, HES and ONS datasets.
Bias	9	Describe any efforts to address potential sources of bias		Biases To reduce biases due to the observational study design, I identified and addressed such biases through careful study design and by incorporating a variety of sensitivity analyses. Based upon weaknesses of observational studies (Hammer et al., 2009), I concentrated on tackling recruitment bias, missing data and misclassifications. Missing data Similarly to Chapter 5, missingness existed in the data, and more so as the eligible population for the NHS Health Check were “healthy” individuals who were less likely to have clinical covariates measured compared to “high-risk” individuals in the NHS Diabetes Prevention Programme. This is because these “healthy” individuals were less likely to have laboratory tests when compared to their NHS Diabetes Prevention Programme counterparts. Therefore, I also used multiple imputation in this chapter too. The following covariates were used in the MICE model, all of which were established using the closest recording before each individual's (estimated) entry date within 5-years: age on entry, gender, ethnicity, index of multiple deprivation, body mass index, glycated haemoglobin, fasting glucose plasma, diastolic blood pressure, systolic blood pressure, serum creatinine, alcohol status, smoking status and disease status (i.e. a type 2 diabetes diagnosis). For numerical covariates (age, body mass index, glycated haemoglobin, fasting glucose plasma, alcohol status and smoking status) the MICE model used linear regression modelling and logistic regression for binary covariates (for example gender and dummy variables for ethnicity). Biases in different baseline covariates Similarly to Chapter 5, I've used propensity score matching to reduce differences in baseline covariates between invitees and non-invitees of the NHS Health Check. In this chapter, the following variables were used to match invitees and non-invitees of the NHS Health Check after multiple imputation was applied: age, ethnicity, gender, index of multiple deprivation, body mass index, blood glucose measures, smoking status, alcohol intake, blood pressure measures, serum creatinine and recorded QRisk2 score. Misclassification One concern was the misclassification of those who were and were not invited to the NHS Health Check based upon the eligibility criteria. To avoid misclassification of chronic kidney disease, type 2 diabetes, heart disease, hypertension, stroke, I used previous work which used systematic reviews (Chapter 4) to generate an evidence-based list of READ codes and phenotyping algorithms within primary care databases such as CPRD, THIN and QResearch. I also used linkage to secondary care datasets to complement missing diagnoses of chronic kidney disease, type 2 diabetes, heart disease, hypertension,

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				stroke in primary care as suggested by Herrett et al., 2013. I also used relevant clinical covariates to establish both the healthcare criteria and clinical outcomes, including serum creatinine for chronic kidney disease, HbA_{1c} and fasting plasma glucose for type 2 diabetes and diastolic/systolic blood pressure for hypertension. To complement any missingness in recording the NHS Health Check intervention, I used a combination of READ Codes and covariate readings which are often collected during an NHS Health Check; as these readings are often collected during the initial registration of a general practice, I only considered readings taken 3 or more months after joining the practice (Artac et al., 2013). External Validity and understanding the role of detecting previously undiagnosed cases Unlike the NHS Diabetes Prevention Programme, there is limited data on the population of the NHS Health Check; therefore I could not compare my cohort's distribution against a database that had universal recording of NHS Health Check activity. Therefore, to understand whether my study is comparable, I used Robson et al., 2017 as a comparator. I choose Robson et al., 2017 as it was the only study whose methods I could replicate to externally validate my results in the NHS Health Check population with an outcome of recording of type 2 diabetes. Therefore, I used the results from Robson et al., 2017 to 1) to understand whether the sociodemographic distributions are similar and 2) to understand the impact of not excluding those who had a first diagnosis of type 2 diabetes within 90 days of the start of follow-up.
Study size	10	Explain how the study size was arrived at		To understand sample sizes in comparison to previous studies analysing the NHS Health Check, I've compared the sample in this chapter to prior studies analysing the NHS Health Check on type 2 diabetic outcomes on an individual level which were identified during my systematic review in Chapter 2: (Robson et al., 2017) and (Chang et al., 2016). Robson et al., 2017 contained 252,259 total participants, of which 85,122 attended an NHS Health Check; this was found to have 30% increased odds for new diabetes recording (OR: 1.30; 95%CI: 1.21 to 1.39). Chang et al,2016 evaluated 138,788 individuals with 29,672 individuals receiving a health check; this was found to also have a 30% increase in diabetes diagnoses (Difference in difference = 1.31, 95% CI = 1.17 to 1.45). In this chapter, I evaluated a total of 293,606 patients, of whom, 105,382 had NHS Health Check activity.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		To evaluate the NHS Health Check impact on patients from different backgrounds, I included demographic, socio-economic and clinically relevant covariates to the NHS Health Check. I used the latest readings up to 5-years before each patient's (estimated) entry date with missing values being imputed (see Biases Missing data section). Indexes of multiple deprivation, ethnicity, alcohol, and smoking categories were kept consistent from Chapter 5. See Table 6-3 for a list of covariates used in this analysis.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) <i>Cohort study</i> - If applicable, explain how		All analyses were completed in R studio software and reported according to the REporting of studies Conducted using Observational Routinely collected Data (RECORD) statement. To account for left censorship due to time-varying eligibility, right censorship due to leaving the CPRD (through general practice transfer or death), and the binary outcome of the phenotypic recorded incident of type 2 diabetes, I conducted a time-to-event analysis using a multivariable Cox proportional hazards model. To understand the preventative effect of the NHS Health Check, I only considered initiators of the programme (incident users). Therefore, patients in the intervention group of the NHS Health Check were assigned an entry date equivalent to their first chronological READ code entry or the first date where they had a combination of readings taken, 3 months after joining their general practice, whichever came first. Control patients were assigned a start of follow up using linear regression (See Control Population section). All patients were followed until the first chronological event of a diagnosis of type 2 diabetes (by READ code or ICD10), a

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		loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses		HbA _{1c} reading of 48 mol/mmol or higher, a fasting plasma glucose reading of 7 mmol/L or higher, dropout (for examples who those leave the CPRD either by changing general practice or through death) or end of study (1 January 2019). Patients were considered determined to have type 2 diabetes if they were either diagnosed with type 2 diabetes in primary or secondary care, had a HbA _{1c} reading of 48 mmol/L or higher, a fasting plasma glucose reading of 7 mmol/L or higher, or if one of their 15 causes of death were recorded as diabetes (see primary outcomes section).
Data access and cleaning methods		..	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	To analyse the NHS Health Check, I used the CPRD dataset. To identify additional cases of chronic kidney disease, type 2 diabetes, heart disease, hypertension and stroke not recorded in the CPRD dataset, linkages to secondary care Hospital Episode Statistics (HES) and Office of National Statistics (ONS) death records were performed (ONS death records were used for the outcome of type 2 diabetes only). See Chapter 4 for phenotyping and Chapter 5 for further details of the linkage periods for the CPRD, HES and ONS datasets.
RESULTS				
Participants	13	(a) Report the numbers of individuals at each stage of the study (e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	RECORD 13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	I found 2,906,324 individuals in the CPRD who did not have a diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension, or stroke prior to the age of 40. After removing those who did not contribute data after the introduction of the NHS Health Check, 2,229,988 participants remained. When removing individuals who were either too young or too old to have participated in the NHS Health Check between 2009 and 2019, 1,928,776 individuals remained. I then removed those with a previous diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke prior to the introduction of the NHS Health Check; this left me with 822,209 individuals. After cleaning data and removing those with a diagnosis of chronic kidney disease, type 2 diabetes, heart disease, hypertension or stroke on entry, 293,606 were considered part of my cohort with 105,382 intervention patients and 188,224 control patients. See Figure 6-3 for how the cohort was derived.

Section	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) <i>Cohort study</i> - summarise follow-up time (e.g., average and total amount)		Population and Characteristics Due to the high missingness of certain covariates, a full case analysis was considered if all the following socio-demographic covariates were available for a patient: age, gender, ethnicity, and index of multiple deprivation quintile. Under a full case analysis, 2026 were included as intervention patients whilst 7020 patients were considered controlled patients (prior to matching). Missingness for sociodemographic covariates was less likely in the NHS Health Check group for all variables except for index of multiple deprivation - see Table 6-4. For clinical covariates such as QRisk Score, BMI, alcohol status, smoking status, and blood pressure, the intervention group was less likely to have missing data due to access to diagnostic tools. See table 6-5 for a breakdown of missingness in my matched group. Full Case Cohort Under a full case analysis, there are significantly more males than females with a similar mean age for both the control and intervention group of 54 years of age on entry. Attendees were of “white” ethnicity with a small proportion of “mixed” ethnicity patients. Deprivation closely mirrors the general population at 20% per quintile, except for deprivation group 1 (least deprived). See Table 6-5 for a full breakdown of the baseline demographics of the cohort and the impact of using multiple imputation by chained equations as well as propensity score matching. Imputed Cohort After applying multiple imputation by chained equations, proportions for those analysed shifted for gender, ethnicity (Asian), deprivation quintile 1 with a lowered mean age compared to a full case analysis. After applying MICE but before applying propensity score matching, there were significant differences between the distribution of the deprivation quintiles and drinking status. After applying propensity score matching on the imputed dataset, the gap in these baselines’ differences had tightened. See Table 6-5 for a full breakdown of the baseline demographics of the cohort and the impact of using multiple imputation by chained equations as well as propensity score matching.
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> - Report numbers of outcome events or summary measures		Of 210,764 individuals (105,382 intervention + 105,382 matched control) who were identified after imputation and matching, 1.55% (n = 3,267) developed diabetes within the 10-year study period (between January 2009 and January 2019) and a maximum of 3547 days of initiating the NHS Health Check. Of the 105,382 intervention patients, 1.04% (n = 1,096, 95%CI: 0.98% - 1.11%) developed type 2 diabetes within 3512 of initiating the NHS Health Check with a median follow up time of 927 days and a mean follow up time 1068 days. Of the 105,382 control (matched) patients, 2.06% (n = 2,171, 95%CI: 1.98% - 2.15%) developed type 2 diabetes within 3547 days of initiating the NHS Health Check with a median follow-up time of 698 days and a mean follow-up time of 902 days. This created a crude hazard ratio of 0.50 (95%CI: 0.46 to 0.54). See Table 6-6 for the unadjusted incidence of type 2 diabetes in the imputed and matched cohort.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make		After adjusting for ethnicity, gender, baseline fasting glucose plasma, baseline HbA_{1c}, IMD, baseline alcohol intake, baseline smoking consumption, baseline BMI, age on entry, baseline blood pressure, and serum creatinine, the hazard ratio for a referral to the NHS Health Check demonstrated that referred patients were 54% (H.R.: 0.46 [95% CI: 0.45 – 0.47]) less likely to develop type 2 diabetes compared to the imputed and matched control group. See Table 6-7 for a full breakdown of the hazard ratios for each covariate.

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		clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses		When conducting a full case analysis, a total of 9046 (2026 intervention and 7020 control) individuals provided data in the intervention and control groups. Under a full case analysis without propensity score matching, the hazard ratio for developing type 2 diabetes in those invited to undergo an NHS Health Check changed to 0.63 [95%CI: 0.54 – 0.73]. Under a full case analysis with propensity score matching, the hazard ratio for NHS Health Check invitation changed to 0.73 [95% CI: 0.58 – 0.84]. When conducting an unmatched analysis using MICE, the hazard ratio stayed at 0.47 [95%CI: 0.46 – 0.48]. See Table 6-8 the hazard ratio under different methods.
DISCUSSION				
Key results	18	Summarise key results with reference to study objectives		In my NHS Health Check population, 1.55% (95%CI: 1.50% to 1.60%) of individuals developed type 2 diabetes during the 10-year study period with a maximum follow-up of 3547 days. My primary analysis provides evidence that the NHS Health Check reduces the incident cases of type 2 diabetes in those between the ages of 40-74 without a prior history of cardiovascular-related diseases. Compared to the NHS Diabetes Prevention Programme, the NHS Health Checks crude 10-year study period incidence rate of type 2 diabetes being 1.55% (95%CI: 1.50% to 1.60%) compared to the NHS Diabetes Prevention Programme's crude 3-year study period incidence rate of 5.96% (95%CI; 5.55% - 6.42%); this is expected due to the different eligibility criteria for an invitation. That is, the NHS Diabetes Prevention Programme targets high-risk individuals whilst the NHS Health Check targets healthier individuals.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	One of the major challenges when evaluating the NHS Health Check is the large amounts of missing data, even more missing amounts of data compared to programmes such as the NHS Diabetes Prevention Programme. This is likely due to the eligibility criteria of the NHS Health Check which consists of “healthier” individuals, who are less likely to have covariates such as blood sugar levels measured. To mitigate this, I have conducted both full case analysis and multiple imputation, although these are both assuming that the data is not missing at random in such a population. Due to previous work demonstrating the CRPD's representativeness, it is likely the data was to some extent missing at random. A recommendation for policy makers to tackle high levels of missingness is to incentivise general practitioners in collecting socio-demographic and clinical data collected as part of the NHS Health Check as part of the Quality Outcome Framework. Not only would this improve data specifically for evaluation of the NHS Health Check, but this would reduce the “social determinants” of missing data and improve models currently used in general practice such as the QRisk2 score currently used as part of the NHS Health Check.

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				A further challenge with establishing participation in public health interventions in administrative datasets is the usage of their clinical codes, particularly at the introduction of the intervention. Unlike the NHS Diabetes Prevention Programme, the NHS Health Check is deployed in all general practises, meaning that I could not mitigate misclassification by using control participants from non-participating general practises. Therefore, I used a combination of READ codes and clinical covariate recording to establish NHS Health Check activity (including none) for each patient, rather than at the level of the practice which introduces more uncertainty around NHS Health Check activity when compared to NHS Diabetes Prevention Programme activity. Consequently, this could introduce two biases that impact the outcome in the opposite directions. Firstly, participants of the NHS Health Check are more likely (in the initial stage) to be detected for disease due to access to diagnostic testing, leading to an underestimate of the NHS Health Check if not controlled for. An alternative bias is that those who were assigned to the NHS Health Check group using a phenotypic recording based upon clinical covariate recording (as opposed to a READ code) were active health seeking participants which could bias the towards over-estimating the preventative effect of the NHS Health Check. Therefore, to reduce these biases, further clinical codes could be used to differentiate participants who are believed to be worried well in the NHS Health Check similarly to the ICD10 code Z71.1 which represents "Person with feared complaint in whom no diagnosis is made." As I used the retrospective observational study design, certain baseline characteristics were significantly different even after matching, meaning that there could be unmeasured confounding variables. I attempted to tackle this by conducting multivariate analysis on top of propensity score matching. Chapters in the next section attempt to address limitations of this study such as the large amounts of missing data. Related to baseline differences is the fact that despite being around for 10 years, not all eligible individuals were not invited to the NHS Health Check. This could result in residual confounding as there may have been (unmeasured) reasons for the propensity of not being invited; for example, if general practitioners did not send out invitations to those who they knew were healthy. Despite the 10-year study period (January 2009 to January 2019), the distribution of the follow up periods were lower, with a mean of 965 days of follow-up with a maximum of 3547 days of follow-up in the NHS Health Check cohort. This likely reflects the limitation of administrative data, where the published average follow-up period in the CPRD is 5.1 years (1861 days) (Herrett et al., 2013).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		Rates of type 2 diabetes in "healthy" adults between the ages of 40 to 74 are relatively low at 1.55% (95%CI: 1.50% to 1.60%) when compared to high-risk patients in Chapter 5. In the population of "healthy" adults, the evidence suggests that after "passing" the screening process of the NHS Health Check, gaining access to the appropriate treatment (including none) can reduce the risk of type 2 diabetes. With a 54% (HR: 0.46 [0.45 – 0.47]) 10-year risk reduction, my findings provide evidence that the NHS Health Check is effective in reducing middle-to-long term incidence of type 2 diabetes.
Generalisability	21	Discuss the generalisability (external validity) of the study results		Overall, my results demonstrate that access to an NHS Health Check reduces individual risk of type 2 diabetes in adults without prior cardiovascular disease [adjusted hazard ratio= 0.46, 95% CI:0.45 – 0.47] and produces results similar to other preventative programmes, such as the NHS Diabetes Prevention Programme for adults without prior type 2 diabetes [adjusted hazard ratio=0.41;95%CI=0.38-0.44]. My previous chapters using an interrupted time series did not detect an effect of a population level reduction in type 2 diabetes. This could be because the incident rate of type 2 diabetes was low in the "healthy" population eligible for the NHS Health Check; 1.55% (95%CI: 1.50% to 1.60%) incidence over an up to 10-

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				year period. Therefore, even with 54% (HR: 0.46 [0.45 – 0.47]) reduction at the individual level against a control group, detecting changes at the population level could be difficult due to the low rates of type 2 diabetes in a “healthy” population. In terms of social determinants of health, this chapter generalises with previous work demonstrating the barriers experienced by minority ethnic populations and groups experiencing deprivation who are disproportionately impacted by non-communicable diseases such as type 2 diabetes. Therefore, it could be reasonable for the NHS Health Check to target high risk individuals as previously suggested (Kypridemos et al., 2018). Whilst the NHS Health Check produced a middle-to-long term reduction in the incidence of type 2 diabetes relative to a control group, its non-targeted approach may only benefit a small proportion of individuals. There is some evidence that a targeted approach is able to improve outcomes of high-risk individuals (i.e., those who need public health interventions the most); that is the NHS Diabetes Prevention programme had a 3-year incident rate of 5.96% (95%CI: 5.5% - 6.4%) compared to the NHS Health Check’s 10-year incident rate of 1.55% (95%CI: 1.50% to 1.60%) in terms of type 2 diabetes. Therefore, future work could investigate the impact of the NHS Health Check on those at high risk of non-communicable, lifestyle modifiable cardiovascular diseases. In terms of the economic impact of the NHS Health Check, results show a 54% (HR: 0.46 [0.45 – 0.47]) relative risk reduction in type 2 diabetes incidence which is a significant result. However, this represents a 1.02% absolute risk reduction (2.06% incidence rate in the control versus 1.04% in the matched intervention group) and potentially delays or prevents 1020 cases of type 2 diabetes per 100,000 adults between the ages of 40-74 without a prior case of chronic kidney disease, heart disease, hypertension, stroke or type 2 diabetes. Cost effectiveness evaluations should be undertaken which consider the results in this chapter and its impact on preventing/delaying type 2 diabetes whilst not forgetting additional health economic analysis on early detection when compared to no NHS Health Check.