ANALYSING RECENT TIME TRENDS IN CORONARY HEART DISEASE AND TYPE 2 DIABETES IN THE UK

THESIS presented for the degree of DOCTOR OF PHILOSOPHY

Field of study: Epidemiology –Applied Medical Statistics

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DECLARATION STATEMENT

I, Sarah Hardoon, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this had been indicated in the thesis.

ABSTRACT

Coronary heart disease (CHD) mortality rates have fallen since the 1960s in the UK. The prevalence of type 2 diabetes (T2DM), in contrast, has increased markedly in recent decades. Few attempts have been made to examine the reasons for these striking, divergent time trends.

The CHD mortality and T2DM prevalence trends likely reflect in part contemporaneous trends in incidence of these conditions. The broad aim of this thesis is therefore to analyse recent trends in CHD and T2DM incidence in the UK, in relation to trends in aetiological exposures and treatment use, and in relation to each other.

This epidemiological research involves statistical analysis of pre-collected data from different UK-based observational data sources, each used according to their strengths: the British Regional Heart Study cohort, The Health Improvement Network primary care database, and the Whitehall II cohort.

The principal findings are that favourable time trends in major modifiable aetiological exposures (smoking, blood pressure and HDL and non-HDL cholesterol) may explain half of a 62% decline in major CHD incidence in men over 25 years. Findings for women are similar. Much of the blood pressure decline, and a third of the non-HDL cholesterol decline was associated with increased preventive medication use. Conversely, unfavourable rising adiposity levels limited the scale of the decline in major CHD incidence, and explain an estimated one quarter of a rise in T2DM incidence since the 1980s. Major CHD incidence declined faster among those with T2DM, than without, corresponding to an attenuation of excess risk of CHD associated with T2DM.

By highlighting what can be achieved in terms of reducing CHD, while showing the adverse impact of rising obesity levels, the results provide evidence to help inform future efforts to reduce CHD further and curb the rise in T2DM, in the UK and in other locations.

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FREQUENTLY USED ABBREVIATIONS

Data sources

BRHS	British Regional Heart Study
THIN	The Health Improvement Network (primary care database)

Disease outcomes

CHD	Coronary heart disease
CVD	Cardiovascular disease
MI	Myocardial infarction
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Exposures

BMI	Body mass index
BP	Blood pressure
DBP	Diastolic blood pressure
HDL	High – density lipoprotein (cholesterol)
LDL	Low – density lipoprotein (cholesterol)
SBP	Systolic blood pressure

Statistical terms

CI	Confidence interval
GEE	Generalised estimating equation
SD	Standard deviation

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Chapter 1 Introduction

1.1 Introduction and rationale for thesis

This thesis considers time trends in the UK in coronary heart disease (CHD) and in type 2 diabetes mellitus (T2DM). Strong evidence suggests that striking and divergent time trends in these two related major non-communicable diseases have occurred in the UK in recent decades. In particular, the "headline" statistics are a fall in mortality from CHD of almost three quarters from 1961 to the present[1], compared with a rise in prevalence of T2DM of around 5% per annum since the 1990s[2-6].

Understanding the reasons for these contrasting disease time trends could yield potentially important public health implications in terms of informing future efforts to reduce CHD mortality and T2DM prevalence in the UK, through gaining insight into which determinants may be most influential. For T2DM this is especially important as the rising T2DM prevalence and associated co-morbidities represent a growing healthcare burden in the UK[7, 8], as is detailed in chapter 2, section 2.4.2. For CHD, although CHD mortality has fallen, the condition remains the leading cause of premature death in the UK among both men and women, responsible for over 25,000 premature deaths in 2008[9]. In addition, knowledge of the influences on the UK CHD time trend could provide insights which may help to control the emerging epidemics of CHD occurring in middle and lower income countries[10, 11].

While the major aetiological factors for CHD are largely established, as summarised in chapter 2, section 2.5.2.1, few studies have examined how much favourable trends in these aetiological factors and in increasing use of effective cardiovascular treatments (particularly those for prevention of CHD) have actually contributed to the

decline in CHD mortality. The few studies of this type[12-15] examining the UK CHD decline have used ecological data and are subject to limitations of ecological analyses; very few studies worldwide have used data on individuals within a single population[16-18] to study CHD time trends. Even fewer formal attempts have been made to explain the rising T2DM prevalence[4, 19].

The decline in CHD mortality could represent a decline in CHD incidence or an increase in survival. Previous studies of trends suggest that the decline in CHD mortality reflects, at least in part, a decline in incidence of major CHD events (principally heart attacks), that is, the proportion of men and women developing major CHD events in the first place[20-24]. Similarly the rise in prevalence of T2DM may reflect at least in part rising incidence of T2DM[4, 6, 25, 26], although evidence on trends in incidence is limited reflecting a paucity of suitable data sources. Therefore, a key step towards understanding the time trends in CHD mortality and T2DM prevalence is to examine time trends in incidence of these two conditions.

T2DM is associated with an estimated two-fold increased risk of CHD[27-33]. It might therefore be expected that the increased prevalence of T2DM would lead to an increase in CHD. Thus the relationship between the opposing trends in these related conditions is another important question to address. In particular, the degree to which the decline in CHD mortality has been curtailed by the increase in T2DM prevalence, or is likely to be curtailed in the future, is of interest.

1.2 Thesis objectives

The overall aim of this thesis is therefore to use individual-level data from relevant data sources to examine recent trends in major CHD and T2DM incidence in the UK both in relation to changes in risk factors and treatment use and in relation to each other. The specific objectives of the thesis are to:

i) Estimate recent time trends in incidence of major CHD in the UK

ii) Estimate recent time trends in incidence of T2DM in the UK

iii) Examine the potential contribution of secular time trends in major aetiological factors and preventative medications to the time trend in incidence of major CHD:

iii)a) Examine the possible contribution of secular time trends in major aetiological factors to the time trend in incidence of major CHD

iii)b) Examine the contribution of increased preventative medication use to the time trends in the major aetiological factors

iv) Examine the possible contribution of secular time trends in major aetiological factors (particularly rising adiposity levels) to the time trend in incidence of T2DM

v) Examine the paradox that CHD has declined while T2DM has increased.

v)a) Estimate whether the time trend in incidence of major CHD among individuals with T2DM differs from the time trend in incidence of major CHD among those without T2DM, and if so, how the excess risk of major CHD among those with T2DM has changed over time.

v)b) Estimate the potential decline in major CHD incidence had no increase in T2DM occurred and the extent to which rising T2DM prevalence has curtailed the decline in major CHD incidence.

1.3 Overview of methodology

The method used to carry out this epidemiological research is statistical analysis of pre-collected data, from a combination of different UK-based observational data sources. The principal data source used is the British Regional Heart Study (BRHS)[34, 35], an established cohort study, which has followed up 7735 British men for CHD outcomes for over 30 years from 1978 to the present. A second data source used is The Health Improvement Network (THIN) national primary care database[36], comprising routinely collected data on General Practice consultations. Data from the London-based Whitehall II cohort[37] of male and female civil servants followed-up from recruitment in 1985-8 is also used. The data sources are each used according to their respective strengths. Statistical models are constructed to relate the time trends in CHD and T2DM to concurrent time trends in associated factors and treatment use. All statistical analyses have been carried out using Stata versions 10-12 (Stata Corp., College Station, Texas).

1.4 Disease definitions

Coronary heart disease (CHD), which normally results from atherosclerosis of the coronary arteries, when severe, is associated with specific clinical syndromes including **angina pectoris** and **myocardial infarction** (MI). Angina pectoris is typically chest pain of limited duration which occurs on exercise or stress, reflecting ischaemia of the myocardium (lack of oxygen to the heart muscle due to restricted blood flow). Angina may be stable or unstable. Unstable angina, as distinct from stable angina, is more severe, and is characterised by prolonged chest pain occurring even at rest, or new-onset chest pain occurring during ordinary activity of low exertion, or previously diagnosed angina that has become more frequent, longer in

duration, or triggered at lower levels of physical exertion[38]. MI, that is, a "heart attack", is a more severe form of CHD, where the blood supply is cut off altogether from part of the heart muscle causing the cells to die (infarction). An estimated 25% or more of MIs are "silent", resulting in no discernible symptoms, only detected retrospectively for example through electrocardiograms (ECGs)[39]. However, in the majority of cases, an MI has serious manifestations, usually severe chest pain, often accompanied by shortness of breath, nausea, palpitations, sweating and anxiety, and can lead to unconsciousness and death. The term "acute coronary syndrome" is often used to describe unstable angina and MI, as distinct from the stable angina.

Focus in this thesis will be on "major" CHD events, defined as an MI, predominantly not silent, or death with CHD as the underlying cause (which might be assumed to be an MI). The rationale for this is two-fold. First, angina is notoriously difficult to define and ascertain, hindering reliable estimation of the patterns and trends in angina, compared with MIs, for which clear defining criteria have been established. Second, the defined major CHD events represent the most severe forms of CHD, which may result in death (and therefore contribute substantially to the CHD mortality trend), and with serious health consequences, and therefore are a substantial public health burden.

The current universal clinical definition of an acute MI, given by the Joint European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation Task Force[40], relies primarily on the [direct quote] "detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following: symptoms of

ischaemia, ECG changes indicative of new ischaemia, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality". MIs may be classified into two types: ST segment elevation MI (STEMI) and non-ST segment elevation MI (NSTEMI). The first (STEMI) indicates MIs where Q waves are evident on the ECG. In the case of the second (NSTEMI), there is no Q waves evidence on the ECG, but other markers of an MI are observed (so as to be distinguished from unstable angina). In the thesis distinction will not be made between NSTEMI and STEMI.

The term **diabetes** loosely refers to a patient with high blood sugar/glucose. There are two main types of diabetes: **type 1 diabetes** (T1DM) and **type 2 diabetes** (T2DM), although other forms also exist such as gestational diabetes, associated with pregnancy. T1DM, also called insulin-dependent diabetes or juvenile onset diabetes, is characterised by an absolute deficiency of insulin, leading to lack of blood sugar control; the condition tends to be first diagnosed in childhood or early adulthood. In T2DM, also called non-insulin dependent diabetes or adult onset diabetes, the lack of blood sugar control arises from the body cells not responding to the insulin produced. T2DM is generally first acquired in adulthood. The current World Health Organisation (WHO) definition[41] for diabetes (which applies to both types) is a fasting blood glucose level over 7mmol/L or a blood glucose level>11.1mmol/L after a 2 hour oral glucose tolerance test (GTT). "Normal" blood glucose levels range between about 4 to 8 mmol/L, varying with meal times; a fasting blood glucose level should be under 6 mmol/L. People with glucose levels above the normal range, but below the limits for diabetes (that is, fasting glucose under 7mmol/L and blood glucose after GTT between 7.8mmol/L and 11.1mmol/L) are defined as having

impaired glucose tolerance (IGT), which is seen as a precursor to T2DM (and as such is also called pre-diabetes). People with slightly raised fasting blood glucose but normal blood glucose levels are defined as having impaired fasting glycaemia, which may also lead on to T2DM. The focus of this thesis is on T2DM. Patients with T2DM comprise the vast majority (over 90%) of diabetes cases, thus representing the majority of the diabetes health burden[42]. Moreover, levels of T1DM have not increased to the same extent as T2DM. Also, T2DM, like CHD, and unlike T1DM, is considered largely preventable through modification of risk factors[43], thus a study of the influences on the rise in T2DM has arguably more immediate and tenable public health implications, in terms of elucidating measures to reduce T2DM in the population.

1.5 Structure of the thesis

The structure of the thesis is as follows: In chapter 2 existing literature related to time trends in CHD and T2DM is discussed. Chapter 3 details the three different data sources used to address the thesis objectives. The results of the analyses related to the thesis objectives are presented in chapters 4, 5, 6, 7, 8, and 9. Specifically, chapter 4 examines time trends in incidence of major CHD and T2DM overall and according to different socio-demographic characteristics, comparing results from the different data sources, in line with objectives i) and ii). Chapter 5 examines the role of time trends in major aetiological factors to the time trend in major CHD incidence, using BRHS data (objective iii)a)). Chapter 6 serves as a validation study, repeating the analyses of chapter 5 in the Whitehall II cohort, thereby providing means to verify and lend support to the findings of chapter 5. Chapter 7 then considers the role of medication use on the time trends in the major aetiological factors (objective iii)b)), again using

BRHS data. Chapter 8 presents results related to objective iv), to examine the role of time trends in aetiological factors (principally adiposity) to the time trend in incidence of T2DM, again with use of BRHS data. Chapter 9 then considers the relationship between the time trends in T2DM and CHD, addressing objective v), using both BRHS and THIN data. Each results chapter comprises a brief background specific to the analyses presented in the chapter; a description of methods specific to the chapter including statistical methods; results of analyses presented as tables and graphs, and summarised in the text; and a discussion including a summary of the main findings, details of strengths and limitations of the analyses, a comparison with existing related literature, and an interpretation of the findings. The main findings of all the results chapters, and their interpretation, are brought together in the concluding chapter 10, along with a discussion of the implications for public health and for future research.

1.6 Thesis publications

Four first-author papers[44-47] based on the material in this thesis have been published in peer-reviewed journals to date. These are listed below, along with accompanying related editorials[48]:

1. Hardoon, S. L., Whincup, P. H., Lennon, L. T., Wannamethee, S. G., Capewell, S., Morris, R. W. (2008). How much of the recent decline in the incidence of myocardial infarction in British men can be explained by changes in cardiovascular risk factors? Evidence from a prospective population-based study. Circulation 117(5), 598-604 doi:10.1161/CIRCULATIONAHA.107.705947.
    - *Accompanying editorial:* Luepker R.V. (2008) Decline in Incident Coronary Heart Disease: Why Are the Rates Falling? Circulation;117(5):592-593, doi:10.1161/CIRCULATIONAHA.107.747477

2. Hardoon, S. L., Whincup, P. H., Wannamethee, S. G., Lennon, L. T., Capewell, S., Morris, R. W. (2010). Assessing the impact of medication use on trends in major coronary risk factors in older British men: a cohort study. Eur J Cardiovasc Prev Rehabil 17(5), 502-508 doi:10.1097/HJR.0b013e3283378865.

3. Hardoon, S. L., Morris, R. W., Thomas, M. C., Wannamethee, S. G., Lennon, L. T., Whincup, P. H. (2010). Is the recent rise in type 2 diabetes incidence from 1984 to 2007 explained by the trend in increasing BMI?: evidence from a prospective study of British men. Diabetes Care 33(7), 1494-1496 doi:10.2337/dc09-2295

4. Hardoon, S. L., Morris, R. W., Whincup, P. H., Shipley, M.J., Britton, A. R., Masset, G., Stringhini, S., Sabia, S., Kivimaki, M., Singh-Manoux, A., Brunner, E. J. (2012). Rising adiposity curbing decline in incidence of myocardial infarction: 20-year follow-up of British men and women in the Whitehall II cohort. Eur Heart Journal. 33(4):478-85 doi: 10.1093/eurheartj/ehr142

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Chapter 2 Review of the existing literature

2.1 Introduction

In this chapter existing studies and data sources on time trends in coronary heart disease (CHD) and type 2 diabetes (T2DM) are reviewed, providing a more detailed background and rationale for the thesis.

Section 2.2 details literature on time trends in CHD mortality and morbidity in the UK. In particular, section 2.2.1 presents literature of time trends in CHD mortality, and section 2.2.2 presents literature on time trends in major CHD morbidity, comparing incidence and case fatality trends.

Section 2.3 details literature on time trends in T2DM in the UK. Section 2.3.1 presents literature on time trends in T2DM prevalence, while section 2.3.2 compares T2DM incidence and relative survival trends.

Section 2.4 presents a summary of the continuing CHD and T2DM health-care burden in the UK, emphasizing the need for the research.

Section 2.5 provides an overview of the various factors to consider when evaluating the time trends in incidence of major CHD or T2DM. Section 2.5.1 concerns those factors which may influence the observed time trend in incidence, but rather than contributing to a true epidemiological shift in the population, these factors may be thought of as confounding the true time trend estimates, potentially leading to under or overestimation of the true time trends. These influences will need to be taken into account when addressing the first two objectives, to evaluate the extent of the time

trends in incidence. The next sections deal with factors to consider when examining the reasons for the (remaining) true epidemiological trend in incidence of major CHD or T2DM, once these other influences have been taken into account (to address objectives iii and iv). Section 2.5.2 is a brainstorm of possible candidate factors which may help to explain a decline in major CHD incidence, based on the literature of the aetiology of CHD. These are major known aetiological exposures which have had the potential to change over time in the population and preventive treatments, where uptake has increased. Section 2.5.3 is similarly a literature-based brainstorm of possible candidate factors which may help to explain a rise in T2DM incidence. Section 2.5.4 then discusses the association of T2DM with CHD, which provides background to the final objective relating the time trends in major CHD and T2DM to each other.

Section 2.6 details existing studies formally examining reasons for the time trends in CHD and T2DM in the UK, which address similar questions to those in the thesis, and therefore studies to which the thesis results may be compared. Section 2.6.1 concerns studies formally analysing reasons for the trends in CHD in the UK, while section 2.6.2 concerns studies formally analysing reasons for the trends in T2DM in the UK.

Section 2.7 provides a summary of the worldwide picture of CHD and T2DM time trends for comparison. First, variations in time trends in CHD and T2DM between different countries, particularly in relation to the "epidemiologic transition" in the developing world, are briefly described. Then, previous studies examining reasons for the time trends in countries other than the UK are explored.

2.2 Time trends in major coronary heart disease in the UK

2.2.1 Time trend in CHD mortality in the UK

2.2.1.1 Overall time trends among men and women

Information on time trends in the UK in mortality from CHD may be obtained from a combination of different sources including routinely collected data, government and other official reports, and published research papers. Much of the data on time trends in CHD mortality, particularly that derived from routine data sources, is helpfully collated on The British Heart Foundation (BHF) Statistics website (www.heartstats.org). In particular, a recent update[1] (Feb 2011) on time trends in CHD mortality reports trends from 1961 to 2009 based on routinely collected official data (England and Wales: Office for National Statistics (ONS); Scotland: General Register Office; Northern Ireland: Statistics and Research Agency). The key finding is that CHD death rates in the UK have declined continuously from 1961 to 2009 among both men and women. The age-standardised annual CHD mortality rate fell by 73% among men over this 49 year period, from approximately 428 CHD deaths per 100,000 population/year in 1961 to 115 deaths per 100,000 population/year in 2009. The decline in women was 78%, from 240 CHD deaths per 100,000 in 1961 to 52 deaths per 100,000 in 2009. The decline was relatively slow over the earlier years from 1961 to the mid 80s, after which point it became more marked (declines of approximately 15% and 30% for men and women respectively over the 25 year period from 1961 to 1985 compared with declines of approximately 68% and 69% for men and women over 25 years from 1985 to 2009). This pattern is particularly apparent among men. It is the more rapid period of decline, from the 1980s to the present, which is the focus of this thesis.

Published material reporting on time trends in CHD mortality in the UK using the same data sources give similar findings, as might be expected[49]. O'Hara et al[50] reported a decline of just over 50% between the periods 1985-89 and 2002-2006 among both men and women in the UK (using data from the World Health Organisation, WHO), which agrees closely with the trends reported on the BHF Statistics website. A "joinpoint" analysis[51] was used which predicts time-points at which a change in the rate of mortality decline has occurred ("change-points"). It was found that the rate of decline in men tended to increase over the period from -2.99% in 1985-1993 to -4.84% in 1993-2003 to finally -7.29% in 2003-2006. A similar pattern was observed among women. An average annual age-adjusted decline of -4.8% occurred among men from 1978-80 to 1998-2000 in the British Regional Heart Study[20] (BRHS), the principal data source used for this thesis. This corresponded to a 63% decline over the whole 20-year period, comparable to the above findings.

2.2.1.2 Age-specific time trends

The above-mentioned report on CHD mortality trends[1] on the BHF Statistics website also shows trends in the age-standardised CHD mortality rate restricted to those aged under 75 years, which represents the premature mortality rate. In contrast to the overall CHD mortality rates, the premature CHD mortality rate remained relatively constant among both men and women between 1961 and the mid 1980s, but then declined consistently and sharply from this point to the present (by approximately 75% in both men and women). The report also highlights somewhat distinct trends in the CHD mortality rates occurring among younger age groups; those aged 55 and under (the early mortality rate), compared to the overall picture which is dominated by the higher mortality rates in the older ages. It alerts to an apparent 25% *increase* in

the early CHD mortality rate in the first part of the period from 1961 to 1975 among both men and women. Moreover, while declines in CHD mortality occurred after this point in this age group, there is some suggestion that the decline has slowed in the most recent years, in contrast to the continuing decline in older age groups. This observation is supported by separate analyses of these routine data sources in three recently published papers[52-54], in which time trends in CHD mortality are estimated for different age-groups. However it is important to note that in the papers some of the rate of change estimates are imprecise - based on limited numbers of deaths in younger age-groups and with correspondingly wide confidence intervals (CIs) - and occur over just a few years. These could therefore be random fluctuations in the trends rather than a true change. Continued monitoring of the CHD mortality rates is therefore needed to confirm the slowing decline. The observed slowing of the decline in younger age groups nevertheless does reflect trends observed in other countries with a comparable risk profile (USA[55], New Zealand[56], Australia[57]).

2.2.1.3 Time trends within different socio-demographic groups

Plots of the standardised mortality ratios for CHD mortality over time by constituent country[1] (relative to England) show the highest CHD mortality rates generally to have been in Scotland throughout the period from 1961 to 2009, followed by Northern Ireland, Wales and then England with the lowest mortality rates. The standardised mortality ratios have fluctuated over time but the net change over the 49 year period is small. This suggests that the total declines in CHD mortality have been broadly similar across the different countries, although the extent of the declines may have varied in different years of this period. A separate analysis of General Register Office for Scotland data compared CHD mortality time trends between 1981 and 1999 in

rural and urban areas of Scotland[58] and found a slightly faster decline among rural areas and small towns compared with urban areas, from a similar starting level (at least a -48% change compared with -42%).

The BHF Statistics website CHD statistics publication[9] (2010) shows time trends in CHD mortality rates in Great Britain from 1994 to 2008 by fifths of social deprivation, as measured using the Carstairs index for local authorities, using data from the Office for National Statistics and General Register Office for Scotland. There is a clear gradient, with higher total and premature CHD mortality rates with increasing deprivation among both men and women, and this gradient persists over the whole period. There is some suggestion that the absolute difference in CHD mortality rates between the deprivation quintiles has narrowed slightly. However, the relative differences comparing the most deprived to least deprived quintile have increased (from 1.3 in 1994 to 1.6 in 2008 in men, with similar figures for women), suggesting a smaller relative decline in CHD mortality in the more deprived quintiles. Separate earlier data also from the BHF Statistics website, shows that over the period from 1978 to 1998, the relative CHD mortality rates, comparing manual and non-manual men and women, tended to increase over time, so that manual men and women remained at excess risk of CHD mortality compared with non-manual men and women (data from the ONS). A number of papers on trends in CHD mortality according to socio-economic background support these findings[54, 59-61], including a previous analysis of BRHS data[61], which showed again a persistence or even an increase in the relative difference in CHD mortality comparing manual to non-manual men (approximately 75% increase in the relative risk from 1978 to 2005). Moreover, regarding the previously mentioned slowing of the decline in CHD mortality in

younger age groups in recent years, it has been shown that the slowing of the decline in Scotland in 1986-2006 is limited to the two most deprived fifths of social deprivation (defined using the Scottish Index of Multiple Deprivation), leading to a widening social inequality in CHD death[54].

A study on time trends in CHD mortality in the UK between 1979 and 2003 according to country of birth[62], using data from the Office for National Statistics, revealed some variations in the CHD mortality time trends by country of birth. CHD mortality among men born in India, Pakistan or Bangladesh was higher relative to men born in England and Wales at the start of the period in 1979 (rate ratios of approximately 1.5, 1.2 and 1.4 respectively). These rate ratios increased over time, indicating a slower decline among men born in India, Pakistan and Bangladesh. Indeed, by 1999-2003, the CHD mortality rate for men born in Pakistan and Bangladesh was approximately double that for men born in England and Wales. CHD mortality trends among men born in the Caribbean and Africa were more similar to that for men born in England and Wales. The patterns among women were broadly similar, although as event numbers were smaller, estimates are less precise. Trends by ethnicity (as opposed to country of birth) are not readily available as country of birth rather than ethnicity has previously been recorded on death certificates. Country of birth is seen as a good proxy for ethnic group among older people[63, 64]. Among younger age-groups, who may be descendents of migrants, there is less correspondence between country of birth and ethnicity. However, since CHD predominantly affects older age groups, the time trends reported here may be a reasonable reflection of time trends by ethnicity.

2.2.2 Time trend in major CHD incidence and case fatality in the UK

The decline in CHD mortality may be attributed to either a decline in the incidence of major CHD (that is, fewer individuals experiencing a major CHD event which could result in death) or an improvement in survival following a major CHD event (that is, those who do experience a major CHD event are surviving longer), or indeed some combination of the two. The available data on major CHD incidence and case fatality time trends in the UK is detailed below.

2.2.2.1 Time trends in major CHD incidence

Much of the available data on time trends in major CHD incidence is again summarised on the BHF Statistics website, and principally comes from independent major studies of cardiovascular disease (Oxford Myocardial Infarction Incidence Study Group (OXMIS), WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) project, and the BRHS). Starting with the earlier data, the OXMIS study reported an average annual decline in age-standardised incidence of major CHD (defined as non-fatal definite MI or fatal CHD) of 1.2% in men and 0.3% in women aged 30 to 69 years between 1966-7 and 1994-5 in Oxfordshire[23]. This corresponds to a total decline among men over the period of 32.7%, from an age-standardised incident rate of 433.8 per 100,000 in 1966-7 to 291.8 per 100,000 in 1994-5, and a smaller, non-significant total decline among women of 8.2% from 102.3 per 100,000 to 93.9 per 100,000. Note though that the event numbers were small among women leading to imprecise time trend estimates (CIs are wide). The WHO MONICA project estimated more recent trends from the mid 1980s to mid 1990s in incidence of major CHD (defined again as CHD death or non-fatal MI) across 37 populations in 21 countries, including two populations in the UK; Glasgow

and Belfast[22]. In Glasgow from 1985 to 1994, an average annual decline in incidence of major CHD of 1.4% was observed in men and an average annual *increase* of 0.2% was observed in women. In Belfast from 1983 to 1993, an average annual decline in incidence of major CHD of 4.6% was observed in men and an average annual decline of 2.4% was observed in women. A previous analysis of BRHS data found an average annual decline in risk of a first major CHD event (defined as a CHD death or non-fatal myocardial infarction) of 3.5% over an overlapping time-period between 1978-80 and 1998-2000 among older British men, adjusting for age[20]. A decline in recurrent major CHD events of 3.9% per annum also occurred. More up-to-date data for Scotland has also very recently been made available on incidence rates of major CHD in the BHF Statistics publication on trends in cardiovascular morbidity[1]. The publication reports on recent trends in Scotland between 1986 and 2008 in incidence of major CHD, defined here as hospitalisations for MI or deaths with CHD as a cause (based on a combination of mortality data and hospitalisation data). A 60% decline in incidence occurred in Scotland between 1986 and 2008 in both men and women (all ages), from incidence rates of 525 events and 242 events per 100,000 in men and women respectively in 1986 to rates of 213 events and 95 events per 100,000 in men and women in 2006, average annual declines of 2.6% and 2.7% in men and women respectively.

Additional data on trends in emergency hospitalisations for MI in Scotland between 1990 and 2000[21] suggest that the rate of hospitalisations for MI declined by approximately 30% over the 10 years, among both men and women. This corresponds to an average annual decline of 3.5%, which agrees closely with the time trend in all first major CHD events in the BRHS, which covers this same time-period. A further

recently published paper (post conception of thesis) used data from The Health Improvement Network (THIN) primary care database, a second data source used in this thesis, to estimate trends in incidence of a first MI by UK country[24]. Incident MI is determined as a record of an MI event in the general practice records for the patient. The study reported average annual percentage declines in incidence of MI of 3.1% and 2.8% in men and women respectively aged 35 years and over in England between 1996 and 2005. Comparable declines occurred in Wales (3.3% and 4.6%), while more modest declines were observed in Scotland (1.9% and 0.6%) and Northern Ireland (0% and 0.8%).

2.2.2.2 Time trends in major CHD case fatality

There is evidence to suggest that case fatality following major CHD events has also declined over time. In Oxfordshire, according to data from the BHF Heartstats cardiovascular morbidity publication[9], case fatality (defined here as the proportion of all incident hospitalised major CHD events resulting in death within 30 days plus CHD deaths outside of hospital) appeared to decline by approximately one-quarter from 1968 to 1998 among both men and women and in all age-groups. A faster relative decline was seen in younger age groups (for example of 27% in 35-39 year old men from 35.5% of events fatal in 1968-1973 to 25.9% in 1994-1998; average annual decline of 1.2%) than older age groups (of 23% in 75-79 year old men from 83.4% to 64.5%; average annual decline of 1.0%). The OXMIS study presents a further analysis of the declines in age-standardised case fatality between 1966-67 and 1994-5[23]. The fatality rate (defined as 28 day case fatality in 1966-67 and 30 day case fatality in 1994-5) fell among men aged 30-69 years from 56.7% of major CHD events being fatal in 1966-67 to 41.0% fatal in 1994-5 (average annual relative

decline of 1.2%). The fatality rate fell among women aged 30-69 years from 64.6% in 1966-67 to 44.1% in 1994-5 (average annual relative decline of 1.4%). Slightly larger declines in case fatality were observed over more recent periods in Belfast and Glasgow (WHO MONICA[22]). In Glasgow, between 1985 and 1994, average annual declines of 1.3% and 2.1% occurred among men and women respectively, aged 35-64 years. In Belfast, between 1978 and 1996, average annual declines of 1.5% and 1.7% occurred among men and women respectively, aged 35-64 years. Time trends in case fatality (death within 28 days of a major CHD event) among men in the BRHS have been reported for the period 1978 to 1995[65]. Adjusting for age, the case fatality rate fell by 2.1% per annum. More recent estimates from the THIN database, suggest considerable average annual declines in 30-day case fatality between 1996 and 2005 among men age 35 years and over of 12.0%, 18.4%, 9.5% and 8.6% in England, Wales, Scotland and Northern Ireland respectively[24]. The corresponding estimated declines among women were similarly large: 11.0%, 12.6%, 9.0% and 13.0%.

Crude 30-day case fatality among patients admitted to hospital for MI (that is, excluding fatal events among patients who do not reach hospital) also declined in Scotland by 23% over 10 years from 25.1% in 1986 to 19.4% in 1995 (data from the Scottish Morbidity Record Database linking all hospital admission records to all mortality data for 5.1 million patients in Scotland[66]). This corresponds to an average annual relative decline of 2.6%. Adjusting for age, deprivation category and prior hospital admissions, the 10-year decline was 46% in men and 27% in women (average annual declines of 6% and 3%). Separate analyses using the same data source showed 28-day case fatality among patients admitted to hospital in Scotland for MI declined by 79% between 1981-83 and 1997-1999 (average annual decline of approximately

1.5%)[58]. The analyses showed further that the decline appeared greater in remote rural areas than in urban and more accessible areas (82-3% in remote areas versus 73-4% in accessible areas). Since fatality rates were initially higher in remote areas, this suggests an attenuation of the excess risk over time. A third more recent study of patients (male and female 18 years and over) hospitalised with MI in Scotland[21] found that 30-day case fatality fell by 12.6% over 10 years from 22.2% in 1990 to 19.4% in 2000, an average annual decline of 1.4%. In Southern Derbyshire, a larger average annual age-sex adjusted relative decline of 9% in the odds of 30-day case fatality occurred between 1995 and 1999 among patients hospitalised with MI[67]. The authors associate the large decline with the prior publication (1994) of the landmark 4S study on the effectiveness of statins in patients with CHD[68]. In Nottingham, over an earlier period from 1982 to 1992, the age-sex adjusted odds of inpatient mortality among patients hospitalised with confirmed MI did not appear to change over time[69].

2.2.2.3 Summary of major CHD incidence and case fatality trends

These results together suggest annual changes in incidence of major CHD in various parts of the UK from the 1960s to the present varying among men between no change and a decline of 3.5%, and varying among women between an increase of 0.2% and a decline of 4.6%. The variations in the estimates could reflect the differing time-periods and locations (although variations in the estimates even occurred over the same time-period and location). The differences could also reflect the previously mentioned difficulty in capturing accurately and consistently incidence of major CHD events. Imprecision in the estimates, particularly for women with lower event numbers, is another possible explanation. It is also possible that different ways of

defining major CHD events (e.g. all major events versus hospitalisations only) could account for differing trends.

The various data sources together suggest a modest decline in overall case fatality (whether defined as fatal hospitalisations only or also including out of hospital deaths) of roughly 1 to 2% per annum before around 1995. Data later than 1995 is limited but one study found declines of above 10% per annum in overall case fatality between 1996 and 2005 across the UK[24], and a second found a 9% decline in the odds of case fatality for hospitalised cases in Derbyshire between 1995 and 1999[67]. This suggests a much faster rate of decline in case fatality post 1995. However caution is needed in interpreting these findings as the results from the national study may be subject to over-fitting as CIs are narrower than might be expected given the number of events, while the Derbyshire study is specific to a small region and a short 5-year period. Also, since case fatality rates begin at lower levels in the more recent studies, the larger relative decline may yet be consistent with a comparable absolute decline to that in previous years.

The overall picture appears to be that declines in both incidence of major CHD and in case fatality have occurred in recent decades, and so both have contributed to the parallel decline in CHD mortality. The WHO MONICA study, which formally assessed the relative contributions of major CHD incidence and case fatality on the mortality trends, is discussed in section 2.6.1.1. However the varying incidence and survival estimates described above suggest the need for further investigations to draw firmer conclusions on the extent of the declines in incidence and case fatality. Also, there is a lack of data on trends beyond 2000, particularly in incidence of major CHD

(apparently just one study outside of Scotland[24]). Compared with CHD mortality rates, UK data on time trends in major CHD incidence and case fatality are limited, particularly for the most recent calendar years. This reflects that the quality and extent of data on CHD incidence and case fatality is poorer than that for CHD mortality as morbidity data is not necessarily recorded routinely and consistently, unlike CHD mortality via death certification[9].

2.3 Time trends in type 2 diabetes in the UK

2.3.1 Time trend in T2DM prevalence in the UK

2.3.1.1 Overall time trends among men and women

Routine data from the repeated cross-sectional surveys of the Health Survey for England (HSE), suggests self-reported diagnoses of diabetes to have approximately doubled between 1994 and 2006 in England, among both men and women[70]. Note that diabetes here is T1DM and T2DM combined, despite the reference to T2DM in the paper title. Over the 14 years, age-standardised prevalence of diabetes increased from 3.74% in 1994 to 7.25% in 2006 in men (an average annual increase of 4.8%), and from 2.28% to 4.88% among women (an average annual increase of 5.6%). A similar picture has been observed in Wales. In Cardiff and the Vale of Glamorgan diabetes prevalence rose between 1996 and 2004 by 46% from 2.4% to 3.5% (average annual increase of 4.3%)[71]. A third study, using diabetes register data covering 32 general practices in North Tyneside observed a larger average annual increase of 10% in diabetes prevalence from 1.14% in 1991 to 2.99% in 2001[72]. The faster rate of increase possibly reflects differences in patient characteristics and demographics in this region relative to the rest of the country, or lower starting prevalence given the earlier baseline.

While these studies do not distinguish between T1DM and T2DM, other studies suggest further that this rise in overall diabetes prevalence reflects primarily a rise in T2DM, which also form the majority of diabetic cases. For example, a recent paper (post conception of this thesis) estimated time trends in prevalence of overall diabetes, and T1DM and T2DM separately, between 1996 and 2005 among men and women aged 10-79 years across the UK, using the THIN primary care database[6]. The study found a 4.9% per annum increase in all diabetes (corresponding to a rise of 54% over 10 years from 2.8% to 4.3%), in line with the findings from HSE and Cardiff. A comparable 4.7% per annum increase in T2DM was observed (corresponding to a 58% increase over 10 years from 2.5% to 3.9%), while in contrast, a more modest 24% increase in T1DM prevalence occurred (from 0.33% to 0.41%). Similarly, a study using repeated cross-sectional data from 10 general practices across the Poole area of England, observed a rise in the age-adjusted prevalence of all diabetes from 1983 to 1996 of 61%, adjusting for age and sex[5]. Prevalence of T2DM increased by 72% from 0.7 to 1.23%, while T1DM increased by 38% from 0.25% to 0.33%, adjusting for age and sex. This study, which predates the others described, suggests further that T2DM prevalence has been rising since the 1980s.

Further studies have focussed specifically on estimating time trends in T2DM prevalence. Data from the Doctors Independent Network (DIN), a primary care database comprising 74 general practices from across England and Wales, showed prevalence of T2DM to have increased between 1994 and 2001 by 50% among men from 18 to 27 cases per 1000 person-years (average annual increase of 6%) and by 30% among women from 16 to 23 per 1000 person-years (average annual increase of 4%)[2]. Among men in the BRHS, we observed an average annual increase in the

prevalence of self-reported T2DM between 1978-2005 of 7%. Moreover, T2DM prevalence appeared to rise at an increasing rate over time, with average annual increases of 4.3% from 1978 to 1985; 5.5% from 1985 to 1992; 6.9% from 1992 to 1996; 5.6% from 1996 to 2000; 10.6% from 2000 to 2003; and 11.8% from 2003 to 2006[3]. In line with the findings in Poole, the results suggests rising T2DM as far back as the beginning of the 1980s. Finally analysis of data from the DARTS (Diabetes Audit and Research in Tayside Scotland) clinical information system, showed T2DM prevalence (defined as a diagnosis of diabetes at aged 35 or over or at a younger age if not on insulin) to have risen over the 12 years from 1993 to 2004 in this region by 6.7% per annum, from 1,492 per 100,000 in 1993 to 3,130 per 100,000 in 2004[4]. This corresponds to more than a doubling in prevalence over the period.

2.3.1.2 Age-specific time trends

Among those studies reporting time trends in T2DM by age-group, the general consensus appears to be that increases have occurred in all age groups. In the DIN primary care database, between 1994 and 2001 average annual increases in prevalence of T2DM among men in England and Wales by age group were as follows: 3.7%, 6.0%, 3.4%, 5.8%, 6.1% and 1.7% for ages 35-44 years, 45-54 years, 55-64 years, 65-74 years, 75-84 years and 85+ years respectively[2]. Among women, average annual increases were: 6.0%, 6.8%, 2.8%, 6.4%, 5.3% and 5.1% respectively. Analysis of BRHS data showed similar average annual increases to have occurred among all age-groups in this cohort of older British men: 5.4%, 5.6%. 7.1%, 6.8% and 7.5% among men aged 50-54 years, 55-59 years, 60-64 years, 65-69 years and 70-74 years respectively[3]. Data from the Health Survey for England also showed increases in prevalence of all diabetes among all age groups[70].

2.3.1.3 Time trends within different socio-demographic groups

According to the analysis of BRHS data, T2DM prevalence increased at a faster rate in Scotland compared with the rest of Britain (11.7% per annum between 1978 and 2005 in Scotland compared with 7.5% in Southern England, 6.2% in the Midlands and Wales, and 6.1% in Northern England)[3]. No other studies show time trends by UK country, but comparing the estimates from different regional studies suggests a similar pattern: in England and Wales (DIN data), the average annual increase between 1994 and 2001 was 4% and 6% among men and women respectively[2], while over a similar period from 1993 to 2004, the increase in Scotland (DARTS data) among men and women combined was closer to 7%[4].

The BRHS analysis also showed that as for CHD mortality, the least favourable time trend in T2DM prevalence occurred in the lowest socio-economic group, defined according to longest occupation held. Among men in unskilled occupations, the average annual age-adjusted increase in T2DM prevalence was 8.9% compared to 5.8% in professional occupations[3]. In the three intermediate groups the average annual increase was between 7 and 8%. Another study considered trends in prevalence of *all* diabetes between 1994 and 2006 in relation to socio-economic status using data from The Health Survey for England[70]. That study found an increase over the period in the T2DM prevalence ratio comparing the lowest to highest socio-economic status quintiles during the study period, when defined as longest-held occupation or education level, among women. This indicates a faster rise in prevalence among women of lower socio-economic status. For men, no difference in the prevalence levels or time trends in prevalence by occupation or education level was observed, but the T2DM prevalence ratio comparing highest to lowest household

income quintiles did increase, suggesting that the increase in prevalence has been more marked in poorer households in more recent years. The study also looked at levels of undiagnosed diabetes (defined as glycated haemoglobin≥6.5% in individuals not known to be diabetic) by social class in 2003-2006. It found that levels of undiagnosed diabetes were higher in lower socio-economic groups, suggesting that if anything, the observed inequalities in diabetes prevalence in the most recent years may underestimate the true extent of the differences.

The 2004 Health Survey for England shows that between 1999 and 2004 T2DM prevalence increased faster among Indian men (from 19.2% to 24.3%) and Black Caribbean men (17.6% to 26.5%) aged 55 and over, compared with the men of the same age in general population (6.9% to 9.7%)[73]. By contrast, among Pakistani and Bangladeshi men, the prevalence appeared to fall. Among women aged 55 and over, the largest increase occurred among Pakistani women from 28.3% to 44.4%. A large increase also occurred among Indian women aged 55 and over (15.3% to 20.5%). The trend among Black Caribbean women was comparatively modest, while a decline occurred among Bangladeshi women.

2.3.2 Time trend in T2DM incidence and relative mortality in the UK

As for the decline in CHD mortality, the rise in T2DM prevalence may be attributed to either a decline in the incidence of T2DM or an improvement in survival among patients with T2DM, or some combination of the two. Some distinctions to note between CHD mortality and T2DM prevalence, when evaluating the roles of incidence and survival: First, the favourable decline in CHD mortality reflects either a decline in incidence of major CHD or a fall in case fatality, both of which are

favourable trends too. In contrast, the unfavourable rise in prevalence could reflect either an unfavourable rise in incidence or a *favourable* fall in mortality among T2DM patients (or both). Thus, although rising T2DM prevalence is an important issue in terms of the increasing public health burden, one could argue that if the rise is seen to reflect mainly improved survival, as opposed to more people developing T2DM, then it is not necessarily an entirely bad news story. An interesting debate in *Diabetologia* in 2005 on whether "there is really an epidemic of T2DM"[19, 74, 75] highlights this: The "for" case considered that rising prevalence alone arguably constitutes an epidemic (irrespective of why prevalence is rising) given the growing major public health burden it entails – thus, yes, there is an epidemic[19]. However the "against" case argued that there is only an epidemic if, following the traditional definition for communicable diseases, an increase in the number of new cases has occurred, that is, incidence has risen, resulting from unfavourable trends in aetiological exposures [74, 75]. The reasoning was that rising prevalence could be the result of a change in the population structure or the result of a favourable improvement in survival[74, 75] – changes that do not necessarily indicate a "problem" to resolve and (in the case of improved survival) could be conceived as public health "success story". Thus to really understand the extent of the issue, it is important to find out why prevalence is rising, and particularly the role of incidence[75]. In essence, by establishing the relative roles of survival and incidence, the very nature of the rising T2DM prevalence as a positive or negative trend, is defined.

A second point to note is that prevalence of T2DM may theoretically rise even if both incidence and mortality remain constant[4], if the numbers of people developing T2DM is consistently greater than the number of T2DM patients dying. Third, when looking

at mortality among patients with T2DM, what is being considered is mortality from any cause. In contrast, for CHD, interest instead lies in case fatality following a CHD event.

2.3.2.1 Time trends in major T2DM incidence

Two studies have reported on time trends in incidence of T2DM as well as prevalence. Analysis of the UK-wide THIN primary care database (published subsequent to the drafting of this thesis) revealed a rise in T2DM incidence between 1996 and 2005 among men and women 10-79 years of age, comparable in size to the rise in prevalence[6]. A 66% increase in T2DM incidence was observed, corresponding to an average annual increase of 5.2% per annum. The paper found a similar rate of increase among women and men (69% versus 63%). The study in Tayside, Scotland, using data from DARTS, observed an average annual age-adjusted increase in T2DM incidence of 6.3% over 12 years from 1993 to 2004[4]. The study did not break down the trends by gender. An earlier report considered the change in incidence of diabetes (T1DM and T2DM combined) between 1994 and 1998[26]. This study involved analysis of 208 general practices contributing to the General Practice Research Database (GPRD), which is an electronic routine database of general practice records, akin to THIN but comprising different practices (although some practices contribute to both THIN and the GPRD). A 26% rise in incidence was observed between 1994 and 1998, corresponding to an average annual increase of 4.8% per annum. Again, similar increases occurred among women and men (28% versus 25%). A further more recent analysis of 197 practices in the GPRD , reported that incidence of type 2 diabetes among patients aged 30 years and over had risen between 1996 and 2006 from 2.23 to 4.37 per 1000 person years in women (average annual increase of 6.3%) and from

3.00 to 5.24 per 1000 person years in men (average annual increase of 5.2%)[25]. The study also highlighted that the age of first diagnosis appears to be falling, particularly among women, while the proportion of all new diagnoses occurring in those aged 30-44 is rising, from 7.9% and 7.5% of diagnoses in men and women respectively in 1996 to 7.9% and 15.8% in 2006.

2.3.2.2 Time trends in relative mortality among patients with T2DM

Two studies also report on time trends in mortality. The paper on patients in DARTS in Tayside, Scotland shows mortality among patients with T2DM to have fallen from 69.0 deaths per 1,000 people with T2DM in 1993 to 53.9 deaths per 1,000 people with T2DM in 2003, a significant decline of 3.7% per annum[4]. The paper on patients in the UK-wide GPRD reports comparable figures of age-adjusted declines in early mortality (that is, within 24 months of diagnosis of T2DM) of 2.7% per annum among men and 5.6% per annum among women between 1996 and 2006[25]. Among men the early mortality rate fell from 47.9 deaths per 1000 cases in 1996 to 25.2 deaths per 1000 in 2006, while among women, the rate fell from 37.4 to 27.6 per 1000. A second paper using data from the GPRD and by the same authors goes further to look at relative mortality[76], that is, the mortality rate among patients with T2DM relative to the general population. As the authors argue, to establish whether time trends in survival are contributing to the rising prevalence, it is not enough to look at overall mortality rates among diabetic patients. This is because a fall in mortality rates among diabetic patients would not lead to rising prevalence, unless the fall is larger than that for the general population. Age and sex-standardised mortality rates for men and women in the UK in 10 year age groups, taken from Interim Life tables for the UK, were used to compute expected survival rates for the general population. The

expected rates were then compared with observed rates in a sample of GPRD patients with T2DM and relative mortality rates computed as the observed rate among T2DM patients divided by the expected rate for the general population. Adjusting for duration of diabetes, age and gender, relative mortality fell by 13% from 1996 to 2001 and by 26% per annum between 2001 and 2006. For example, among men diagnosed with T2DM for less than one year, relative mortality fell from 1.41 in 1996-1997 to 1.23 in 2006. Among women diagnosed with T2DM for less than one year, relative mortality fell from 1.40 in 1996-1997 to 1.09 in 2006. Among patients diagnosed with T2DM more than a year prior, relative mortality rates also declined, but less sharply as relative mortality was already closer to 1.

2.3.2.3 Summary of T2DM incidence and relative mortality trends

Data on incidence and survival is sparser than that for T2DM prevalence, again reflecting a lack of suitable data sources, consistently monitoring incidence or survival over a period. The available data suggests that, between the 1990s and 2000s at least, the rising T2DM prevalence may be a combination of the positive influence of improved survival alongside the negative influence of rising incidence (around 5% per annum). The DARTS study formally assesses the relative contributions of incidence and mortality over the period – this is discussed in section 2.6.2. However, data on time trends in incidence and survival before and after this period is limited, and thus the influences outside of this period are less clear.

2.4 Continuing healthcare burden of coronary heart disease and type 2 diabetes

2.4.1 Continuing healthcare burden of coronary heart disease

The favourable time trends in CHD mortality and morbidity represent a good news story. In 1999 the Department of Health publication "Our Healthier Nation" set a target to reduce the death rate from CHD in England by at least two-fifths by 2010[77]. The extent of the decline in CHD mortality has resulted in this target being met in 2007. Similarly, the target set by the Welsh Assembly Government to reduce CHD mortality in 65-74 year olds from 600 per 100,000 in 2002 to 400 per 100,000 in 2012[78] was met in 2006. The target set by the Scottish Executive was to reduce mortality rates from CHD among people under 75 years by 60% between 1995 and 2010[79]. Mortality estimates for 2010 are not yet available but the time trend so far suggests this target is on course to have been met by 2010 too.

However despite the favourable decline, and despite meeting the targets, CHD remains a considerable public health concern and there is still much room for improvement. At least up until 2008 (latest date of data availability), CHD has remained the leading single cause of all deaths and of premature deaths, cited as a cause of 18% of all deaths in 2008 among men and 13% among women, and cited as a cause of 18% of premature deaths in men and 9% in women[9]. This corresponds to over 88,000 deaths in the UK in 2008 due to CHD, of which over 28,000 were premature. CHD also represents a considerable economic cost. According to the 2010 BHF Statistics CHD statistics publication, in the year 2006, the total cost to the UK of CHD was estimated to be almost £9 billion[9]. This is above average per capita compared to other countries within the European Union[80]. Moreover, the cost of

CHD has risen over time, despite the declining major CHD incidence rates. Earlier studies give estimates of the total economic burden of CHD as £7.06 billion in 1999[81] and of £8.5 billion in 2004[82]. Approximately £3.2 billion (36% of the total CHD costs) was for health care. The largest proportion of this expenditure was for inpatient care (73% of the total cost), which implies it is the major forms of CHD which necessitate hospital stay which constitute the greatest health care costs.

That CHD remains the leading cause of death emphasizes the potential value of analysing the trend in CHD, as a means to inform efforts to reduce CHD mortality further. The observation that the greater part of CHD healthcare costs are for major CHD events emphasizes the value of investigating the incidence of major CHD events in particular, which is the focus of this thesis.

2.4.2 Continuing healthcare burden of type 2 diabetes

According to figures from the Quality and Outcomes Framework (QOF), the known diagnosed population of people with diabetes (T1DM and T2DM combined) in the UK stood at 2.8 million in 2010[83], corresponding to a prevalence of 4.3%. The majority of these cases are T2DM. Due to the nature of this initially silent condition, there are likely to be additional patients with diabetes, yet undiagnosed. Thus the true prevalence is likely to be even higher. Indeed, data from the HSE[84], suggests that in 2003, prevalence of undiagnosed diabetes (defined as glycated haemoglobin≥6.5% in individuals not known to be diabetic) was as high as 3.0% in men, and 0.7% in women.

Diabetes in general and T2DM in particular represent a considerable and growing public health burden in the UK, both in terms of costs directly related to the condition, and in terms of complications such as cardiovascular (CVD) events, vision loss, renal complications, and peripheral damage to legs and feet[7]. A recent study showed average total primary care costs (including consultation and prescribing costs) for T2DM patients to have risen from £602 per person per year in 1997 to £1080 per person per year in 2007[8], corresponding to a 79% increase, a two-thirds higher per person cost and a larger relative increase than that for the general population. A companion study estimated further that 9.3% of hospital admissions were for patients with diabetes (mainly T2DM), amounting to a total cost of £3 650 869 per 100,000 population, or 12.6% of the total hospital expenditure[85]. This represents an increase in the relative burden of diabetes, as the authors previously estimated diabetes admissions to correspond to 7% of all admissions and to 8.7% of all hospital expenditure 10 years prior in 1994[86]. Moreover, the burden is projected to grow. Projected total annual healthcare costs for patients with T2DM (all NHS financial costs including inpatient costs, outpatient costs, community care, primary care, and drug costs) were £1.8 billion in 2010 rising to almost £2.1 billion in 2060[7]. Since the future projection assumes incidence rates to remain constant, it may well be an underestimate of the true future burden, if incidence continues to rise at the rates observed in the few studies of incidence trends. This emphasizes the need to examine incidence trends.

2.5 Considerations when evaluating time trends in incidence of major coronary heart disease and type 2 diabetes

2.5.1 Considerations when establishing the extent of the incidence time trends (towards objectives i and ii)

In the previous sections 2.2 and 2.3, the existing literature on time trends in CHD and T2DM was examined. The existing studies suggest that changes in incidence of major CHD and T2DM have occurred alongside the time trends in CHD mortality and T2DM prevalence and may therefore have contributed to the CHD mortality decline and T2DM prevalence rise. However it was noted above that data on incidence is poorer relative to data on CHD mortality or T2DM prevalence trends, with a limited range of suitable data sources which have captured incident events over a number of years. Thus the extent of the time trends in incidence is less certain than for CHD mortality and T2DM prevalence.

As well as the limited number of suitable data sources, establishing the extent of the time trends in incidence is also hindered by incident events not necessarily being recorded consistently over time, particularly if the guidelines for and methods of identifying and defining cases of T2DM or CHD have changed during the period of interest. Changes in the identification and recording of cases may alter the numbers of patients identified (with new patients being identified as having major CHD or T2DM who may not have been previously identified as such, or vice versa). In turn, these changes may induce an apparent trend in incidence over time. Estimates of time trends may therefore be confounded by the changing identification methods and may be to an extent an artefact of changes in how the diseases are defined, rather than a true epidemiological shift in the population.

The possible influences under this heading include changes in case ascertainment (that is, the proportion of all events occurring that are known and do not go undiagnosed), changes in diagnostic criteria and, for fatal CHD events, which may be ascertained from death certificates, changes in the coding of cause of death. In terms of major CHD incidence, given the nature of major CHD events, normally with evident serious manifestations, case ascertainment is unlikely to be a major issue, unlike for T2DM which can go undiagnosed. A major change in the diagnosis of MI occurred in 2000, with the introduction of the measurement of cardiac troponins as the new reference standard for diagnosing myocardial injury[87], compared with the prior World Health Organisation (WHO) definition of acute MI of unequivocal electrocardiogram (ECG) changes and/or unequivocal enzyme changes[88, 89]. The potential impact of the introduction of the use of troponins is an increased sensitivity, with more events classed as major CHD events which might not have been previously classed as such[90-92]. In terms of fatal events, cause of death as recorded on death certificates is coded in the UK using the International Classification of Diseases (ICD) coding system. During the period from the 1960s to the present, the ICD system has been revised a number of times, which may have implications for both the estimates of the time trends in major CHD incidence and in CHD mortality. The principal changes occurred in 1968 (ICD-7 to ICD-8) and in 2001 (ICD-9 to ICD-10). In addition, the rules for coding changed over the period 1984-92 whereby direct causes of death could be coded less often, while more secondary causes could be coded more often.

In terms of T2DM incidence, diagnostic criteria for diabetes changed in the late 1990s, with the publishing of new criteria from the American Diabetes Association in

1997[93] and then from WHO in 1999[94]. The key differences between these new criteria, and the existing WHO criteria used before this time[95], were the greater emphasis on the use of fasting glucose (as opposed to previous criteria based mainly on the post-load glucose measurements) along with a reduced diagnostic fasting glucose threshold to indicate diabetes of 7.0 mmol /l rather than 7.8 mmol/l previously. The change in the type of measurements taken, from use of post-load glucose measurements to fasting glucose has been shown to lead to different patients being identified as having T2DM[96].

It is also possible that the ascertainment of T2DM has increased over time. A patient may have T2DM without knowing and without a diagnosis. In the light of increasing awareness of the condition among both patients and practitioners, more patients are being tested for T2DM and so the proportion of patients with undiagnosed T2DM may have declined over time. This would lead to an apparent rise in incidence when in fact the number of diabetes cases may not have changed; it is simply that more cases are being uncovered. Public health policy changes could have lead to an increase in testing. Specifically, recommendations on cardiovascular prevention from the late 1990s[97] and the introduction of Quality and Outcomes Framework (QOF; www.pcc.nhs.uk) for managing patients in General Practice in 2004 may have increased T2DM ascertainment.

Another factor which may lead to observed changes in incidence over time is a change in the population structure. That is, if the distributions of age, gender or other socio-demographic characteristics in the population change over time, since CHD and T2DM risks are known to vary by these characteristics. However, interest in this

thesis lies primarily in explaining time trends occurring within the different demographic groups, or adjusting for demographic characteristics, rather than assessing whether changes in demographic characteristics of a population may explain the trends seen. In this way focus is on those modifiable factors which have changed over time in a fixed population, with thus arguably more immediate public health implications in terms of potential to influence future time trends through management of these factors. Trends due to changing population demographics, by contrast, while important for assessing the health burden, are less informative for identifying ways to reduce numbers of events.

In Chapter 4 of the thesis, the first results chapter, the magnitude of recent trends in incidence of major CHD and T2DM is estimated (objectives i and ii). Absolute and relative changes in incidence over time are estimated using the various data sources at hand, and the findings are considered alongside the existing data described in the previous sections. The trends are both adjusted for and stratified by demographic characteristics, to account for shifts in the population structure. In addition, the likely impact of the changes in diagnostic criteria, case ascertainment, and the public health policy measures are considered when interpreting the results of the analyses, in order to evaluate the extent to which the trends are true or an artefact of the diagnostic/ascertainment changes.

2.5.2 Candidate factors to explain a decline in major CHD incidence (towards objective iii)

Having established the extent of the true epidemiological trends in incidence in major CHD in chapter 4, accounting for population shifts and diagnostic changes, the next steps in the thesis are to examine the reasons for the trend (objective iii). Towards this objective, in this section, a likely group of possible "candidate" factors are identified, which may help to explain the trend seen, and so should be considered in the analyses. This "brainstorm" of possible factors is based on the literature of the aetiology of CHD, and trials of preventive treatments.

There are two groups of factors. The first group comprises major aetiological factors (lifestyle or clinical) with established likely causal associations with CHD. The lifestyle factors may operate at least in part through alteration of major modifiable clinical factors. Importantly however, an established association with the disease is not enough in itself to influence the time trend. The distribution of the factor needs to also have changed over time in the population in a direction in accord with the time trend in the disease. Specifically, to potentially explain the decline in CHD, a favourable change in the factor is needed. The results chapters addressing objective iii will look therefore first at how these major factors have changed over time, and then, once the extent of any trends in these factors have been established, their potential contribution to the trend in major CHD incidence may be evaluated.

The second group comprises preventive treatments (medications, surgical interventions) which may directly influence risk of the disease, or indirectly through

altering the major aetiological exposures. Provided uptake of these treatments has increased over time, they may also help to explain a decline in major CHD incidence.

2.5.2.1 Major established modifiable aetiological exposures

The three major modifiable aetiological factors for CHD are **cigarette smoking**[98, 99], high **blood pressure**[100, 101] and **dyslipidemia**[102, 103]. Each factor is widely distributed in the population, is associated with a high relative risk for CHD, and is modifiable and reversible (a reduction in the factor is associated with a fall in CHD risk). They are therefore key candidates for explaining a decline in major CHD incidence, dependent on the time trends in these factors.

The risk of incident CHD is two to three fold higher among smokers compared to non-smokers[98]. It is estimated that 24 to 30% of all CHD is attributable to smoking[98]. In younger age groups, among whom CHD events are rare, this figure is even higher (closer to 75%). CHD mortality[100] and CHD incidence[101] have been shown to increase more or less in a continuous monotonic log-linear fashion with increasing systolic blood pressure (SBP) and diastolic blood pressure (DBP) within all age groups, from a usual SBP of 115mmHg and a usual DBP of 75mmHg upwards. Dyslipidemia[102, 103] principally refers to raised **total and low density lipoprotein (LDL) cholesterol** levels, but increasingly low **high density lipoprotein (HDL) cholesterol** has also been implicated in increasing CHD risk. As for blood pressure, continuous monotonic log-linear relationships have been found between CHD mortality[103] and CHD incidence[102] and total cholesterol, HDL cholesterol, non-HDL cholesterol (the difference between total and HDL cholesterol, thus mainly reflecting LDL cholesterol) and the total-to-HDL ratio. Moreover, HDL and non-HDL

cholesterol have been shown to operate on CHD risk largely independently of one another[102].

A further major modifiable lifestyle risk factor which may be implicated is **high adiposity[104-106].** Different adiposity measures (body mass index (BMI), waist circumference, waist-to-hip ratio) have been shown to be similarly associated with CHD risk, with hazard ratios of approximately 1.3 for a 1 standard deviation increase in each measure (corresponding to 4·56 kg/m^2 higher BMI, 12·6 cm higher waist circumference, and 0·083 higher waist-to-hip ratio), adjusting for age, sex and smoking status[106]. Meanwhile, **physical activity** has been shown to be protective against CHD risk[107-111], operating partly independently of adiposity[107, 110, 111]. Moderate physical activity levels (in terms of amount or intensity) are associated with a 20 to 25% reduced risk of CHD compared to low physical activity levels, while high physical activity levels are associated with a 30 to 35% reduced risk[111] . Meanwhile, sedentary individuals are estimated to have almost twice the risk of CHD compared with those with high activity[112]. **Diabetes** has also been shown to be a major clinical risk factor for CHD[27-33]. The relationship between diabetes, particularly T2DM, and CHD risk, which is a key aspect of this thesis, is considered in detail in a separate section 2.5.4.

Various **aspects of diet** have been associated with risk of CHD[113], although the evidence is not as robust as for the other established risk factors, reflecting the complexity of diet and difficulty in accurately and precisely ascertaining levels of consumption of different dietary factors for the purposes of study. The dietary patterns principally associated with reducing CHD risk include high fruit and

vegetable consumption[114], replacement of saturated fats with unsaturated fats[115-118] and limiting salt intake[119]. In addition, both abstaining from **alcohol[120]** and excessive drinking (particularly binge drinking patterns[121]) are associated with increased CHD risk, compared to regular alcohol consumption.

The roles of the above factors have generally been long established. A number of other different factors have been connected to CHD risk. These include psychosocial factors[122-126] (notably depression[123-127]); genetic factors[128-133]; factors in gestation[134, 135], from birth (for example low birth weight)[136] and in childhood and earlier life (life-course influences)[137-139]; and a range of emerging novel risk factors[140] (including C-reactive protein, homocysteine level, leukocyte count, periodontal disease). While many of these factors may well play a role in explaining time trends in CHD, focus in this thesis is on the roles of the major established modifiable clinical and lifestyle factors described. This is for several reasons. First, to attribute the time trend in CHD to a particular factor, a causal relationship is assumed and at present evidence for a causal relationship between these emerging factors and CHD is generally weaker than for the established factors. Second, some of the novel factors may be considered markers of CHD rather than independent aetiological exposures, potentially useful for identifying patients at high risk of CHD, but less useful here where the purpose is to explain time trends. Third, the driver behind the search for novel factors has been the evidence from studies of population attributable risks of CHD, which suggest that the established factors do not fully account for all CHD cases occurring[141], but this view has been questioned more recently[142]. The INTERHEART study for example, estimated population attributable risk fractions (PARFs) of the major factors for non-fatal MI, using data from 52 countries[143]. The study found PARFs of 90% in men and

94% in women, (both old and young and in all regions of the world) for the combined effects of smoking, dyslipidemia, hypertension, diabetes, obesity, diet (fruit and vegetable consumption), alcohol use, physical activity and psychosocial factors. That is, virtually all of the variations in risk of MI between individuals could be attributed to differences in the established major factors. A previous analysis of data from the BRHS found the three factors dyslipidemia, hypertension and smoking together corresponded to a PARF of 86% for major CHD[144]. Given that the major factors may explain much of the variations in CHD risk between individuals, one may also expect the major factors to explain much of the variations in CHD risk over time.

Assuming the age-distribution remains constant over time, secular temporal trends in major CHD risk may be seen to be the result of variations in CHD risk according to year of analysis arising from period effects (changing aetiological exposures with calendar year close to the time of the event), but could also reflect variations in CHD risk by year of birth arising from cohort effects (changing exposures according to birth year). If variations in CHD risk by birth cohort are seen, this would suggest a role of cohort effects, which include birth and early-life factors. Birth cohort effects and life-course influences are beyond the scope of this thesis, the focus being on the roles of recent trends in aetiological exposures. However, studies which have investigated age, period and birth cohort effects on CHD incidence/mortality have tended to show appreciable period effects, with possible cohort effects, but with period effects dominating (particularly in the most recent decades – the period of interest for the thesis)[52, 145-147]. Therefore life-course influences may anyway have less potential to explain the major CHD incidence trends seen, than the major aetiological exposures.

The "metabolic syndrome" indicates the presence of a cluster of the major clinical risk factors in combination (diabetes or impaired glucose tolerance, hypertension, dyslipidemia, and (abdominal) obesity)[148]. It has been suggested that the metabolic syndrome may predict CHD risk more strongly than the individual risk factors. However, studies have tended to show that presence of the metabolic syndrome predicts risk of CHD no more strongly than the individual risk factors in combination[149]. Thus, for the purposes of this thesis, it is arguably sufficient to consider the role of the individual risk factors, alone and in combination, on the time trend in major CHD.

2.5.2.2 Preventive treatments

The key treatments shown to be effective in reducing risk of major CHD events and currently used in primary prevention of major CHD (as recommended by NICE[150, 151] and Joint British Societies' guidelines[113]), that is among those with angina or at high risk of developing CHD, (as opposed to solely as treatment post-MI) are evidence-based medications, specifically **lipid-lowering medications** (predominantly statins)[68, 152-155] to lower total and LDL cholesterol levels, and **anti-hypertensive medications**, to lower blood pressure[156-160].

The potential effectiveness of lipid-lowering medications in preventing major CHD events was recognised following publication of the first randomised controlled trials of statins in the early 1990s[68]. Meta-analyses of randomised controlled trials show consistently around 30% reduction in risk of major CHD events among patients without history of major CHD[152-155].

There are several different types of anti-hypertensive medications including chiefly; beta-blockers, calcium channel blockers, ACE-inhibitors, angiotensin receptor blockers and thiazide-type diuretics. Meta-analyses of randomised controlled trials show all these drugs to be similarly safe and effective in preventing major CHD events in relation to their blood pressure lowering effects[158-160], regardless of existing CVD and blood pressure levels before treatment (around 11-17% reductions in risk of a CHD event[160]). Combinations of the drugs may confer added benefit[161].

Aspirin and other anti-thrombotics, used in secondary prevention, have also been recommended in the past for primary prevention[113]. However, recent meta-analyses, considering specifically the use of aspirin for primary prevention, did not show conclusive evidence of benefits in terms of CVD risk reduction, while at the same time reporting significant risk of bleeding as a side-effect[162, 163]. A low absolute risk reduction is outweighed by the side effects. Therefore the relative benefit of aspirin for primary prevention is uncertain.

Some studies have suggested considerable potential for preventing CVD events when these different types of medication are used in combination, notably Wald and Law, in their paper proposing the "Polypill"[164]. The proposed pill combines six different treatment components: a statin (to lower cholesterol), three anti-hypertensive drugs (to lower blood pressure), aspirin (for platelet function) and folic acid (for serum homocysteine). The estimated effect of this medication combination was as much as an 88% reduction in CHD events. The authors conclude by suggesting prescribing of the pill to all over a certain age as a primary prevention measure. Similarly, Yusuf postulated a cumulative effect of a 75% risk reduction, for the combination of aspirin,

two anti-hypertensive drugs (beta blockers and ACE inhibitors), and a lipid lowering drug, assuming independent effects[165]. These estimated effects have been met with some scepticism; particularly regarding the independence of the different drugs (although other studies suggest the independence assumption may indeed be valid[166]). There is also concern regarding the blanket prescribing to anyone of a certain age, leading to so-termed "medicalising of the population"[167]. However, the estimated combined effects suggest, depending on uptake levels, the various medications have the potential to help explain a good proportion of the decline in CHD.

In addition to drugs, surgical interventions (revascularisations), namely coronary artery bypass grafts (CABGs) or percutaneous coronary interventions (PCIs), may be indicated for major CHD prevention for certain groups (those with the most severe forms of angina)[168]. However, while seen to alleviate symptoms, the evidence regarding the effectiveness in terms of reducing risk of future major CHD events (and therefore a contributor to the decline in major CHD incidence) is less conclusive (although CABG may lead to a better prognosis than PCI)[168].

In the past, some studies (predominantly observational) have suggested that use of hormone replacement therapy among post-menopausal women is associated with a reduced risk of CHD[169]. However there is a growing body of clinical trial evidence conversely supporting no benefit or even an increased risk of CHD with use of hormone replacement therapy[170-173], which now outweighs the earlier suggestions of favourable effects.

2.5.3 Candidate factors to explain a rise in T2DM incidence (towards objective iv)

As for major CHD, having established the extent of the true epidemiological trends in incidence in T2DM in chapter 4, accounting for population shifts and diagnostic changes, the next steps in the thesis are to examine the reasons for the trend (objective iv). This section comprises a literature-based "brainstorm" of possible "candidate" factors which may help to explain the trend seen, and so should be considered in the analyses.

As for major CHD, major modifiable aetiological factors with established likely causal associations with T2DM are identified. However, for the factor to explain the rise in T2DM, an unfavourable change in the factor needs to have occurred over time in the population. The results chapters addressing objectives 4 will look therefore first at how these major factors have changed over time, and then, once the extent of any trends in these factors have been established, their potential contribution to the trend in T2DM incidence may be evaluated.

Preventive treatments were identified as possible explanations for the decline in major CHD incidence. However, since rising use of treatments which reduce risk of the disease are generally thought of as a favourable change over time, treatment use is unlikely to explain the unfavourable time trend in T2DM, and so is not considered here. That said, recent studies suggest statins used in CHD prevention may be associated with increased risk of T2DM[174]; other drugs indicated for other conditions may also have adverse metabolic effects or be associated with increased T2DM risk. This is considered further in the results chapter 8 addressing objective iv.

2.5.3.1 Major established modifiable aetiological exposures

T2DM has some risk factors in common with CHD, although the relative importances of the risk factors differ. The most important modifiable factor implicated in increasing risk of T2DM is **high adiposity[43]**. The association between adiposity and T2DM is well-established[43], following findings from major prospective observational studies such as the Nurses Health Study[175], the Health Professionals Study[176], and the studies of Pima Indians[177], showing striking "dose-response" relationships between BMI and subsequent risk of T2DM. For example, among women in the Nurses Health Study[175], the age-adjusted 14-year relative risks of T2DM, compared to women with a BMI <22kg/m^2 at baseline, were 2.9, 4.3, 5.0, 8.1, 15.8, 27.6, 40.3, 54.0, and 93.2 for BMIs of 22.0-22.9, 23.0-23.9, 24.0-24.9, 25.0-26.9, 27.0-28.9, 29.0-30.9, 31.0-32.9, 33.0-34.9 and ≥35.0kg/m^2 respectively. Moreover, the study also showed that, compared to women whose weight remained stable between age 18 and the study baseline (aged 35 to 55 years), women who lost weight were at significantly reduced risk of T2DM, while women who gained weight were at increased risk, implying that reducing adiposity levels can reduce risk of T2DM. Studies suggest a PARF of T2DM from overweight and obesity combined of generally around 36 to 50%[178-181], but ranging from 3%[181] to 77%[182]. The wide variation may be explained in part by differences in the prevalence of overweight and obesity between different populations. Consideration of biological mechanisms for the relationship between adiposity and T2DM suggests visceral adipose tissue to be the component of adiposity particularly implicated in the development of insulin resistance and T2DM[183, 184]. However, recent studies have shown BMI generally to be as strong a predictor as the abdominal adiposity measures[180, 185, 186], reflecting the high correlation between BMI and abdominal adiposity.

Other factors with established associations with T2DM are **physical activity**[187, 188] and **aspects of diet**[189-198], which may operate partly through changing adiposity levels, but also partly independently. A recent meta-analysis found that regular participation in moderate physical activity was associated with a significant 30% lower risk of T2DM relative to being sedentary: relative risk of 0.69 (95% CI 0.58 to 0.83)[188]. After adjustment for BMI, the relative risk was attenuated to 0.83 (95% CI 0.76 to 0.90), but remained significant, suggesting that the effects of physical activity is in part through BMI, but in part independent of BMI. Moreover, even light intensity activity could be beneficial[187]. Investigating the role of diet is complex, and as such, is not fully understood. Several studies, including the Nurses' Health Study[193] and Health Professionals study[197], highlighted a significant association between a poor "Western-style" diet (high in red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets and desserts) and risk of T2DM, even after adjustment for BMI. Individual dietary elements which may reduce T2DM risk include replacing saturated fats with unsaturated fats[191, 194, 196, 198], a diet with a low glycaemic index[192, 195], milk and dairy consumption[190] , and limiting intake of red meat and processed meat[189] .

Cigarette smoking[199], **alcohol consumption** [200]and **blood pressure**[201, 202] may also possibly play a role in T2DM risk, although the evidence for these factors is weaker. A recent meta-analysis estimated the relative risk comparing smokers to non-smokers to be 1.44 (95% CI 1.31 to 1.58), with evidence of a dose-response relationship[199]. Moderate alcohol consumption may be associated with up to a 40% lower risk, relative to lifetime-abstainers, as well as a lower risk relative to heavy drinkers[200]. The MONICA Augsberg study reported the risk of T2DM among people with

hypertension to be roughly double that for people with normal blood pressure, regardless of BMI, indicating a possible effect independent of BMI[202].

The above factors together have been shown to explain most of the cases of T2DM in various populations: Among women in the US (Nurses' Health Study), the PARF of T2DM was 87% for the combination of overweight/obesity, low physical activity, and poor diet (high in trans fats and glycaemic load, low in cereal fibre, low ratio of polyunsaturated to saturated fat)[203]. Being a smoker or teetotal increased the PARF only very modestly to 88% and 91% respectively. In Finland, overweight/obesity, lack of exercise, excess alcohol consumption, smoking, and low vitamin D amounted to a PARF of 82%[182]. In Hawaii, overweight/obesity, lack of exercise, poor diet (high red meat, low fibre), being teetotal and smoking corresponded to a PARF of 78% in men and 83% in women; socio-demographic characteristics (age, ethnicity, education) and hypertension increased the PARFs to 92% and 95% in men and women respectively[179]. Moreover, favourable changes in the major risk factors (BMI, physical activity and diet) can lead to substantial reductions in risk of T2DM[204].

Specific to women, development of transient diabetes during pregnancy (gestational diabetes) is associated an increased risk of subsequently developing T2DM[205] (studies suggest between a 17% and 63% increased risk in the 5 to 16 years following the affected pregnancy[206]).

As for CHD, increasing research is being carried out to explore the relationship between psychosocial factors[207] (notably depression[207, 208]), genetic factors[177, 209-211], and T2DM risk. However, research into these factors is relatively recent so as yet

evidence is weaker, and, as outlined above, the established risk factors may already explain much of the T2DM burden. Life-course influences (particularly low birth weight[212, 213], and adiposity levels throughout the life-course[214-216]) have been shown to be associated with risk of T2DM, independent of current adiposity levels. However, as for CHD, birth cohort effects and therefore life-course influences are beyond the scope of this thesis, the focus being on recent trends in aetiological exposures, reflecting that recent time trends may more likely reflect period rather than cohort effects[217]. Other factors (dyslipidemia and polycystic ovary syndrome) have been previously postulated to influence T2DM risk, but current evidence does not support this[218].

2.5.4 T2DM and risk of major CHD (towards objective v)

Diabetes (T1DM and T2DM) is associated with a substantially elevated risk of a major CHD event, with the risk among patients with diabetes generally shown to be at least two-fold greater than that of patients without diabetes[27-33]. The excess risk among women with diabetes, compared to women without diabetes, is greater than that for men, such that relative CHD advantage of being female in the general population is all but lost in the diabetic population[219]. A recent meta-analysis of 37 studies[27] showed the fatal CHD rate to be 5.4% for diabetics, compared with 1.6% among people without diabetes, with corresponding pooled relative risks comparing diabetics to non-diabetics of 3.50 (95% CI 2.70 to 4.53) for women and 2.06 (95% CI 1.81 to 2.34) for men. The authors attribute the gender difference in the relative risks in part to women with diabetes having a more adverse risk profile in terms of major CHD risk factors, relative to women without diabetes, than men. Possible treatment gender bias is also put forward as a potential explanation. More recently, The

Emerging Risk Factors Collaboration meta-analysis estimated a hazard ratio of 2.32 (95% CI 2.11 to 2.56) for all vascular deaths, comparing diabetes versus no diabetes[29]. In the BRHS, age-adjusted hazard ratios of a major CHD event, compared to no diabetes or prior MI were 1.70 (95% CI 1.20 to 2.42) and 2.93 (95% CI 1.81 to 4.74) for late onset diabetes (aged over 60 years at onset) and early onset diabetes (aged under 60 years at onset) respectively[33]. A subsequent large UK-population based study (using data from the General Practice Research Database)[28], similarly observed the hazard ratios of incident MI comparing those with and without T2DM to be 2.13 (95% CI 2.01 to 2.26) and 2.95 (95% CI 2.75 to 3.17) among men and women respectively, adjusting for age, smoking, BMI, hypertension and abnormal lipids. As well as the gender difference, the hazard ratios varied with age, with the largest hazard ratios seen in the younger age groups. For example, the hazard ratios in the 35-54 years age group were 2.69 (95% CI 2.07 to 3.49) and 4.86 (95% CI 2.78 to 8.51) in men and women respectively. There was also some suggestion that, adjusting for age, the longer the duration of T2DM, the greater the risk of MI. This has been observed in other studies too[30], including in the BRHS[33]. In line with inequalities in the general population, among diabetic patients, the more deprived patients have a higher prevalence of CVD and a more adverse risk profile (in terms of smoking status and obesity), relative to their less deprived counterparts[220, 221].

In terms of explaining the excess risk of CHD among diabetics, one reason is that diabetic patients tend to have more adverse levels of the major established CHD risk factors (particularly blood pressure, lipid levels, and BMI) than their diabetes-free counterparts, as reported in the meta-analysis[27] (described above), and also observed other studies, including the UK population-based study[28] and Framingham cohort[222].

The relative risk of CHD comparing those with and without T2DM is attenuated after adjustment for these risk factors, indicating that the excess risk among diabetics operates in part through these factors[27]. However, as the relative risk is not fully attenuated, the diabetic condition itself is also thought to be an independent risk factor for CHD, primarily through glucose intolerance. Indeed studies have shown a dose-response relationship between glucose level (whether measured as fasting glucose, non-fasting glucose or the HbA1c level) and CHD risk[223-225], supporting a possible casual relationship between glucose intolerance and CHD. This dose-response relationship is seen not only among those with diabetes, but below the diabetes threshold among those with impaired glucose tolerance[226]. The mechanism by which glucose intolerance raises CHD risk is not fully resolved but possibilities include a direct toxic effect of high glucose levels, (for example, in promoting cellular damage or causing atherosclerosis through accumulation of "advanced glycation endpoints" on blood vessel walls or increasing oxidative stress)[226].

Current NICE public health guidance[227] promotes use of lipid-regulating drugs, anti-hypertensive drugs, and therapies to lower glucose levels in the management of T2DM, to help lower CHD risk. Meta-analyses of trials of lipid-lowering drugs among diabetic patients reveal significant reductions in CHD events, and that diabetic patients benefit at least as much as non-diabetic patients[228, 229]. Patients with diabetes also benefit from use of anti-hypertensive medications[230, 231], although the evidence for the effectiveness of glucose therapies on reducing CHD risk is more mixed[232-237], with certain drugs recently withdrawn from practice due to possibly increased CHD risk[238]. Improved management of T2DM may attenuate the excess risk of CHD

among patients with T2DM. The thesis will explore whether the relative risk of CHD among patients with T2DM has changed over time.

2.6 Current literature examining reasons for the time trends in major coronary heart disease and type 2 diabetes in the UK

2.6.1 Reasons for time trends in major CHD

The previous sections have summarised the available literature on time trends in CHD morbidity and mortality and discussed factors which might have influenced the time trends such as clinical and lifestyle risk factors and use of preventive treatments. Very few studies in the UK however have attempted to understand and directly analyse the relationship between the CHD morbidity or mortality decline and concurrent trends in the various factors, to ascertain which factors may be responsible for the favourable decline in CHD. That is, studies which address similar questions to those in the thesis, and studies therefore to which the thesis results may be compared. This partially reflects a lack of suitable data on CHD morbidity and risk factor levels[239]. Indeed, apparently there are only two studies of this kind involving UK populations: The WHO MONICA project (based on a series of ad-hoc population surveys) and the IMPACT policy model (based on modelling of population data from different data sources) (Table 2.1, studies identified by a *). These projects, detailed below, have made important contributions to our understanding of the reasons for the trends in CHD morbidity and mortality in recent decades in various countries and dominate the research worldwide in this area.

2.6.1.1 WHO MONICA Project

The motivation for the WHO MONICA (MONItoring trends and determinants in CArdiovascular disease) Project[240, 241] came from the 1978 Bethesda Conference on the Decline of CHD mortality which highlighted the need for monitoring of trends in CVD in different countries. The aim was to monitor over the next decade time trends in CVD mortality, as well as CVD risk factors and treatment use, in different populations across the world, enabling both analyses of trends within each population and analyses of trends combining the data from the different populations (facilitated by use of common data collection methods). The principal objective was to "measure the trends in CVD mortality and CHD and cerebrovascular disease morbidity and to assess the extent to which these trends are related to changes in known risk factors, daily living habits, health care, or major socioeconomic features measured at the same time in defined communities in different countries" [direct quote from protocol][241].

By 1985 the project involved a total of 41 different populations in 27 countries across 4 continents, including two UK populations (the cities of Belfast and Glasgow). The populations comprised men and women in the chosen city/ region aged 35 to 64 years. Each population was followed for at least 10 years from the mid 1980s to the mid 1990s. The Belfast population was followed from 1983 to 1993, while the Glasgow population was followed from 1985 to 1994. Routine census data and official statistics were used to ascertain population denominators and incidence of CVD events/CVD mortality. In addition, random samples of the populations were surveyed a number of times over the course of the decade to determine the distribution of risk factors. Of the many papers since published from the project, several papers

specifically explore explanations for the time trends in CHD mortality and morbidity in the different populations[13, 14, 22].

One of the key papers analysing trends in CHD mortality, published in 1999, explored relative contributions to changes in CHD mortality between the mid-1980s and mid-1990s of trends in case fatality and trends in incidence[22]. The analysis is based on the principle that the average annual percentage change in CHD mortality may be partitioned into the sum of the average annual percentage change in incidence of major CHD and the average annual percentage change in case fatality. Thus a greater percentage change in incidence suggests the CHD mortality change is predominantly influenced by a change in the number of people experiencing major CHD events, rather than a change in the proportion of major CHD events which are fatal. There was considerable variation in the change in CHD mortality over the period; while the majority of populations experienced different degrees of decline, certain populations experienced an increase (mainly Eastern European populations, Russia and China). There was also variation in the relative contributions of incidence changes and case fatality changes between different populations. However, the general tendency was for a greater change in incidence, compared with case fatality, particularly where a decline in CHD mortality occurred, implying that the decline in CHD mortality could be mainly attributed to a decline in incidence over the period (the authors suggest a two-thirds versus one-third contribution of incidence versus fatality). Among the UK populations there was no consistent pattern; among men in Glasgow, as described in section 2.2.2, the average annual relative change in incidence of major CHD was -1.4% and in case fatality was -1.3%, giving a total decline in CHD mortality of -2.7%, and suggesting roughly equal contributions of incidence and case fatality trends.

Among women in Glasgow, the average annual relative change in incidence of major CHD was +0.2% and case fatality was -2.1%, giving a total decline in CHD mortality of -1.9%, this time solely influenced by case fatality declines. Among men in Belfast, the average annual relative change in incidence of major CHD was -4.6% and case fatality was -1.5%, giving a total decline in CHD mortality of -6.1%, predominantly influenced by incidence declines. Finally, among women in Belfast, the average annual relative change in incidence of major CHD was -2.4% and case fatality was -1.7%, also predominantly influenced by incidence declines. The general picture though is that both incidence and case fatality rates can be improved, and have been influential in reducing CHD mortality.

Having considered the relative roles of incidence and case fatality trends, the investigators then went further to consider the role of risk factors and coronary care in the incidence and case fatality trends[13, 14]. The risk factor trends themselves are reported separately in detail[242-245]. Using data on 38 populations from 21 countries with adequate quality data (including Belfast and Glasgow), an ecological analysis was carried out regressing the average annual change in **major CHD incidence** against the average annual changes in different major coronary risks factors for each population (such that each population was the unit of analysis)[246]. The percentage of the variation between the incidence trends in the different population that was explained by the risk factor trends was then estimated[247]. A lag period between the risk factor changes and subsequent incidence rate changes of 4 years was incorporated in the analysis; this led to a greater proportion of the variation in the trends in major CHD event rates explained by risk factor trends than with no time lag. The findings were that cigarette smoking trends alone explained approximately 20% of the

variation in the incidence trends in men aged 35 to 64 years, while total cholesterol explained 19% of the variation, and systolic blood pressure explained 6%[13]. BMI trends were estimated to explain a large proportion (36%) of the variation in incidence trends in isolation, but the coefficient of BMI in the corresponding analysis model was negative indicating counter-intuitively declining CHD risk with increasing BMI. The negative coefficient was found to have been predominantly influenced by the declining BMI in five former USSR populations, compared with rising BMI elsewhere. Excluding these former USSR populations, the total explained variation by the risk factors combined was 38%, with or without inclusion of BMI. Among women, the proportions of the variation in trends in incidence explained by the risk factors were much lower: smoking 0%, total cholesterol 0%, systolic blood pressure 11%, BMI 19% and all risk factors (excluding former USSR populations) 18%. The variation in the trends was therefore by no means fully explained by the risk factor changes. The authors cite possible explanations for the unexplained variation as imprecision in the analyses, modelling limitations (such as inadequate accounting for lag times or non-linearity of time trends) or the roles of other factors not included in the analyses. In a companion paper, published at the same time, a similar analysis was carried out to establish the role of treatment trends in the variation between populations in the time trends in major CHD event rates, 28-day case fatality and CHD mortality, based on 31 of the MONICA study populations[14]. Reflecting the available evidence at the time, the study, reported substantial and significant increases between the mid 1980s and mid 1990s in the use of beta blockers, anti-platelet drugs, thrombolytic drugs and ACE inhibitors in the majority of the populations studied. In particular, for the two included UK population samples (Glasgow and Belfast), significant increases in the use of all four treatments occurred (approximately one-

and-a-half fold increases in the age-standardised proportion of patients given beta-blockers, a quadrupling in the age-standardised proportion of patients given anti-platelets and thrombolytics and an increase from no patients receiving ACE inhibitors in the mid 1980s to roughly one quarter receiving the medication at the time of the MI in the mid 1990s). The study found that, in isolation, trends in the use of the different treatments, before or at the time of a major CHD event, could explain the following percentages of the variation in **28-day case fatality trends** between the different populations (men and women combined): beta-blockers before the major CHD event: 15% and at the time of the event: 18%; anti-platelets before: 24% and during event: 31%; ACE inhibitors before: 38% and during: 32%; coronary artery procedures before: 29%; thrombolytics during: 35%. The combination of all the treatment trends (as a score taking account of the combined effects of the treatments) could explain 51% of the variation in the 28-day case fatality trends (61% in men and 41% in women). In terms of **major CHD event rates**, 41% of the variation (52% in men, 30% in women) in the time trends between populations could be explained by the combined treatment trends. Finally, in terms of overall **CHD mortality rates**, 64% of the variation (72% in men, 56% in women) in the time trends between populations could be explained by the combined treatment trends. The influence of treatments appears greater than that of risk factors on the time trends in **incidence of major CHD** events (52% versus 38% of variation explained in men), which the authors suggest could be due to the treatment changes being particularly large, and that treatment use may be easier to measure. There is likely to be considerable overlap between the risk factors and treatment roles, since some of the treatments will work by reducing the risk factor levels (particularly cholesterol and blood pressure). Thus the percentages cannot simply be added to give the total variation explained by risk

factors and treatments. A third paper gives an alternative way of considering the role of treatments[245]. The study investigated the role of medication on the decline in blood pressure (and so indirectly on the trends in CHD) by comparing the shape of the distribution of blood pressure in the mid-1980s with that in the mid-1990s in the different world-wide populations. The hypothesis was that the effect of blood pressure-lowering medication would be realised in a selective depression of the top end of the population bell curve over time (reflecting the impact of blood pressure-lowering medication as a high risk as opposed to mass population intervention). The authors found no significant evidence for such a medication effect (mean blood pressure changes, pooled across all the populations, were similar in the different blood pressure centiles), concluding that lifestyle changes rather than medication have had greater influence on the blood pressure trends, at least over this period. Considering the UK populations in isolation however gives a different picture. In Glasgow, use of anti-hypertensive medications increased from 7% to 10% of the study population, between 1985 and 1994. Over the same period, average systolic blood pressure declined by -4.5mmHg and diastolic blood pressure declined by -3.6mmHg in men. The declines were greatest among participants above the 80th blood pressure centiles, that is, with the highest blood pressure: declines of -6.0mmHg and -4.0mmHg for systolic and diastolic blood pressure respectively. A similar pattern was seen among women: systolic blood pressure declined by -6.9mmHg on average and by -7.0mmHg among women above the 80th centile; diastolic blood pressure declined by -5.9mmHg on average and by -7.0mmHg above the 80th centile. This suggests a selective depression of the top end of the bell curve over time which in turn suggests an influence of medication on the blood pressure trends. In Belfast, use of anti-hypertensive medication did not increase; at the same time blood pressure levels

changed little, which neither supports nor refutes an influence of medication in blood pressure time trends in general.

2.6.1.2 IMPACT Policy model project

The IMPACT project has used aggregate data to examine and model the influence of different factors on the decline in CHD mortality in England and Wales[15, 248] and in Scotland[12] in recent decades, as well as in a number of other countries[249-255]. The IMPACT model synthesized data from a range of different sources on risk factor and treatment trends in the population of interest over a given time period to estimate the expected total number of CHD deaths prevented or postponed by the trends in the different factors/treatments. This expected figure is then compared with that actually observed to give an estimate of the size of the contribution of each factor to the mortality change. In Scotland, the period under consideration was 1975 to 1994. In England and Wales, trends over the period 1981 to 2000 were investigated. Different formulae are employed to assess the impact of the risk factors and treatments. A "best estimate" of the number of deaths prevented or postponed by a given treatment = no. eligible patients in latest calendar year × no. patients receiving treatment in latest year × relative risk reduction × case fatality rate. Several adjustments are made to take account of treatment use (albeit modest) at the start of the period; treatment compliance; and double-counting of patients in the various eligible patient groups. Polypharmacy (the combined effect of multiple treatments in an individual) is also considered. A "best estimate" of the number of deaths prevented or postponed by time trends in the risk factors smoking prevalence, blood pressure and cholesterol = no. of deaths from CHD in the first year × subsequent reduction in the risk factor × regression coefficient for change in CHD mortality per unit absolute change in the

risk factor in the population. A "best estimate" of the number of deaths prevented or postponed by time trends in the risk factors obesity, diet, physical activity and social deprivation = no. of deaths attributable to risk factor in the first year of the period – no. of deaths attributable to risk factor in final year (since suitable data on regression coefficients were not available for these factors). Since the regression coefficients and relative risks for the attributable risk calculations came from multiple regression analyses, they thus represent the (independent) benefit in the presence of other risk factors. Any decline in mortality unaccounted for by the treatments and risk factors considered is then attributed to unmeasured factors such as diet and life course effects. It should be noted that some of the risk factors could lead to an increase rather than decrease in the number of deaths. Population and patient data came from routine sources such as Hospital Episode Statistics and The Office for National Statistics (for the England and Wales analysis) or the Scottish Health Statistics (Scotland analysis). Estimates for the treatment relative risk reductions came from meta-analyses or multi-centre randomised controlled trials and estimates of risk factor effects and trends came largely from MONICA analyses, cross-sectional surveys such as the Health Survey for England, with some data also from the BRHS.

The IMPACT findings for England and Wales were that, comparing the number of deaths in 2000 with the number anticipated had the CHD mortality rate remained the same as in 1981, an *observed* total of 68 230 fewer deaths occurred, corresponding to decreases in the CHD mortality rate of 62% in men and 45% in women over this 20 year period[15]. The IMPACT model predicted that 25 805 deaths were *expected* to be prevented by uptake of different treatments. This is 38% of the observed total number of deaths prevented, indicating a 38% contribution of treatments. An estimated 4779

deaths (7%) were prevented by immediate treatment for an MI (including resuscitation, thrombolysis, aspirin, primary angioplasty, beta-blockers and ACE inhibitors), while 6899 deaths were prevented by secondary prevention after MI or after revascularisation. 3424 further deaths were prevented by treatments among patients with chronic angina and 912 with unstable angina, 7760 with heart failure and 1888 with hypertension. A small number (143) were prevented among the disease-free population due to use of statins for primary prevention. A larger portion, 35 944 (52%) of the deaths prevented, could be accounted for by major risk factor changes. Declining cigarette smoking had the greatest impact, preventing 29 715 deaths (44%). Favourable changes in blood pressure and total cholesterol accounted for the prevention of 5868 and 7900 deaths respectively (close to 10% each). Declining deprivation had a modest impact, preventing 2126 deaths. Conversely, physical activity, obesity and diabetes trends all had negative impacts, resulting in increased rather than reduced numbers of deaths (2662, 2097 and 2888 deaths respectively). 10% of the total 68 230 observed deaths prevented were not accounted for by risk factor or treatment changes, and were thus attributed to the unmeasured factors. In a separate paper, the numbers of deaths prevented was used to estimate further the life-years gained as a result of the time trends in risk factors and treatments[256]. The findings were that the changes in treatment would correspond to 194 145 life-years gained, while the changes in the risk factors would correspond to an additional 731 270 life-years gained, that is, 79% of the total life-years gained. Thus in terms of longevity, as opposed to mortality, the trends in risk factors have been considerably more influential than the trends in treatments. A separate analysis was later carried out, giving an alternative means of interpreting the data, by apportioning the prevented deaths by risk factor changes into those resulting from primary prevention

measures and those resulting from secondary prevention[248], that is, comparing those due to changes in risk factors among the healthy disease-free population with those due to changes in risk factors among patients with existing CHD. There were 45 370 deaths prevented due to favourable changes in smoking, blood pressure and cholesterol (by lifestyle changes or medication use). Of these, 36 625 (81%) were among the disease-free population (so primary prevention) while 8745 (19%) were among those with CHD (secondary prevention). This implies that of the total 68 230 deaths prevented, 36 625 (54%) can be attributed to primary prevention measures; the remaining deaths attributed to secondary prevention as a combination of the changes in risk factors among those with CHD (~13%) or other treatments among those with CHD (~33%).

In Scotland, looking at trends over an earlier period from 1975 to 1994, a total of 6205 fewer deaths occurred than anticipated in 1994, had rates stayed at the 1975 levels[12]. Of these, the IMPACT model predicted that 2178 deaths were prevented by uptake of different treatments (35% of the total number of deaths prevented), while 3425 (56%) were prevented by risk factor changes; the remaining 9% (approximately 600) was attributed to unmeasured factors. In terms of treatment, treatments at the time of the MI prevented close to 10% of deaths, while secondary prevention after the MI prevented 6% of deaths, secondary prevention after revascularisation prevented 2%, secondary prevention for angina prevented 5%, secondary prevention for heart failure prevented 8% and treatment of hypertension prevented 9%. Among the risk factors, again declining cigarette smoking had the greatest impact, preventing approximately 36% of deaths. Favourable changes in blood pressure and total cholesterol accounted for close to 6% each and declining deprivation accounted for

close to 3%. Physical activity, obesity and diabetes were not considered in this analysis due to lack of suitable data sources. A separate report from the IMPACT group suggests that three-quarters of the corresponding life-years gained, were attributable to risk factor changes, and one-quarter due to treatment changes[257]. However, the life-years gained estimates appear to be based on different numbers of prevented deaths so direct comparison between the estimates of the deaths prevented and life-years gained in this case is not straightforward.

2.6.1.3 Summary of extent of literature explaining UK CHD trends

Both the MONICA project and IMPACT project are ecological studies involving analyses based on comparing aggregate characteristics of groups of individuals where the groups are different cities (WHO MONICA) or different calendar years (IMPACT). They are thus subject to ecological limitations[258]. In particular, examples of an "ecological fallacy" may occur. This is where an association is seen between two factors A and B at the population level, comparing characteristics of groups of individuals (suppose A appears to be prevalent in a group if B is prevalent), but this is not a true association because it is not seen at the individual level, comparing characteristics of individuals (that is, an individual's likelihood of having factor B is independent of whether they have factor A). This situation arises when both A and B are prevalent in a group, but within the group, the individuals who have factor A are not the same as the individuals who have factor B. As an illustrative example, in the BRHS study at the population level, blood group 0 is associated with CHD (towns with a greater proportion of men in blood group 0 also have a higher incidence of CHD)[259]. However, at the individual level, this association is not seen (an individual with blood group 0 is not at higher CHD risk)[259]. The IMPACT model makes the

assumption that individual-level relative risks of risk factors carry across to the population level. Conversely, the MONICA analysis relies on the assumption that the regression coefficients found at the population level will apply to individuals.

Moreover, in both studies, different aggregate data sources are combined (some providing event data, some providing risk factor data). Critchley et al highlight the potential benefits of such modelling approaches, for example where data on sections of the population is scarce[260]. However, if the different aggregate data sources are not entirely representative of the populations of interest, they may not completely overlap in terms of the populations covered, risking further false associations. Also the risk factor/ treatment effect sizes found in the published studies and used to inform the IMPACT model may not be reflective of the strength of associations in the population, if the published study or trial populations differ from the population of interest, or because effect estimates in an (ideal) trial setting may be overestimates of the likely efficacy in the general population.

At the time the thesis was conceived, no studies in the UK had to my knowledge used individual level data to explore time trends in CHD mortality or morbidity. Moreover, there was a lack of research either at an individual level or on an ecological scale attempting to explain time trends in CHD incidence in the UK, which is the focus of this thesis. The IMPACT model looked only at CHD mortality, while WHO MONICA considered trends in CHD incidence but was limited to two UK cities (Belfast and Glasgow). Further, the nature of the MONICA analyses was such that the relationship between the trends in CHD and the influencing factors within the

individual cities was not examined. Instead the role of the factors in explaining the differences between the various cities in terms of the CHD trends was estimated.

2.6.2 Reasons for time trends in T2DM in the UK

Even fewer studies have to my knowledge explored time trends in T2DM either in the UK or indeed in other countries (see section 2.7.2 below), perhaps reflecting the more recent time-frame for the occurrence and description of the T2DM trend, as well as the lack of data on T2DM morbidity and risk factor levels[261]. One study in Tayside, Scotland, sought to ascertain whether the rising T2DM prevalence between 1993 and 2003 was the result of rising incidence or falling mortality rates[4]. The study found prevalence to have risen over this period by on average 6.7% per annum adjusting for age. Meanwhile, a 6.3% per annum age-adjusted increase in incidence occurred, and mortality fell by 3.7% per annum, adjusting for age. The study then went further to compare the actual observed rise in prevalence with the expected rise in prevalence under three different scenarios: 1- assuming incidence to have risen at the observed rate while mortality remained constant at 1993 levels, 2 – assuming mortality to have fallen as observed but incidence to have remained constant, and 3 - assuming both incidence and mortality to have remained constant. The findings were that the estimated prevalence rise under scenario 1 was close to that observed, while that under scenario 2 was somewhat lower, implying that rising incidence has had a greater impact than falling mortality on the changing prevalence rates. That said, the prevalence rise under scenario 3 (no change in incidence or mortality) was 60% of that observed, highlighting the interesting point that much of the increase in prevalence would have occurred anyway, even in the absence of changes in incidence and mortality, due to incidence being consistently higher than mortality throughout.

A second study compared time trends in early mortality with time trends in the use of different medications (glucose regulating drugs, anti-hypertensives, statins) among T2DM patients in the UK between 1996 and 2006[25]. Based on the observed concurrent decline in mortality and rise in medication use, and the known effectiveness of the medications in reducing mortality rates, the authors concluded that increased medication prescribing may have contributed to the improved survival. However the study did not formally assess the medication contribution. Although rising T2DM and rising obesity are often seen as companion public health issues, going hand in hand[43, 262], no studies have directly estimated the possible role of adiposity trends or trends in other aetiological factors, to the time trends T2DM prevalence or incidence in the UK.

2.7 Worldwide picture

2.7.1 Describing and explaining time trends in major CHD

In line with the trends in major CHD in the UK, declines in CHD mortality and major CHD incidence have also been observed in North America[252, 254, 263], other countries in Western Europe[249-251, 253, 255, 264], Australasia[265, 266] and Japan[267]. In contrast, in other regions of the world (Asia[10, 11], Eastern Europe[268]), in predominantly low and middle-income countries, CHD mortality rates have not been declining, and appear even to be increasing, leading to a growing CHD healthcare burden. The unfavourable rising CHD burden (along with other non-communicable diseases) in these countries ties in closely with the phenomenon of "epidemiological transition"[269, 270]. The epidemiologic transition defines the development and increased wealth of a middle or lower-income country which has contributed to improved control of the spread of infectious diseases, which were previously prevalent. This has positively

led to a decline in early- and childhood- infectious disease mortality rates. The resulting increased life-expectancy, along with changing lifestyles, in turn means that more people live to an age to develop a non-communicable disease such as CHD, and so the CHD incidence and mortality rates rise, and there is a shift or "transition" from the burden and priority of communicable diseases to non-communicable diseases. This transition can be observed both in the overall shift from communicable to non-communicable diseases, and also within CVD, with a shift from rheumatic heart disease in childhood to coronary artery diseases in later life[270]. Indeed, estimates from the WHO Global Burden of Disease Study suggest a 10% increase in the relative share of non-communicable diseases, principally CVD, in the disease burden of low-and-middle income countries between 1990 and 2001[271]. The extent of transition differs between countries; countries such as China[11] and India[10, 272], and parts of Eastern Europe are currently transitioning and as such are experiencing increased CHD mortality rates. Some specific countries in Sub-Saharan Africa are yet to transition and may be faced with a sizeable CHD burden in the future[273]. It has been estimated that the number of CHD deaths worldwide may almost double between 1990 and 2020[270]; CVD is already the leading cause of death worldwide and the third highest cause of disability[274]. The growing burden of CHD in other countries re-emphasizes the potential value of understanding and exploring the reasons for the decline in CHD mortality in the UK, as a means to inform how to reduce the CHD burden in other countries.

In terms of understanding and explaining trends, numerous studies have compared time trends in CHD mortality with time trends in aetiological factors and medication use, and subsequently hypothesized a relationship between the two[275]. However,

fewer have gone further to attempt to quantify the extent to which aetiological factors and/or medication trends have contributed to the CHD trends. Those that do are summarised below and in Table 2.1. Most of these studies have focussed on explaining time trends in CHD mortality; a very limited number have modelled trends in incidence or survival (CHD morbidity). Furthermore, most rely on synthesis of different sources, rather than relating individual CHD status to individual levels of aetiological exposures.

Dominating the list are studies applying the IMPACT model to many different world-wide populations to explain CHD mortality trends, including Auckland in New Zealand[265], Beijing in China[276], Finland[253], Ireland[250], USA[252, 277], Sweden[251], Canada[254], Iceland[249], and Italy[255]. In addition to the principal MONICA analyses involving all the MONICA populations, a few studies have examined CHD trends within a single MONICA population (in Reykjavik, Iceland[278] and in the North Karelia and Kuopio regions of Finland[279]), although still involving synthesis of different data for risk factors and for CHD death rates to compare observed and expected declines in CHD mortality. In general, where a decline in CHD mortality has occurred, risk factors have tended to make a larger contribution than treatments. Risk factors appear to have made the largest contributions, relative to treatments, in the Nordic countries and in Australia and New Zealand, while the contributions of risk factors and treatments are approximately 50:50 in the USA, UK, and Ireland. The relative size of the contribution of each of the individual risk factors appears to vary between populations.

Just one study worldwide[17] was found to have previously explored the relationship between time trends in CHD ***incidence*** (rather than mortality) and associated factors, using **individual level data** to relate an individual's CHD status to their risk factor levels or treatment use, thus avoiding the ecological limitations. That is, an analysis directly comparable with the analyses in this thesis. This US-based study (US Nurses Health Study) examined the decline in major CHD (fatal CHD or non-fatal MI) incidence over 14 years between 1980 and 1994[17]. Incidence in 1992-4 was roughly two-thirds of that in 1980-2 (relative risk from logistic regression of incidence on time-point = 0.69, adjusted for age). 68% of the decline in incidence could be explained by combined changes in smoking, diet (particularly a decrease in saturated fat, an increase in fibre) and post-menopausal hormone use, in the presence of an adverse secular change in BMI. This figure was derived from the analyses which revealed that the relative risk of 0.69 was attenuated to 0.90, after adjustment for the trends in these risk factors (that is, the risk factor levels over the two time-points). Thus, the proportion of the decline explained by the risk factors (= percentage attenuation of relative risk) is [(1-0.90)-(1-0.69)]/(1-0.69) = 68%. Decreased smoking prevalence accounted in isolation for 42% of the decline in CHD (from models adjusting only for smoking), changes in diet accounted for 52% and an increase in post-menopausal hormone use accounted for 29%. However the validity of the observed reduced risk with the use of hormone replacement therapy in this study is uncertain, in the light of more recent evidence that post-menopausal hormone use increases CHD risk[170-173], as outlined in section 2.5.2.2. Blood pressure, lipid levels, and diabetes were not considered in these analyses. The main mechanisms through which diet is seen to increase risk of CHD is by raising cholesterol, blood pressure and BMI[280, 281], thus inclusion of diet arguably captures some of the effects of these

factors. However, the full role of these factors is unlikely to be ascertained, and the impact of use of anti-hypertensive medications and lipid-regulating drugs is also not considered. Finally the study includes women only; the generalisability of the findings to men is not certain.

2.7.2 Describing and explaining time trends in T2DM

Global prevalence of diabetes (primarily T2DM) is estimated to be rising and is predicted to continue to rise[282-284]. Increases have been observed in many countries in both the developed and developing world. One study projecting global prevalence of diabetes estimated a prevalence of 2.8% in 2000, corresponding to a total of 171 million people with diabetes worldwide[284]. The study, based on data from about 40 world-wide populations, further projected the prevalence to almost double to 4.4% by 2030, corresponding to 366 million with diabetes by this time. The greatest increases in the numbers of people with diabetes were projected to occur in developing countries. One-and-a-half fold increases in the numbers of people with diabetes were projected for much of Asia, Sub-Saharan Africa, Latin America and the Caribbean, and the Middle East, whereas a 50% increase was estimated for the established market economies. The individual countries with the highest numbers with diabetes in both 2000 and 2030 were projected to be India, followed by China and the US, partially reflecting the large population sizes of these countries. A similar study, based on more recent data from 91 countries, estimated current (2010) global prevalence to be 6.4% (285 million diabetic individuals) and suggested an even higher world-wide prevalence by 2030 than that in the previous study of 7.7%, corresponding to 622 million people with diabetes[283]. While India, China and the US have the largest numbers of people with diabetes, the study showed that the Middle Eastern countries

tended to have the highest prevalence rates (estimated to be over 20% in the United Arab Emirates by 2030, and over 15% in Kuwait, Bahrain and Saudi Arabia). The projections in both studies are based primarily on the changing population demographics (population growth, ageing populations and urbanisation[285] being particularly implicated in the estimated increased prevalence rates). If adiposity or other aetiological factors are contributing to the rise in T2DM, the projected rates are likely to be underestimates. Indeed, two projection studies specific to the US population, where risk factor levels are taken into account in the analyses[286-288], suggest higher numbers of people with diabetes in early 2030 than that reported for the US in these global projection studies (44.1 million and 37.7 million in the US-specific studies versus 30.3 and 36.0 million in the global studies).

Studies in several different populations have shown parallel rises in obesity and T2DM prevalence[178, 289, 290], suggesting an association between the two trends, especially when considered with the PAR for T2DM of obesity[178]. However, no studies to my knowledge have formally attempted to quantify the extent to which rising adiposity levels, or other factors, may have contributed to rising T2DM prevalence or incidence, reflecting a paucity of data sources[75]. The two sides of the afore-mentioned debate in *Diabetologia* (section 2.3.2) on whether "there really is an epidemic of diabetes" do attempt to untangle the reasons for the rising prevalence[19, 74, 75]. The argument in favour of an epidemic considers five possible mechanisms which could lead to an increase in prevalence: a fall in mortality, demographic changes, a change in the ratio of diagnosed: undiagnosed cases, an earlier age of onset and finally an increase in incidence[19]. A combination of modelling and logical reasoning is used to determine that only about one quarter of the rise in prevalence can be attributed to

factors other than rising incidence, leaving around 75% unaccounted for. Much of this unexplained rise may have occurred even if incidence remained constant (as long as it exceeds the mortality rate). However, the authors estimate that the required incidence rate for this to occur, given the mortality and prevalence rates, is too high and therefore argue that incidence must have increased over time. The converse argument involves an analysis of data from a pharmaco-epidemiological database in Denmark[74]. The analysis showed that while prevalence (of treated T2DM) had increased rapidly in this population, incidence had remained constant, and instead the rising prevalence reflected a small decline in mortality (and is therefore not an epidemic as incidence is not rising). Both sides highlighted the lack of data to confirm the arguments, and, being a debate, the modelling methods are not detailed (particularly for the "pro" argument) and so it is difficult to assess the validity and robustness of the analyses.

2.8 Summary of literature review findings

The available data sources indicate a favourable decline in CHD mortality rates of almost three quarters from the 1960s to the present in the UK population, as outlined in section 2.2.1. In contrast an unfavourable increase in T2DM prevalence has been observed since the 1990s of around 5% per annum (section 2.3.1). The falling CHD mortality may be seen to reflect either falling incidence of major CHD events or falling case fatality following such an event. The rising T2DM prevalence may be seen to reflect either rising T2DM incidence or improved (relative) survival. Reports on incidence and fatality trends for CHD or T2DM are relatively limited, reflecting a lack of suitable data sources which have monitored incidence or fatality rates consistently over a period of time. However, both declines in major CHD incidence

and declines in major CHD case fatality have been documented, such that it is likely that both have contributed to the falling mortality rates (section 2.2.2). Meanwhile, studies of morbidity trends similarly suggest that both rising incidence of T2DM and improvements in survival rates have concurrently occurred, and so may be contributing to the prevalence rise (section 2.3.2).

The broad aim of the thesis is to evaluate and try to identify the drivers behind the trends in incidence of these two conditions. Understanding the reasons for the incidence trends could help to inform future efforts to reduce CHD and T2DM, both in the UK and in other countries. This is important because despite the favourable decline in CHD mortality, reports indicate that CHD remains the leading single cause of death, both overall and premature, in the UK (section 2.4). Meanwhile, health economic studies project a considerable and growing health burden of diabetes and its associated complications. Moreover, CHD and T2DM event rates are rising in many other countries (section 2.7).

A first step towards evaluating the incidence trends is to try to untangle the true epidemiological change (reflecting changes in modifiable exposures) from trends that simply reflect a changing population structure or artefact trends arising from changes in diagnostic criteria or case ascertainment (section 2.5.1). Possible influences to consider under these headings are, for major CHD, the change in the definition of MI in 2000, and changes in ICD coding of cause of death at various time points, which may influence the numbers of fatal CHD events identified. For T2DM, trends may be influenced by the change in diagnostic criteria in the late 1990s and possible improved case ascertainment, driven by public health policy such as QOF. Assuming an

epidemiological trend is identified, after accounting for population structure change and diagnostic and ascertainment changes, the next step towards explaining the trends is to identify candidate factors which could have contributed to the trends, for inclusion in the analyses. These are modifiable exposures with a likely aetiological association with CHD or T2DM risk. Their influence will depend on the extent to and direction in which exposure levels have changed over time in the population. Based on the epidemiological, aetiological and trial literature, for a decline in major CHD incidence, factors include primarily cigarette smoking, blood pressure, lipid levels, adiposity, physical activity, diabetes, dietary factors, alcohol consumption and use of blood pressure lowering and lipid regulating medications (section 2.5.2). For a rise in T2DM, factors include adiposity (key), and also physical activity, dietary factors, and possibly smoking, alcohol consumption and blood pressure (section 2.5.3). Studies consistently show about a two-fold excess risk of major CHD among patients with diabetes (section 2.5.4), highlighting the need to consider the trends in incidence of these two conditions together.

To my knowledge few studies have sought to formally analyse the reasons for the time trends in major CHD in the UK, or worldwide. The two previous studies of CHD trends involving UK populations (IMPACT and WHO MONICA) offer important insights into the trends in CHD mortality and major CHD incidence respectively but are subject to limitations, particularly the use of population rather than individual level data (both), the use of exposure effect sizes from external data sources in the models which may not reflect the true effect in the population (IMPACT) and the restriction to two UK cities (WHO MONICA) (section 2.6.1). Just one study worldwide was found which used individual level data to analyse the

decline in major CHD incidence (Nurse's Health Study, US); that is, an analysis directly comparable to those carried out in the thesis, but was limited to women and excluded key factors such as lipid and blood pressure levels (section 2.7.1). There appeared to be a lack of studies formally addressing the rise in T2DM, in the UK or worldwide (sections 2.6.2 and 2.7.2). Thus the analyses in this thesis provide the opportunity to gain new insights, and address current gaps in the knowledge of CHD and T2DM time trends, to in turn help address the ongoing CHD and T2DM burdens in the UK and elsewhere.

Table 2.1 **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

	Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
*	WHO MONICA - >30 populations from >20 countries including Belfast and Glasgow[14]	Ecological analysis with population as unit of analysis; regression of CHD trend on contributory factor trend	mid 1980s - mid 1990s	**CHD mortality**	Varies by population - variations in trends between populations modelled		men 72%, women 56%			Includes revascularisation surgery and medications before event and medications during event	men 27%, women 44% (treatments only considered)
*	IMPACT - Scotland[12]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1975 - 1994	**CHD mortality**	Decline; 6205 fewer deaths than expected in 1994	56%	35%	Smoking 36%, Cholesterol 6%, BP 6%, Deprivation 3%		Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, antihypertensives for prevention	9%
*	IMPACT - England and Wales[15]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1981 - 2000	**CHD mortality**	Declines of 62% in men and 45% in women; 68,230 fewer deaths than expected in 2000	52%	38%	Smoking 44%, Cholesterol 10%, BP 10%, Deprivation 3%	Diabetes - 5%, Physical activity - 4%, Obesity - 3%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, statins and antihypertensives for prevention	10%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
IMPACT - Ireland[250]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1985 - 2000	**CHD mortality**	Decline of 47%; 3,763 fewer deaths than expected in 2000	48%	44%	Smoking 26%, Cholesterol 30%, BP 6%,	Physical inactivity - 4%, Diabetes - 6%, Obesity -4%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, lipid-lowering and antihypertensives for prevention	8%
IMPACT - Finland[253]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1982 - 1997	**CHD mortality**	Declines of 56% in men and 64% in women; 373 fewer deaths than expected in 1997	53%	23%	Smoking 9%, Cholesterol 37%, BP 8%		Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure,	24%
IMPACT - Sweden[251]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1986 - 2002	**CHD mortality**	Declines of 53% in men and 52% in women; 13,180 fewer deaths than expected in 2002	55%	36%	Smoking 9%, Cholesterol 40%, SBP 7%, Physical inactivity 6%,	Diabetes - 5%, BMI - 2%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, lipid-lowering and antihypertensives for prevention	9%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
IMPACT - Iceland[249]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1981 - 2006	**CHD mortality**	Declines of 79% in men and 82% in women; 295 fewer deaths than expected in 2006	73%	25%	Smoking 22%, Cholesterol 32%, SBP 22%, Physical inactivity 5%,	Diabetes - 5%, BMI - 4%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, lipid-lowering and antihypertensives for prevention	2%
IMPACT - Italy[255]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1980 - 2000	**CHD mortality**	42,930 fewer deaths than expected in 2000	55%	40%	Smoking 4%, Cholesterol 23%, SBP 25%, Physical inactivity 6%,	Diabetes - 2%, BMI - 1%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, statins and antihypertensives for prevention	5%
IMPACT - Auckland, New Zealand[265]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1982 - 1993	**CHD mortality**	Decline of 24%; 558 fewer deaths	60%	35%	Smoking 30%, Cholesterol 12%, DBP 7%		Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, antihypertensives for prevention	5%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
IMPACT - USA[252]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1980 - 2000	**CHD mortality**	Declines of 50%; 337,658 fewer deaths than expected in 2000	44%	47%	Smoking 12%, Cholesterol 24%, SBP 20%, Physical inactivity 5%,	Diabetes - 10%, Obesity -8%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, statins and antihypertensives for prevention	9%
IMPACT - Ontario, Canada[254]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1994 - 2005	**CHD mortality**	Decline of 35%; 7585 fewer deaths than expected in 2005	48%	43%	Smoking 10%, Cholesterol 23%, SBP 20%, Physical inactivity 4%,	Diabetes - 6%, BMI - 2%	Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, lipid-lowering and antihypertensives for prevention	9%
IMPACT - Beijing, China[276]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1984 - 1999	**CHD mortality**	RISE of 50% in men and 27% in women; 160 EXTRA deaths	113%	-40%	Smoking 1%, Cholesterol 77%, BP 0%, BMI 4%, Diabetes 19%		Includes surgical and medical treatments during event, after event, after revascularisation, for angina, for heart failure, antihypertensives for prevention	27%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

	Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
A	US[291]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1968 - 1976	**CHD mortality**	Decline	>50%	40%	Smoking, Cholesterol		Treatment in coronary care units, for angina and medications for hypertension	
	US[263]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1980 - 1990	**CHD mortality**	Decline of 34%; 127,000 fewer deaths than expected in 1990	50%	43%	Smoking 6%, LDL cholesterol 24%, HDL cholesterol 10%, DBP 14%		Treatment during event, for angina	7%
	Minnesota Heart Survey, Minnesota, US[292]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1970 - 1984	**CHD mortality**	Decline; 212 fewer deaths than expected in 1984		6%			CABG	94% (only CABG considered)

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
California, US[293]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1989 - 1997	**CHD mortality**	Decline; 33,300 fewer deaths between 1989 and 1997 than expected			Tobacco control program in 1989-1992			
WHO MONICA North Karelia and Kuopio regions, Finland[279]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1972 - 1992	**CHD mortality**	Decline of 55% in men and 68% in women	men 80%, women 72%		Men: smoking 18%, cholesterol 47%, DBP 27%, Women: cholesterol 51%, DBP 46%,	Women: smoking - 16%		men 20%, women 28%
The Netherlands [264]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1978 - 1985	**CHD mortality**		23%	67%	Smoking 23%, Cholesterol 0.4%		Treatment in coronary care units, including revascularisation and medications; hypertension treatment for prevention	10%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
9 Health Districts, Italy[294]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1984 - 1987	**CHD mortality**	Decline; 10% in men, 30-59 yrs, 7% in men, 40-69 yrs, 8% in women, 30-59 yrs, 10% in women, 40-69 yrs,	men>50%, women >100%		Smoking, Cholesterol, BP	BMI		
Auckland, New Zealand[295]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1974 - 1981	**CHD mortality**	Decline; 126 fewer deaths than expected in 1981		40%			Resuscitation before admit. hosp 16%, Coronary Care Units 5%, Beta blockers during event 2%, Surgery 5%, antihypertensives 12%	60% (only treatments considered)
New Zealand[296]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1980 - 2004	**CHD mortality**	Decline	men 73%, women 87%		Men: Smoking 28%, Cholesterol 26%, SBP 40%, Women: Smoking 20%, Cholesterol 52%, SBP 47%,			men 23%, women 13%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

	Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
	Australia[266]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1980 - 1991	**CHD mortality**	Decline; average annual percentage changes ranging from -3.7 and -10.7, depending on age and gender	men ~50%, women ~25%		Men: Smoking ~8-31%, Cholesterol ~-4-9%, BP ~11-31%, Women: Smoking ~1-13%, Cholesterol ~1-35%, BP ~8-29%			men ~50%, women ~75%
A	Australia[297]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1968 - 2000	**CHD mortality**	Decline of 83%	men 74%, women 81%		Men: Smoking 16% (mainly in 1980s), Cholesterol 22% (mainly in 1970s), DBP 36% (whole period), Women: Smoking 5% (mainly in 1980s), Cholesterol 20% (mainly in 1970s), DBP 56% (whole period)			men 26%, women 19%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

	Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
*	WHO MONICA - >30 populations from >20 countries including Belfast and Glasgow[13, 14]	Ecological analysis with population as unit of analysis; regression of CHD trend on contributory factor trend	mid 1980s - mid 1990s	**Major CHD incidence**	Varies by population - variations in trends between populations modelled	men 38%, women 18%	men 52%, women 30%	Men: Smoking 20%, Cholesterol 19%, SBP 6% (BMI 36%), Women: Smoking 0%, SBP 11%, Cholesterol 0% (BMI 2%)		Includes revascularisation surgery and medications before event (and medications during event)	? (**NOTE** Portions explained by risk factors and treatments estimated in two **separate studies** so not independent)
	Hunter Region MONICA cohort, New South Wales, Australia[298]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1985 - 1993	**Major CHD incidence**	Declines; average annual decline of 3.3% in men and 4.3% in women	men 95%, women 80%	men 5%, women 0%	Men: Smoking 39%, Cholesterol 27%, DBP 30%, Women: Smoking 18%, Cholesterol 32%, DBP 29%		Men Daily aspirin 5% Women Daily aspirin 0%	men 0%, women 20%
	Nurses' Health Study, US[17]	Individual level data; percentage attenuation of relative risk	1980 - 1994	**Major CHD incidence**	Decline of 31%	68%		Smoking 42%, Diet 52%, Post-menopausal hormone use 29%	BMI -12%		32%

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

	Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
*	WHO MONICA - >30 populations from >20 countries including Belfast and Glasgow[14]	Ecological analysis with population as unit of analysis; regression of CHD trend on contributory factor trend	mid 1980s - mid 1990s	**Major CHD 28-day case fatality**	Varies by population - variations in trends between populations modelled		men 61%, women 41%			Includes revascularisation surgery and medications before event and medications during event	men 39%, women 59% (treatments only considered)
	Perth MONICA cohort, Australia[16]	Individual level data; percentage attenuation of relative risk	1984 - 2005	**12-year major CHD case fatality, given survival to 28-days or 1 year**	Declines of 40% and 28% given survival to 28-days and 1 year respectively		~100%			Thrombolysis, anti-platelets, beta-blockers, ACE inhibitors, lipid lowering drugs in hospital during event or on discharge, Revascularisation within 12 months of event	

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Table 2.1 *cntd* **Studies assessing the contributions of risk factor and treatment trends to CHD trends in different countries**

Study and population	Analysis Method	Time period	Outcome	Trend in outcome	Portion of trend explained by risk factor trends	Portion of trend explained by treatment trends	Details of individual risk factors contributing to trend	Details of individual risk factors counter to trend	Details of Individual treatments	Portion of trend un-explained
Hunter Region MONICA cohort, New South Wales, Australia[298]	Synthesis of aggregate data sources; comparing observed CHD trend with that expected given trends in likely contributory factors	1985 - 1993	**Major CHD 28-day case fatality in hospital**	Declines; average annual decline of 8.9% in men and 6.9% in women		men 36%, women 41%			Men: Aspirin 23% Fibrinolytic therapy 8% Beta blockers 3% ACE inhibitors 3%, Women: Aspirin 25% Fibrinolytic therapy 6% Beta blockers 3% ACE inhibitors 4%	men 64%, women 59% (treatments only considered)
Twin Cities, Minnesota, US[18]	i) Synthesis of aggregate data ii) individual level analysis	1985 - 1990	**Major CHD 28-day case fatality**	Decline of 26% in men and 16% in women		i) synthesis method: 20% ii) individual analysis: 30%			Thrombolytic therapy during hospital stay	80% (thrombolytic therapy alone considered)

Notes: *Study includes section of UK population; A = only abstract of paper seen; blank cells = no data

Chapter 3 Methodology

3.1 Introduction

The chief method employed to address the thesis aims is statistical analysis of pre-collected data, which come from a combination of different sources. Since the purpose of this thesis is to address trends in the UK, the data sources are all UK-based, representative of different sectors of the British population. The principal data source used is the British Regional Heart Study (BRHS)[34, 35], a prospective cohort study comprising a national sample of British men, who were middle aged when recruited. A second data source used is The Health Improvement Network (THIN) database[36], comprising national routinely collected data on General Practice consultations. In addition, certain analyses have been carried out on another prospective study; the London-based Whitehall II cohort[37] of male and female civil servants. The data sources each have different strengths and thus complement one another, enabling a fuller picture of trends to be obtained than would be possible from each dataset in isolation. The data sources are each utilised according to their respective strengths. Repeating the same analyses in different datasets allows validation of the results and also enables assessment of the extent to which the same results apply to different sectors of the population. Sections 3.2, 3.3 and 3.4 introduce each of the different data sources in turn. The type of data source is described, along with descriptions of the constituent study participants, the follow-up of the participants, and assessment of disease outcomes and explanatory factors. Their suitability for use to address different questions, in relation to their particular strengths, is discussed. Note that the collection of data for each source, detailed in sections 3.2.1, 3.2.2, 3.2.4, 3.2.5, 3.3.1, 3.3.2, 3.4.1, 3.4.2, 3.4.4, and 3.4.5, was not

carried out by myself, the thesis author, but necessarily described here for information and clarification. The remaining sections detail how the data has been managed and organised for analyses specific to the thesis, and this data management has been carried out by me, including sub-studies to explore validity of the data. The statistical methods used to analyse the datasets are detailed in each of the subsequent results chapters.

3.2 The British Regional Heart Study

3.2.1 Description of data source

The BRHS is a prospective study of cardiovascular disease in a socially and geographically representative cohort of middle-aged men in Britain, established in 1978[34, 35]. Two towns were selected from each of 12 metropolitan regions in Britain, to result in 24 towns in all for study. The choice of towns depended on the town having a medium sized population (50-100 000) in 1971 and the town being representative of the region in terms of cardiovascular mortality rates, water quality, and socio-economic status (according to the Webber classification[299]). High mobility towns (new towns and large conurbations) were excluded. The 24 towns selected are shown in the map of Britain in figure 3.1. Within each of the 24 towns, a General Practice was selected. Criteria for selecting a practice included its size (practice population over 7500 and two or more partners), its representativeness of socioeconomic composition and characteristics of the town population and willingness to participate. 400 men, aged from 40 and up to 60 years, were then selected at random, stratified by four 5-year age groups (40-44, 45-49, 50-54 and 55-59 years), from age-sex registers within each practice, over a recruitment period from 1978 to 1980. Basing the recruitment and selection of study participants within

General Practices facilitated the administration and organisation of the study, at a time when age-sex registers were uncommon (1977), but General Practice lists covered >95% of the population. The men were invited to attend a local initial health screening, usually at the Practice premises. A small number of men (<10) in each town were excluded from the invitation list by the General Practice due to poor physical or mental health, that prevented the men from attending the screening. The response rate for those men invited was 78%, resulting in a total of 7735 men recruited for study (corresponding to approximately 300 from each town).

3.2.2 Description of follow-up

The men have been followed up since baseline (recruitment in 1978-80) until the present for all-cause mortality through the NHS central registers. In addition, at regular biennial intervals a standard form (available on the study website at www.ucl.ac.uk/pcph/research-groups-themes/brhs-pub) has been sent to the General Practices, to request confirmation of each man's continuing registration, current address, and any new cardiovascular events and (from 1990 onwards) new diagnoses of cancer or diabetes that have occurred within the last two years. A man who removes from the General Practice and re-registers elsewhere is traced to the new General Practice. The study now includes over 1100 General Practices nationwide, in addition to the 24 original practices. Follow-up has been maintained for 98% of surviving men throughout. Follow-up data up to 2007 were available for use during this thesis. However certain analyses, carried out first, were completed before the latest follow-up data were available and are therefore based on earlier data.

At the initial health screening at baseline, a series of anthropometric and physiological measurements were made, including height, weight, blood pressure, electrocardiogram (ECG), and lung function. In addition, blood samples were taken and the men completed a nurse-administered health and lifestyle questionnaire. A second examination took place at 20-years follow-up in 1998-2000. The same measurements were made as at baseline, with the addition of measurements of bio-impedance, waist and hip circumference, triceps and sub-scapular skin-folds. Blood sample were again taken and the men self-completed a questionnaire. The men have also completed regular postal questionnaires on health and lifestyle over the course of the follow-up to date; in 1983-1985 (at 5 years follow-up), in 1992 (12 to 14 years follow-up), in 1996 (16 to 18 years follow-up), in 2003 (23 to 25 years follow-up), and in 2005 (25 to 27 years follow-up), at the time of writing. Copies of the datasheets showing measurements taken at the physical examinations and the questionnaires are available on the study website. Response rates for each questionnaire are presented in table 3.1. Postal questionnaire response rates were high, ranging from 98% at 5 years follow-up to 79% in 2005. 77% attended the 20-year physical examination. A timeline of the study, showing when relevant data used in the thesis has been collected for participating men over the course of the follow-up, is shown in figure 3.2.

3.2.3 Intended use of data source

The intention is to use to the data source to estimate trends in incidence of major coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM), and to explore the contribution of concurrent trends in major risk factors and medication use to the

trends (thesis objectives iii and iv). The data source will also be used to assess the contribution of trends in T2DM to the trend in major CHD (objective v).

3.2.4 Assessment of disease cases

The disease endpoints chiefly considered in this thesis are major CHD events and new diagnoses of T2DM. A major CHD event was defined as a fatal or non-fatal myocardial infarction (MI). Diagnosis of fatal MI in the BRHS was based on deaths with CHD as the underlying cause, including sudden death of presumed cardiac origin (international classification of diseases, ninth revision (ICD-9)[300], codes 410-414), ascertained from the NHS central registers. Definite non-fatal MI was ascertained from the regular review of General Practice records. All new major CHD events reported by the practices were followed-up with an enquiry form to the General Practice or hospital consultant to obtain confirmatory evidence that case criteria have been met. Specifically, the following criteria need to be satisfied (WHO MONICA study criteria[241]): chest pain symptoms suggestive of MI, supported by either ECG changes or specific levels of cardiac enzymes, or both. New diagnoses of diabetes (with date) were identified from regular reviews of General Practice records from 1990. Further new diabetes diagnoses occurring between 1983-5 and 1990 were identified from retrospective self-report of a diagnosis of T2DM, with diagnosis date, in the questionnaire in 1992, confirmed by separate subsequent review of the man's General Practice records. Therefore, incident T2DM data with validated diagnosis dates were available from the time of the 1983-1985 questionnaire onwards (figure 3.2). Any new diagnosis of diabetes was taken to be a diagnosis of T2DM rather than type 1 as men were aged 45 and over at the start of follow-up for diabetes in 1983-1985.

3.2.5 Repeated assessment of coronary and diabetic risk factors

Cigarette smoking, weekly alcohol intake and physical activity levels were ascertained in each of the interview-administered questionnaires and postal questionnaires using comparable questions each time (figure 3.2). This provided repeated information over the follow-up on these different coronary risk factors. The one exception was that physical activity was not included in the questionnaire at 5 years follow-up (1983-5) and the questions on physical activity varied over time, partially to reflect the changing lifestyles over time as the men entered retirement. From the information given, men were categorised at each questionnaire time-point as "current", "ex" or "never" smokers. Information in previous questionnaires was used to inform the smoking status in the later questionnaires – for example, if a man reported being a cigarette smoker in an earlier questionnaire, and then reported being a non-smoker in a later questionnaire, his smoking status in the later questionnaire would be defined as "ex smoker". The men's alcohol consumption was categorised as: "never", "occasionally", "light", "moderate" and "heavy", as outlined previously[301]. Answers to questions relating to recreational activities, regular walking and cycling and sporting activity were combined to give each man a physical activity score. Men were grouped into six categories based on their score: "inactive", "occasional", "light", "moderate", "moderately vigorous" and "vigorous". This score has been previously detailed and validated[302], by demonstrating the score to be strongly related to subsequent cardiovascular risk.

Seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the physical examinations at baseline and after 20 years of follow-up (figure 3.2). Blood pressure was measured at baseline using The London School of

Hygiene and Tropical Medicine (LSTHM) sphygmomanometer and at 20 years using the Dinamap 1846SX vital signs monitor (Critikon Inc, Tampa, FL, USA). On both occasions the mean of two successive readings, adjusted for observer variation, was used.

Blood samples taken at the two examinations (non-fasting at baseline, fasting at 20 years) were analysed for serum total cholesterol by a modified Liebermann–Burchard method on a Technicon SMA 12/60 analyser (Technicon Instruments, Tarrytown, NY, USA) at baseline and with a Hitachi 747 automated analyser (Roche Diagnostics, Indianapolis, IND, USA) at 20 years. High density lipoprotein (HDL) cholesterol was measured by the Liebermann–Burchard method or enzymic procedures after precipitation with magnesium phosphotungstate. Low density lipoprotein (LDL) cholesterol was not directly measured. Instead, non-HDL cholesterol was computed as the difference between the total and HDL cholesterol levels, thus mainly representing LDL cholesterol. Use of non-HDL cholesterol avoids the biases that may arise when estimating LDL cholesterol values by the Friedewald formula[303]. In meta-analyses, the hazard ratio for major CHD incidence per standard deviation increase in non-HDL has been shown to be comparable to that for directly measured LDL cholesterol[102], supporting use of non-HDL. At baseline and 20 years, body mass index (BMI) was calculated directly from height and weight measurements taken at the physical examinations as weight divided by height^2. At both time-points, height (without shoes) was measured to the nearest millimetre using a Harpenden Stadiometer (Critikon Service Centre, Berkshire, United Kingdom). Weight (in light clothing and without shoes) was measured to the nearest 0.1kg using an MPS110 field survey scale (Critikon Service Centre) at baseline[304] and using a Soehnle digital

electronic scale (Critikon Service Centre) at 20 years[305]. At the times of the other questionnaires, height was estimated by linear interpolation between the baseline and 20 years measurements, and weight was obtained via self-report in the postal questionnaires.

In the questionnaires at each time point, each man was asked about his medication use. In particular, it was possible to identify use of lipid-lowering medications or blood pressure-lowering medications at each time-point. The questions varied slightly according to the questionnaire. Some or all of the following items were ascertained: whether he was regularly receiving lipid-regulating or blood pressure lowering drugs from a doctor, whether he had used lipid lowering drugs or blood-pressure lowering drugs in the last 24 hours, and to list all the medications he currently used with reasons.

3.2.6 Sub-study 1: Investigating comparability between the risk factor ascertainment methods used at each time point

To ensure as far as possible fair and unbiased estimates of time trends in the risk factors, which is of particular importance in the analyses for this thesis, the techniques used to ascertain the risk factor levels at each time point need to be consistent, or if not, potential differences between the risk factor ascertainment techniques need to be identified and accounted for. In this section the comparability of the repeated measurements of each of the risk factors in turn is explored.

As outlined above, the risk factors cigarette smoking and alcohol use were ascertained via questionnaire only and using broadly consistent questions each time. Moreover

information in previous questionnaires was used to inform and validate the smoking status in the later questionnaires. Thus the ascertainment methods for cigarette smoking and alcohol use are arguably suitably consistent over time.

Physical activity was also measured solely via questionnaire. However in the case of this risk factor, the questions on physical activity differed between questionnaires, as outlined above, which may limit comparability between different time-points. Results related to physical activity trends in the BRHS are thus interpreted with caution throughout.

A previous study has investigated the consistency between the different blood pressure measuring equipment (LSHTM sphygmomanometer at baseline versus Dinamap 1846 at 20 years follow-up)[306]. This study found significant systematic overestimation by the Dinamap 1846 of 8mmHg for SBP, but no significant difference between the two apparatus for DBP. In light of these findings, in all analyses the 20 year SBP measurements have been adjusted by 8mmHg downwards to be consistent with the baseline measurements (as in all analyses of BRHS data).

Data were available to investigate the comparability between the different assay techniques used at baseline and the 20-year examination for total and HDL cholesterol as a small number of residual baseline samples for total and HDL cholesterol levels had been re-measured using the assay techniques applied at the 20 year examination. Using a paired t-test, in 47 subjects, the mean within-person difference in total cholesterol (re-measured minus baseline) was 0.072 (standard deviation (s.d.) 0.718) mmol/L, p=0.5. The mean within-person difference in HDL cholesterol (re-measured

minus baseline) was 0.067 (s.d. 0.552) mmol/L, p=0.4. Since the differences were not significantly different from zero, and were based on samples stored for almost 20 years, these differences have not been taken into account in the main analyses. However because comparability between the baseline and 20 year measurements is particularly important in the analyses in this thesis additional sensitivity analyses have been conducted using baseline measurements adjusted for the small mean differences observed.

Height and weight were measured by comparable methods at the physical examinations at baseline and 20 years. The repeated measurement of height at 20 years enabled validation of the baseline measurements, as well as allowing for possible height loss with increasing age. A possible source of inconsistency however between the different BMI measurements is the use of self-reported weight at the times when a postal questionnaire only was administered, compared with weight measured by research nurses at the baseline and 20-year examinations. It has been shown that study subjects, when self-reporting, tend to underestimate their weight[307-310]. A comparison between the measured and self-reported weights was made possible as at the 20-year examination as men self-reported their weight before having their weight measured. In all, 3837 (70%) of 5516 men alive at 20 years follow-up, had both self-reported and measured weight at this time-point. A paired t-test revealed a difference in means of 0.643 (s.d. 3.02) kg; $p<0.001$, (the self-reported weight was a mean of 0.643kg lower than the measured value). This figure agrees closely with previous estimates of differences between self-report and measured weight in British male populations[307-310], lending support to the finding. The self-reported weights at the other time points were therefore corrected by the mean

difference between the two weights to improve consistency between the different corresponding BMI measurements.

3.2.7 Sub-study 2: Deriving physical activity at 5 years follow-up

Physical activity was not ascertained in the questionnaire at 5 years follow-up. In order to make best use of the data in multivariable analyses involving physical activity, imputation or "filling in" of the missing physical activity data was considered. Without physical activity at 5 years follow-up, all risk factor data would have to be excluded from any multivariable analyses involving physical activity, leading to considerable loss of information in this complete case analysis. The physical activity category at 5 years of follow-up was computed as the median of the category at baseline and the category at the next questionnaire time-point in 1992, rounded to the nearest integer, with the categories ordered from "inactive" up to "vigorous." The effect of imputing this physical activity data is explored when discussing findings related to this risk factor.

3.2.8 Description of study population

As outlined in section 3.2.1, the BRHS cohort comprised at baseline 7735 men, aged 40 to 60 years, with even numbers of men in each 5-year age-band. The recruitment methods were designed such that the sample of men would be socially and demographically representative of the town in which they lived at baseline and, in turn, given the choice of towns, broadly representative of Britain as a whole. Indeed the distribution of socio-economic status in the BRHS men reflects closely the distribution in the general UK population in the 1981 census, the census closest to the 1978-80 baseline recruitment period[311]. The study sample included men who had

previous CHD or T2DM diagnoses. Men with these prevalent conditions at baseline are included or excluded from the analyses as appropriate for each chapter (exclusions detailed in the relevant results chapter). The majority of men are white; fewer than 1% of men are of other ethnicities. Characteristics of the men at baseline in 1978-1980 (including socio-demographic characteristics, coronary and diabetic risk factor levels, and prevalent CHD or T2DM) are presented in table 3.2. At baseline, 30% of men were from the South of England, as opposed to Northern England (43%), Midlands and Wales (16%) and Scotland (12%). The most common socio-economic position (as defined by longest-held occupation at baseline, based upon the Registrar General's Social Class Classification) was III skilled manual (43%, e.g. bricklayers), followed by II intermediate (23%, e.g. teachers and sales managers). 41% of men were current cigarette smokers, while 11% of men were heavy drinkers and 9% were physically inactive. One-quarter of men had a history of CHD (including angina and/or MI), and around half of these men had had a MI (determined from a combination of ECG evidence and self-report of recall of doctor diagnosis). Prevalence of (known doctor-diagnosed) diabetes (type 1 or type 2) was 1.3%. A small proportion (5%) of men reported use of blood pressure lowering medication. Mean BMI was 25.5kg/m^2 and 54% of men were overweight or obese (BMI over 25kg/m^2). Mean SBP was 145.2mmHg and mean DBP was 82.2mmHg. Mean total cholesterol was 6.3mmol/L, mean HDL cholesterol was 1.15mmol/L and mean non-HDL cholesterol was 5.15mmol/L.

3.2.9 Strengths in relation to intended analyses

A key strength of this data source is the availability of a continuous follow-up over an extended period for the principal disease endpoints, major CHD and T2DM, alongside

concurrent repeated measurements of the major coronary and diabetic risk factors. This makes the BRHS particularly suitable for modelling the role of trends in the major risk factors in the trends in incidence of major CHD and T2DM. There is a paucity of similarly suitable data sources (see chapter 2, sections 2.6.1.3 and 2.6.2), emphasizing the value and uniqueness of the analysis. As outlined above, the risk factor data has generally either been consistently collected or validation of different ascertainment techniques has been possible, limiting bias in the estimates of the time trends in the risk factors and their roles in the trends in major CHD and T2DM. The social and geographical representativeness of the cohort is a further strength, supporting generalisability of the findings to the wider British male older population.

Nevertheless this data source has certain limitations in relation to addressing the objectives of the thesis. First, the data source comprises men only. In order to obtain a more complete picture of trends in the UK it would be useful to be able to also examine trends in women. Second, while calculations have shown that the study has adequate power to detect differences in risk factor levels and cardiovascular risk within 5-year periods of follow-up[34], the cohort is too small for precise estimation of time trends in major CHD and T2DM incidence rates within different socio-demographic groups, or to estimate annual major CHD and T2DM incidence rates (as opposed to rates over several years combined). Also the number of men in the cohort with T2DM, forming the denominators for estimation of time trends in survival from major CHD among patients with T2DM (towards objective v), is too few for adequate power. Thus in order to address the thesis aims as fully as possible two additional data sources have been employed, each comprising suitable population samples in which to carry out those analyses which are less feasible using the BRHS data.

3.3 The Health Improvement Network Database

3.3.1 Description of data source

The THIN database[36] is a UK-wide primary care database comprising computerised anonymised longitudinal patient records retrieved from participating general practices across the UK. Eligible general practices are those using the Vision (In Practice Systems, InPS) computer patient record-keeping system for recording patient notes, including medical diagnoses and symptoms (using the hierarchical Read coding system[312]) and prescriptions, test results, immunisations and other health information.

The database is dynamic, in the sense that data is continuously collected and updated, and patients may join and leave the database at different times. Upon joining THIN an initial Full Data Collection (FDC) from the General Practice, which includes all retrospective data, is sent to EPIC, the database providers. Following this, Incremental Data Collections (IDCs) are made each month by automaton, electronically downloaded from the General Practice. This method of data collection ensures minimal disruption to daily practice activities. THIN data collection first began in November 2002, however the initial FDCs include considerable retrospective data (as far back as the time when records were first computerised in the practice). That said, data prior to the early 1990s (particularly mortality data) is less complete and so data before 1994 has not been used in this thesis. Patient data up to July 2009 were available in the latest update of the database before the end of the period of research for the thesis. This update comprises data from 446 General Practices, including 8.2 million patients, contributing a combined total of approximately 51 million patient years of data. Note that not all practices are present and contribute data in THIN throughout. Indeed many practices only began use of computerised record systems in

more recent years and a small number have left THIN after having contributed in earlier years (see table 3.3). Patients may opt out. However exclusions by patient choice or otherwise are rare.

3.3.2 Description of follow-up

The data are anonymised at the source general practice, before leaving the practice computer system. However (encrypted) computer generated identifiers are available for each patient and each General Practice, enabling different General Practice visits for the same patient to be linked together such that patients can be followed-up over time. Each patient may be followed from the latest of the following dates: (i) the date that the patient registered at a contributing General Practice (ii) the date by which the practice was fully using their computer system for recording of diagnoses and prescriptions (termed Acceptable Computer Usage, or ACU), and (iii) the date by which computerised recording of patient death for the practice had reached an acceptable level. The need for a date of Acceptable Computer Usage stems from awareness that when a practice first starts using computerised records in place of traditional paper records, it takes time for the computer system to be fully adopted by the practice (for example they may start by recording only certain events or appointments for each patient). Using data from this initial period, the records would be likely incomplete leading to biased and incorrect inferences. For each practice, we have identified the time point at which the practice is first fully using their computer system based on empirical evaluation of the quantity of each type of record. For a practice to have acceptable computer usage they would need to have an *average* of at least one medical record, two prescriptions and one additional health data (for example a blood pressure measurement) recorded per patient per year[313]. The date at

which recording of deaths in the practice was deemed to have reached an acceptable level was the start date of the period when the observed number of deaths in the practice was consistently within 30% of the expected number of deaths for that time period, given the age-gender distribution of the practice (using the "acceptable mortality rate date" or "AMR date" as defined by the database providers[314]).

3.3.3 Intended use of data source

The intention was to use the data source to estimate time trends in incidence of major CHD and T2DM within different demographic groups (objectives i and ii), and to explore the relationship between the time trends in T2DM and in major CHD (objective v).

3.3.4 Identification of cases of major CHD or T2DM

A patient was identified as having had a major CHD event if the general practitioner (GP) had recorded a Read code in the patient's records relating to major CHD. All Read codes that referred to major CHD were identified as follows: An initial list of all CHD events was obtained using a previously published list of Read codes for all CHD in The Key Health Statistics (KHS) from General Practice[315]. Then the list was narrowed down to those codes referring to major CHD only (specifically acute MI or to an ECG result corresponding to an MI), with the aid of my Clinical Supervisor. The Read code dictionary was scanned to identify any extra relevant codes not captured in the KHS, for example codes added to the Read code dictionary subsequent to publication of the list. Finally the list was compared with that in the Quality and Outcomes Framework (QOF) rules for CHD management[316] (which describes how

General Practices will be assessed on CHD management and lists all the Read codes used to identify CHD patients).

Patients were identified as having T2DM if they had at least one diagnosis in the medical records with a Read code indicating T2DM *or* if they had Read codes for non-specific diabetes and were aged 30 years or over on the date of the first diabetes diagnosis, and had no codes at any time to indicate T1DM. The inclusion of non-specific diabetes codes was because many patients did not have a code specifically indicating T1DM or T2DM. Indeed 20% of the patients included as having T2DM in the analyses had only non-specific codes. Because of the stipulation of being aged over 30 years on the first diagnosis date, the majority of patients with these non-specific codes should have T2DM, and although we cannot rule out the possibility that some patients will have late onset T1DM (particularly the youngest patients), the number of misclassified patients is likely to be very small. A list of relevant Read codes pertaining to diabetes was obtained from scratch using established methods[317] by first selecting those Read codes from the chapter C10 (Diabetes mellitus) and including additionally any other Read codes from other chapters whose descriptions included words starting with "diab" or including acronyms such as "NIDDM" (non-insulin dependent diabetes mellitus) or "DKA" (diabetic keto-acidosis) or the word "insulin". All codes identified were checked manually that they did in fact refer to the patient having diabetes, and the resulting code list was checked by a clinician.

3.3.5 Ascertainment of socio-demographic characteristics

Demographic characteristics available were age (from year of birth information), gender, and constituent UK country of residence. In addition, the deprivation of the local area in which the patient resides has been obtained by means of anonymised linkage of the patient's postcode. The local area is defined to be an enumeration district, covering a population of approximately 150 households. Deprivation of the local area is assessed by computing the Townsend score[318] of multiple deprivation for the local area, using 2001 census data. The Townsend score combines the following criteria: the percentage of households without access to a car; the percentage of households not in owner occupied accommodation; the percentage of households in overcrowded accommodation; the percentage of the economically active population aged 16-74 who are unemployed. To maintain anonymity, the exact scores are not available; instead each patient is assigned to a quintile of area deprivation based on the quintiles of Townsend score for the UK population as a whole. When a patient moves home, their score is updated in the database to reflect the new area of residence.

3.3.6 Description of study population

The THIN database comprises General Practices from across the UK, including Northern Ireland. The number of practices and patients belonging to THIN is transient and varies each year. Table 3.3 presents the number of General Practices and patients contributing to THIN and the proportion of the UK population included in THIN in the latest update (to 2009) by calendar year. The number of General Practices and patients contributing to THIN increased year on year from 1988 to 2009, with the exception of the most recent year 2009, likely due to delays in

collecting 2009 data from some practices. The coverage of the UK population also increased steadily with calendar year, to over 6% in the most recent five years. The distributions of basic demographic characteristics of patients in THIN, according to calendar year from 1994, are shown in table 3.4 (data before 1994 is limited). The mean age of patients contributing data to THIN in each calendar year remained approximately constant, rising only very gently from 40 to 41 years over the period. The proportion of patients who were male also remained constant at slightly under half. While the proportions of patients within each fifth of Townsend score of deprivation of area of residence remained largely fixed, the proportions of patients resident in each country of the UK did change. Specifically, with increased calendar year the proportion of patients from Northern Ireland, Scotland and Wales generally rose, from a combined proportion of 11% in 1994 to 16% in 2009. According to population data from the Office for National Statistics, in 2009 49% of the UK population was male, a proportion corresponding closely to that for patients in THIN. The same data source gives the proportions of the UK population residing in England, Wales, Scotland and Northern Ireland in 2009 as 83.8%, 4.9%, 8.4% and 2.9% respectively. By comparison, in 2009 the proportion of THIN patients residing in England, Wales, Scotland and Northern Ireland were 83.5%, 6.4%, 6.7% and 3.3% respectively. Therefore by 2009 Wales and Northern Ireland are slightly overrepresented in THIN, while Scotland is underrepresented. In earlier calendar years Northern Ireland was also underrepresented in THIN. Table 3.4 shows that throughout the period patients were not evenly distributed across the five Townsend deprivation quintiles; there were fewer people in THIN in the two most deprived quintiles than the other quintiles. Since the quintiles are based on the distribution of deprivation in the UK as a whole, this indicates that the THIN database population is

less deprived than the UK population as a whole. It has been shown that THIN is nationally representative in terms of CHD prevalence, when compared with QOF data[319] and incidence of CHD is comparable to that in the UK QResearch Primary Care database[320]. A further study found data on diabetes in THIN to correspond well with data in the Health Survey for England[6].

3.3.7 Strengths in relation to intended analyses

The key strength is the very large number of patients contributing to the THIN database, enabling precise estimation of the time trends in major CHD and T2DM incidence within different demographic groups, and precise estimation of annual major CHD and T2DM incidence (towards objectives i and ii). The large size is such that estimates are still precise enough when the population is restricted to just those patients with T2DM, to explore the relationship between T2DM and major CHD incidence (objective v). A second advantage is the nationwide scope of the THIN database, encompassing men and women of all ages, regardless of health status, and so including those (typically most vulnerable) groups of patients frequently ineligible to participate in randomised controlled trials and cohort studies. Thus the findings are widely applicable and generalisable. In these ways the THIN database complements the BRHS.

The key limitation is the paucity of risk factor data. The nature of this routine database is such that coronary and diabetic risk factors (smoking, blood pressure levels, lipid levels, physical activity, adiposity etc) are not necessarily recorded by the GP, either on a regular basis or at all. Moreover the risk factors remain inconsistently measured, with variations in recording levels between practices and importantly for

this thesis, over time, leading to potentially biased trend estimates. Therefore, inference of the contribution of risk factor changes to disease trends is less feasible and so analyses using THIN are mainly restricted to describing the major CHD and T2DM time trends.

3.4 The Whitehall II Study

3.4.1 Description of data source

The opportunity arose to analyse data from a second observational cohort study – the Whitehall II cohort[37]. Between 1985 and 1988, all men and women, aged 35-55years, in 20 civil service departments in London (the target study population) were invited to participate, by letter, in a screening examination. The response rate, after excluding those who were ineligible, was 73% (74% among men, 71% among women), resulting in recruitment of a total of 10308 patients who attended the screening examination and also completed a baseline questionnaire.

3.4.2 Description of follow-up

Nine follow-up phases, identified as phases 1 to 9 in chronological order have been completed at the time of writing. At phase 1 (baseline, 1985-8), phase 3 (1991-3), phase 5 (1997-9), phase 7 (2002-4) and phase 9 (2007-2009) the participants attended clinical screening examinations, where physical measurements were made and blood samples taken, and questionnaires were completed. At phase 2 (1989-1990), phase 4 (1995-1996), 6 (2001) and 8 (2006) the participants completed questionnaires only. The questionnaires in all phases incorporated questions relating to social and demographic characteristics such as age; health status; work characteristics; social

networks and type of social supports; and health behaviours such as smoking status and diet. A summary of the different follow-up phases, along with the corresponding response rates is given in table 3.5. Data from the screening phases 1, 3, 5 (for the risk factors) and 1, 3, 5 and 7 (for the events) were made available for the analysis in this thesis. Participants were also flagged at the National Health Service Central Registry, which provided information on the date and cause of death.

3.4.3 Intended use of data source

The intention is to use to the data source to carry out analyses comparable to those carried out in the BRHS – in particular to investigate the contribution of risk factor changes to the decline in major CHD risk (objective iii). The data will be used to a) compare and contrast the results for this select professional group based in and around London against the findings in the national BRHS and so assess the degree of coherence between the results from the two studies b) extend the analyses to women.

3.4.4 Assessment of major CHD events

Fatal CHD events were identified from flagging with the National Health Service Central Registry as a record of death with CHD as the underlying cause, including sudden death of presumed cardiac origin (international classification of diseases, ninth revision, codes 410-414). Potential new cases of nonfatal MI were ascertained from questionnaire items on chest pain and the physician's diagnosis of heart attack in the questionnaires up to phase 7 (2002-4). Confirmation of each potential nonfatal MI case according to MONICA criteria was sought, using data from ECGs, markers of myocardial necrosis, and chest pain history from the patient's GP-held medical

records. Only those nonfatal MIs confirmed as such according to the MONICA criteria were included as events in the analyses.

3.4.5 Repeated assessment of coronary risk factors

At each of the three study phases: baseline (1985-8), phase 3 (1991-3), and phase 5 (1997-9), cigarette smoking status, physical activity levels, elements of diet and alcohol consumption were ascertained from the lifestyle questionnaires, while fasting lipid levels, SBP and BMI were obtained from clinical examinations, using consistent techniques each time[321, 322]. Total cholesterol was measured in a centrifugal analyser by enzymic colorimetric methods. HDL cholesterol was determined after precipitation with dextran sulphate-magnesium chloride[321]. Non-HDL cholesterol was again computed as the difference between total and HDL cholesterol. At baseline, 9065 participants (88%) had no HDL cholesterol measurement, but serum apolipoprotein-A1 was available for almost 80% of participants[321]. Alcohol consumption in the previous week was measured as units per week, then categorised as none, within recommended limit for gender (<21 units for men, <14 units for women), over recommended limit, and very heavy (>50 units for men and >35 units for women). Cigarette smoking categories were non-smoker, ex-smoker, and current smoker. Dietary data available was usual milk consumption (categorised as none, whole milk, semi-skimmed, skimmed and other), usual bread consumption (white, wholemeal, granary or wheatmeal, other brown bread, other) and usual fruit and vegetable consumption (<3 times/week, 3-4 times/week, 5-6 times/week, daily, ≥2 times/day). Physical activity was measured by self-report of frequency and duration of mild, moderate and vigorous intensity activities. At Phase 5, the questionnaire was modified to include 20 items on frequency and duration of different physical activities e.g.

walking, cycling, sports. Hours per week of moderate and vigorous activity were computed using these data. Activity levels were then categorised as low, medium or high with low corresponding to <2 hours per week of moderate activity and <1 hour of vigorous activity; high corresponding to ≥2.5 hours per week of moderate activity or >1 hour of vigorous activity; and medium corresponding to levels in between low and high[323].

3.4.6 Sub-study 1: Derivation of HDL cholesterol at baseline

As stated in section 3.4.5, 9065 participants (88%) had no baseline HDL cholesterol data, however most participants had serum apolipoprotein-A1. Age and gender-adjusted linear regression of the available baseline HDL data on apolipoprotein-A1 was used to estimate the relationship between the two variables and then predict baseline HDL for those participants without this measure. Baseline HDL measurements were available for 1217 (11.8%) of participants (those aged 45-55 at baseline). There is a strong correlation (0.8) between baseline HDL cholesterol and baseline Apolipoprotein-A1 for these participants (figure 3.3). Given this correlation, simple linear regression of baseline HDL cholesterol on baseline Apolipoprotein-A1 (centred at the mean value), adjusting for age and gender, was used to estimate the relationship between the two measurements. Powers of Apolipoprotein-A1 (squared, cubed etc.) were added consecutively into the model until no longer significant. The resulting regression model was used to predict the missing baseline HDL cholesterol measurements.

The final regression model took the form:

Variable	Coefficient (95% CI)	Standard error	P-value
a*	0.0123472 (0.0116141, 0.0130803)	0.0003737	<0.001
a^2	0.0000329 (0.0000127, 0.0000532)	0.0000103	0.001
a^3	-0.000000781 (-0.00000106, -0.000000506)	0.000000140	<0.001
age†	-0.0024061 (-0.0064422, 0.00163)	0.0020572	0.242
sex	0.1177088 (0.0896203, 0.1457972)	0.0143168	<0.001
constant term	1.320945 (1.117275, 1.524614)	0.1038109	<0.001

*a = Apolipoprotein-A1, centred at the mean value of 154.4g/L
†age = age at baseline $R^2 = 0.6704$; Root mean squared error = 0.22745.

Note that while squared and cubic terms in Apolipoprotein-A1 were significant, they were so close to 0 as to make little difference to the HDL cholesterol estimates, although they are included in the final model. HDL cholesterol measurements in later phases were not used to predict the earlier measurements as it was felt this could lead to an artificially induced trend in HDL cholesterol. In all, HDL cholesterol was predicted in this way for 7,372 of the 9,065 participants missing this variable; the remaining participants were also missing Apolipoprotein-A1, preventing HDL cholesterol prediction.

3.4.7 Description of study population

The study population comprised at baseline in 1985-1988 6,895 men (67%) and 3,413 women, aged 35 to 55 years, and predominantly white (89%). Key characteristics (including socio-demographic characteristics, coronary and diabetic risk factor levels, and prevalent CHD or T2DM) of the study population at baseline are presented in table 3.6. 38% of men in Whitehall II belonged to the two most senior employment

grades at baseline, compared to 11% of women. Half of the 3,413 women in the Whitehall II cohort instead belonged to the clerical employment grade, ranked as the most junior. Employment grade is taken to be a marker for socioeconomic position, with the more senior grades corresponding to a higher socioeconomic status. 16% of men and 23% of women were current smokers. 22% of men and 42% of women had low physical activity levels. Mean alcohol consumption was 13 units per week for men and 6 units per week for women. In terms of diet, the type of milk most frequently consumed was whole milk (over half of men and women); among breads wholemeal was favoured (over 40% of men and women); and over half of men and women consumed fruit and vegetables at least daily. Very few men and women in this London-based cohort had a history any CHD (2% of men and 1.5% of women), while <1% of men and women had had an MI before baseline. Mean BMI was 24.6kg/m^2 among men and 24.8kg/m^2 among women. 40% of men and women were overweight or obese. Mean SBP was 124.6mmHg among men and 120.1mmHg among women. Mean total cholesterol levels among men and women were similar at 5.98mmol/L and 5.92mmol/L respectively. However women had higher mean HDL cholesterol levels and lower non-HDL cholesterol levels. Details of exclusions for particular analyses are given in the relevant results chapter. The levels of total cholesterol, HDL cholesterol, non-HDL cholesterol, systolic blood pressure, BMI, cigarette smoking and history of CHD and MI among men in Whitehall II were more favourable than in men in the BRHS at baseline. This may partly reflect the slightly younger age-range and later baseline, but may also be associated with the confined geographic scope and more favourable socio-economic circumstances of participants in Whitehall II (no manual workers or unemployed) compared with the BRHS.

3.4.8 Strengths in relation to intended analyses

As discussed in section 3.4.3, I have obtained access to this second cohort to enable me to repeat the analysis of the role of risk factors in the decline in major CHD carried out in the BRHS (objective iii). The value of repeating the analysis using this additional source of data is firstly the extension of the findings to women since the cohort comprises both men and women, as opposed to the BRHS study population. Although THIN comprises both men and women too, the lack of risk factor data renders THIN unsuitable for these analyses. Secondly, since this type of analysis (individual level time trends analysis) has not been carried out in the UK population before (as discussed in chapter 2, section 2.6.1), the repetition of the analyses in a second data source is important to assess the robustness of the findings. Thirdly, as the socio-economic circumstances are on average more favourable among participants in Whitehall II compared with men in the BRHS, the analyses will indicate whether the findings differ given differing (more favourable) circumstances. While socio-economic data is available in the BRHS, the study population is too small to enable reliable, adequately powered subgroup analyses by socio-economic group. Fourthly, measures of key biochemical risk factors were taken approximately every five to six years, enabling more precise estimation of trends in risk factors than possible for the BRHS which currently has only two physical examinations, twenty years apart. Repeated dietary data is also available, enabling some exploration of the role of diet. The key limitation of the Whitehall II cohort however is that the London-based cohort is not geographically representative of Britain, hence the use of the BRHS as the primary data source for this thesis on national trends.

Table 3.1 **Attrition and questionnaire response rates in the British Regional Heart Study**

	Lost to follow-up at time-point*:		**Remaining participants†:**	**Response rate:**
Time-point	**Deaths**	**Emigrations, participants living overseas, ONS cancellations, and those self-withdrawn from study**	**Total remaining survivors able to participate**	**Total remaining participants responding to questionnaire (%)**
5-years follow-up 1983-1985	290	49	7396	7275 (98%)
12-14 years follow-up 1992	1136	115	6484	5925 (91%)
16-18 years follow-up 1996	1562	177	5996	5263 (88%)
20-years follow-up 1998-2000	2080	139	5516	4252 (77%)‡
23-25 years follow-up 2003	2718	127	4890	3980 (81%)
25-27 years follow-up 2005	3173	81	4481	3540 (79%)

Notes:
Emigrations, participants living overseas, ONS cancellations, and those self-withdrawn from study is not a cumulative count (unlike the deaths, which increase with time) as some participants withdrawn or emigrated or overseas at one time-point may be re-enter the study at a later time-point
*Total number lost to follow-up by time-point
†Remaining participants = 7735 – (deaths + emigrations etc), where 7735 is the total number of participants at baseline
‡The lower response rate at 20-years follow-up compared to both earlier and later years reflects that only men who attended the physical examination at this time-point were asked to complete the questionnaire; postal questionnaires at the other time points were sent to all men

Table 3.2 Key **characteristics of the British Regional Heart Study men at baseline (1978-80)**

	Men aged 40-49 years, N = 3,736	**Men aged 50-60 years, N = 3,999**	**All men, N = 7735**
	N (%)	**N (%)**	**N (%)**
Region of Britain			
South	1122 (30.0)	1158 (29.0)	2280 (29.5)
Midlands & Wales	614 (16.4)	594 (14.9)	1208 (15.6)
North England	1546 (41.4)	1739 (43.5)	3285 (42.5)
Scotland	454 (12.2)	508 (12.7)	962 (12.4)
Missing	*0*	*0*	*0*
Socio-economic position			
I Professional	327 (8.8)	279 (7.0)	606 (7.8)
II Intermediate	869 (23.3)	866 (21.7)	1735 (22.5)
III Skilled non-manual	353 (9.5)	367 (9.2)	720 (9.3)
III Skilled manual	1544 (41.4)	1782 (44.7)	3326 (43.1)
IV Semi-skilled	367 (9.8)	417 (10.5)	784 (10.2)
V Unskilled	155 (4.2)	163 (4.1)	318 (4.1)
Armed forces	116 (3.1)	115 (2.9)	231 (3.0)
Missing	*5*	*10*	*15*
Cigarette smoking			
Never	1081 (29.0)	738 (18.5)	1819 (23.6)
Ex-smoker	1163 (31.2)	1552 (38.9)	2715 (35.2)
Current smoker; 1-19 a day	532 (14.3)	656 (16.4)	1188 (15.4)
Current smoker; 20 a day	377 (10.1)	458 (11.5)	835 (10.8)
Current smoker;21-39 a day	405 (10.9)	441 (11.0)	846 (11.0)
Current smoker;40 or more	168 (4.5)	148 (3.7)	316 (4.1)
Missing	*10*	*6*	*16*
Alcohol consumption			
None	174 (4.7)	292 (7.3)	466 (6.0)
Occasional	893 (23.9)	952 (23.8)	1845 (23.9)
Light	1193 (31.9)	1351 (33.8)	2544 (32.9)
Moderate	1028 (27.5)	1014 (25.4)	2042 (26.4)
Heavy	446 (11.9)	386 (9.7)	832 (10.8)
Missing	*2*	*4*	*6*
Body mass index, kg/m^2			
<20	121 (3.2)	148 (3.7)	269 (3.5)
20-24.99	1702 (45.6)	1576 (39.4)	3278 (42.4)
25-29.99	1627 (43.5)	1923 (48.1)	3550 (45.9)
30-39.99	286 (7.7)	347 (8.7)	633 (8.2)
40+	0 (0)	2 (0.1)	2 (0.03)
Missing	*0*	*3*	*3*
Physical activity			
Inactive	288 (7.8)	398 (10.1)	686 (9.0)
Occasional	1039 (28.1)	1306 (33.2)	2345 (30.7)
Light	813 (22.0)	948 (24.1)	1761 (23.1)
Moderate	590 (16.0)	615 (15.6)	1205 (15.8)
Moderately vigorous	663 (17.9)	457 (11.6)	1120 (14.7)
Vigorous	301 (8.1)	212 (5.4)	513 (6.7)
Missing	*42*	*63*	*105*

Table 3.2 *continued*. **Key characteristics of the British Regional Heart Study men at baseline (1978-80)**

	Men aged 40-49 years, N = 3,736	Men aged 50-60 years, N = 3,999	All men, N = 7735
	N (%)	**N (%)**	**N (%)**
History of myocardial infarction			
No	3404 (91.1)	3379 (84.5)	6783 (87.7)
Yes	332 (8.9)	620 (15.5)	952 (12.3)
Missing	*0*	*0*	*0*
History of coronary heart disease†			
No	3003 (80.4)	2788 (69.7)	5791 (74.9)
Yes	733 (19.6)	1211 (30.3)	1944 (25.1)
Missing	*0*	*0*	*0*
History of diabetes mellitus (type 1 or 2)			
No	3693 (98.9)	3933 (98.4)	7626 (98.7)
Yes	40 (1.1)	64 (1.6)	104 (1.3)
Missing	*3*	*2*	*5*
Use of blood pressure medication			
No	3637 (97.4)	3715 (93.0)	7352 (95.1)
Yes	96 (2.6)	279 (7.0)	375 (4.9)
Missing	*3*	*5*	*8*
	Mean (sd)	**Mean (sd)**	**Mean (sd)**
Body mass index, kg/m^2	25.4 (3.2)	25.6 (3.3)	25.5 (3.2)
Missing	*0*	*3*	*3*
Systolic blood pressure, mmHg	141.4 (19.2)	148.7 (22.0)	145.2 (21.0)
Missing	*4*	*4*	*8*
Diastolic blood pressure, mmHg	81.6 (12.9)	82.8 (13.5)	82.2 (13.2)
Missing	*6*	*4*	*10*
Total cholesterol, mmol/L	6.29 (1.07)	6.30 (1.02)	6.30 (1.04)
Missing	*22*	*23*	*45*
HDL cholesterol, mmol/L	1.14 (0.26)	1.15 (0.27)	1.15 (0.27)
Missing	*149*	*166*	*315*
Non-HDL cholesterol, mmol/L	5.15 (1.11)	5.15 (1.07)	5.15 (1.09)
Missing	*152*	*168*	*320*

Notes:

*Socio-economic position based on longest-held occupation of men at baseline, using the Registrar General's Social Class Classification – I Professionals (e.g. physicians and engineers); II Intermediate (e.g. teachers and sales managers); III Skilled non-manual (e.g. clerks and shop assistants); III Skilled manual (e.g. bricklayers); IV Semi-skilled (e.g. postmen); V Unskilled (e.g. porters and general labourers) and lastly, Armed forces

†History of coronary heart disease includes angina and/or myocardial infarction

Table 3.3 **Total numbers of General Practices and patients contributing data to THIN and coverage of the UK population by calendar year**

Year	No. of practices contributing patient data on 30 June of year*	No. of patients contributing data on 30 June of year	Total UK population (mid-year counts)‡	% coverage of UK population†
1988	7	26,539	56,916,448	0.05
1989	10	42,109	57,076,451	0.07
1990	37	226,430	57,237,493	0.40
1991	52	312,084	57,438,658	0.54
1992	62	396,162	57,584,530	0.69
1993	73	488,315	57,713,889	0.85
1994	78	539,833	57,862,145	0.93
1995	84	596,120	58,024,799	1.03
1996	103	788,839	58,164,374	1.36
1997	125	1,037,038	58,314,249	1.78
1998	150	1,241,705	58,474,943	2.12
1999	191	1,620,773	58,684,427	2.76
2000	248	2,140,318	58,886,065	3.63
2001	289	2,528,339	59,113,497	4.28
2002	334	2,981,521	59,318,779	5.03
2003	372	3,317,392	59,552,182	5.57
2004	387	3,461,688	59,841,892	5.78
2005	412	3,693,249	60,235,498	6.13
2006	416	3,828,620	60,584,338	6.32
2007	422	3,947,871	60,985,677	6.47
2008	424	4,047,366	61,398,226	6.59
2009	409	3,950,335	61,791,956	6.39

Notes:

Number of patients contributing data on 30 June is computed by counting the number of patients for whom 30 June of that year lies between the patient's "entry date" and "exit date". A patient's "entry date" = maximum of (date of patient registration at practice, date when practice data recording became at an acceptable level) and a patient's "exit date" = minimum of (date of death, date of patient transfer out of practice, date of last data collection from practice). Number of practices contributing patient data on 30 June is computed by counting the number of practices for which the number of patients contributing data on 30 June is greater than zero.

*Number of practices in each calendar year is less than the total of 446 practices contributing data to THIN over the whole period as practices start and stop contributing data at different time-points

‡mid-year count of UK population from Office for National Statistics http://www.statistics.gov.uk

†% coverage of UK population = 100% × no. of patients contributing data on 30 June / mid-year count of UK population

Table 3.4 **Demographic characteristics of THIN patients by calendar year (every 3rd year selected)**

	Year					
	1994	**1997**	**2000**	**2003**	**2006**	**2009**
Total patients	539,833	1,037,038	2,140,318	3,317,392	3,828,620	3,950,335
Mean age in years (sd)	39.9 (23.2)	40.3 (23.3)	40 (23.3)	40.2 (23.3)	40.6 (23.4)	41.2 (23.5)
Gender, N (%)						
Male	265063 (49.1)	505788 (48.8)	1047591 (48.9)	1619953 (48.8)	1865550 (48.7)	1914186 (48.5)
Female	274770 (50.9)	531236 (51.2)	1092648 (51.1)	1697230 (51.2)	1962722 (51.3)	2035728 (51.5)
Unknown/indeterminate	*0*	*14*	*79*	*209*	*348*	*421*
Townsend score of deprivation of area of residence, N (%)						
1 = least deprived	138927 (28.3)	267160 (28.0)	523291 (26.7)	787181 (26.0)	898738 (25.5)	913603 (25.4)
2	107684 (21.9)	212144 (22.2)	440358 (22.5)	684633 (22.6)	799559 (22.7)	801136 (22.3)
3	92057 (18.7)	184090 (19.3)	403543 (20.6)	632039 (20.8)	741826 (21.0)	755743 (21.0)
4	84765 (17.3)	171188 (17.9)	351530 (17.9)	554852 (18.3)	646327 (18.3)	669169 (18.6)
5 = most deprived	67930 (13.8)	120361 (12.6)	241216 (12.3)	374262 (12.3)	439189 (12.5)	460658 (12.8)
Unknown	*48,470*	*82,095*	*180,380*	*284,425*	*302,981*	*350,026*
Country of UK, N (%)						
England	480076 (88.9)	928423 (89.5)	1892113 (88.4)	2827158 (85.2)	3201578 (83.6)	3300359 (83.5)
Northern Ireland	13364 (2.5)	14605 (1.4)	40081 (1.9)	99071 (3.0)	141704 (3.7)	130626 (3.3)
Scotland	18673 (3.5)	45241 (4.4)	103475 (4.8)	221746 (6.7)	259056 (6.8)	265408 (6.7)
Wales	27713 (5.1)	48768 (4.7)	104648 (4.9)	169416 (5.1)	226281 (5.9)	253941 (6.4)
Unknown	*7*	*1*	*1*	*1*	*1*	*1*

Notes: *Area of residence updated in database if patient moves home; Townsend score corresponds to area of residence record closest to calendar year of interest

Table 3.5 **Follow-up phases for the Whitehall II study and response rates**

Phase	Dates	Type of data collection	No of participants	Response Rate*
1	1985-1988	Screening + questionnaire	10,308	-
2	1989-1990	Questionnaire	8,132	79%
3	1991-1994	Screening + questionnaire	8,815	86%
4	1995-1996	Questionnaire	8,628	84%
5	1997-1999	Screening + questionnaire	7,870	76%
6	2001	Questionnaire	7,355	71%
7	2002-2004	Screening + questionnaire	6,967	68%
8	2006	Questionnaire	7,173	70%
9	2007-2009	Screening + questionnaire	6,761	66%

Notes:
Reproduced from the Whitehall II cohort website: http://www.ucl.ac.uk/whitehallII/study-phases
*Response rate defined as proportion of Phase 1 responders who participated in the follow-up phase. Note the difference in definition to that for the British Regional Heart Study, where the response rate was the proportion of those eligible to participate in the relevant follow-up stage (so excluding those who died prior to the follow-up stage from the denominator).

Table 3.6 **Key characteristics of the Whitehall II cohort at baseline (1985-1988)**

	Men, N = 6,895	**Women, N = 3,413**	**All participants, N = 10,308**
	N (%)	**N (%)**	**N (%)**
Employment grade*			
Civil Service grades 1-6 (=most senior)	1015 (14.7)	118 (3.5)	1133 (11.0)
Civil Service grade 7	1632 (23.7)	263 (7.7)	1895 (18.4)
Senior Executive officer	1228 (17.8)	198 (5.8)	1426 (13.8)
Higher Executive officer	1498 (21.7)	478 (14)	1976 (19.2)
Executive officer	881 (12.8)	660 (19.3)	1541 (15.0)
Clerical (=most junior)	641 (9.3)	1696 (49.7)	2337 (22.7)
Missing	*0*	*0*	*0*
Cigarette smoking			
Never	3259 (47.7)	1803 (53.2)	5062 (49.5)
Ex-smoker	2482 (36.3)	792 (23.4)	3274 (32.0)
Current smoker	1090 (16.0)	793 (23.4)	1883 (18.4)
Missing	*64*	*25*	*89*
Body mass index, kg/m2			
<20	326 (4.7)	284 (8.3)	610 (5.9)
20-24.99	3843 (55.8)	1800 (52.8)	5643 (54.8)
25-29.99	2362 (34.3)	953 (27.9)	3315 (32.2)
30-39.99	347 (5.0)	351 (10.3)	698 (6.8)
40+	5 (0.1)	23 (0.7)	28 (0.3)
Missing	*12*	*2*	*14*
Physical activity			
Low	1455 (22.2)	1311 (41.6)	2766 (28.5)
Medium	643 (9.8)	400 (12.7)	1043 (10.8)
High	4447 (67.9)	1442 (45.7)	5889 (60.7)
Missing	*350*	*260*	*610*
Usual milk consumption			
None	201 (2.9)	140 (4.1)	341 (3.3)
Whole milk	4121 (60.0)	1777 (52.4)	5898 (57.5)
Skimmed milk	1339 (19.5)	578 (17.1)	1917 (18.7)
Semi-skimmed milk	1047 (15.3)	766 (22.6)	1813 (17.7)
Other/combination	156 (2.3)	127 (3.7)	283 (2.8)
Missing	*31*	*25*	*56*
Usual bread consumption			
White bread	1533 (22.3)	659 (19.5)	2192 (21.4)
Wholemeal	2860 (41.7)	1461 (43.2)	4321 (42.2)
Granary or wheatmeal	1068 (15.6)	511 (15.1)	1579 (15.4)
Other brown bread	186 (2.7)	77 (2.3)	263 (2.6)
Combination	1215 (17.7)	671 (19.9)	1886 (18.4)
Missing	*33*	*34*	*67*
Usual fruit and vegetable consumption			
<3 times per week	882 (12.8)	323 (9.5)	1205 (11.7)
3 or 4 times per week	1062 (15.4)	463 (13.6)	1525 (14.8)
5 or 6 times per week	1124 (16.3)	443 (13)	1567 (15.3)
Daily	2790 (40.6)	1487 (43.7)	4277 (41.6)
≥2 times per day	1018 (14.8)	683 (20.1)	1701 (16.6)
Missing	19	14	33

Table 3.6 *continued* **Key characteristics of the Whitehall II cohort at baseline (1985-1988)**

	Men, N = 6,895	Women, N = 3,413	All participants, N = 10,308
	N (%)	**N (%)**	**N (%)**
History of myocardial infarction			
No	6860 (99.5)	3412 (99.97)	10272 (99.7)
Yes	34 (0.5)	1 (0.03)	35 (0.3)
Missing	*1*	*0*	*1*
History of coronary heart disease†			
No	6753 (98.0)	3363 (98.6)	10116 (98.2)
Yes	141 (2.0)	50 (1.5)	191 (1.9)
Missing	*1*	*0*	*1*
	Mean (sd)	**Mean (sd)**	**Mean (sd)**
Body mass index, kg/m2	24.6 (3.1)	24.8 (4.3)	24.6 (3.5)
Missing	*12*	*2*	*14*
Systolic blood pressure, mmHg	124.6 (14.1)	120.1 (15.7)	123.1 (14.8)
Missing	*14*	*1*	*15*
Alcohol consumption, units/week	12.8 (14.5)	5.50 (7.7)	10.4 (13.1)
Missing	*55*	*39*	*94*
Total cholesterol, mmol/L	5.98 (1.16)	5.92 (1.18)	5.96 (1.17)
Missing	*35*	*39*	*74*
HDL cholesterol‡, mmol/L	1.28 (0.31)	1.60 (0.37)	1.39 (0.37)
Missing	*1,719*	*779*	*2,498*
Non-HDL cholesterol, mmol/L	4.71 (1.15)	4.31 (1.16)	4.58 (1.17)
Missing	*1,722*	*785*	*2,507*

Notes:
*Employment grade is used as a marker for socio-economic position (more junior grade corresponds to a lower socio-economic position)
†History of coronary heart disease includes angina and/or myocardial infarction
‡HDL cholesterol data includes imputed values

Figure 3.1 **The 24 towns constituting the British Regional Heart Study**

Reproduced with permission from the British Regional Heart Study

Figure 3.2 **Timeline for the British Regional Heart Study, illustrating follow-up of study men and collection of data used in the thesis**

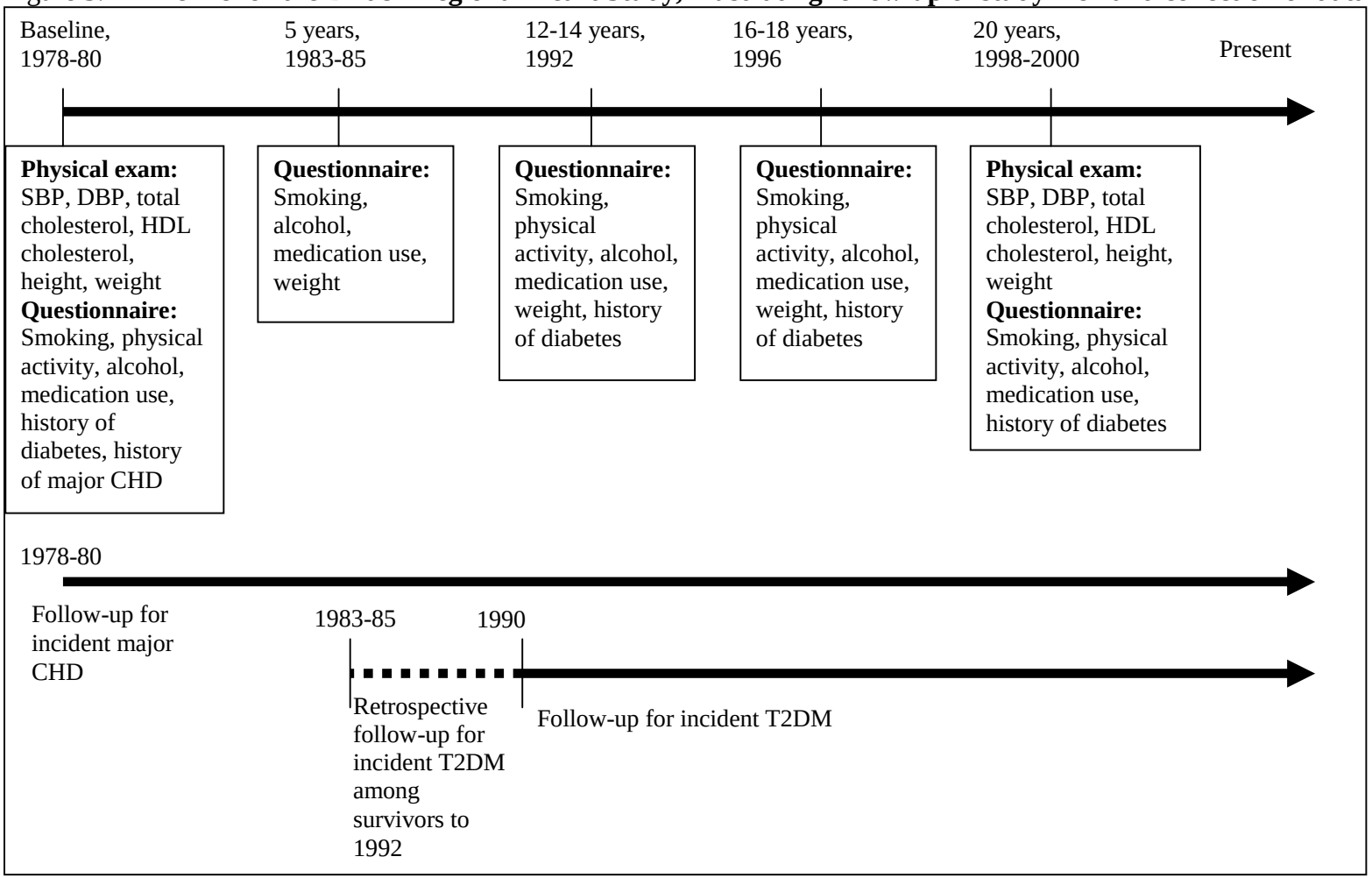
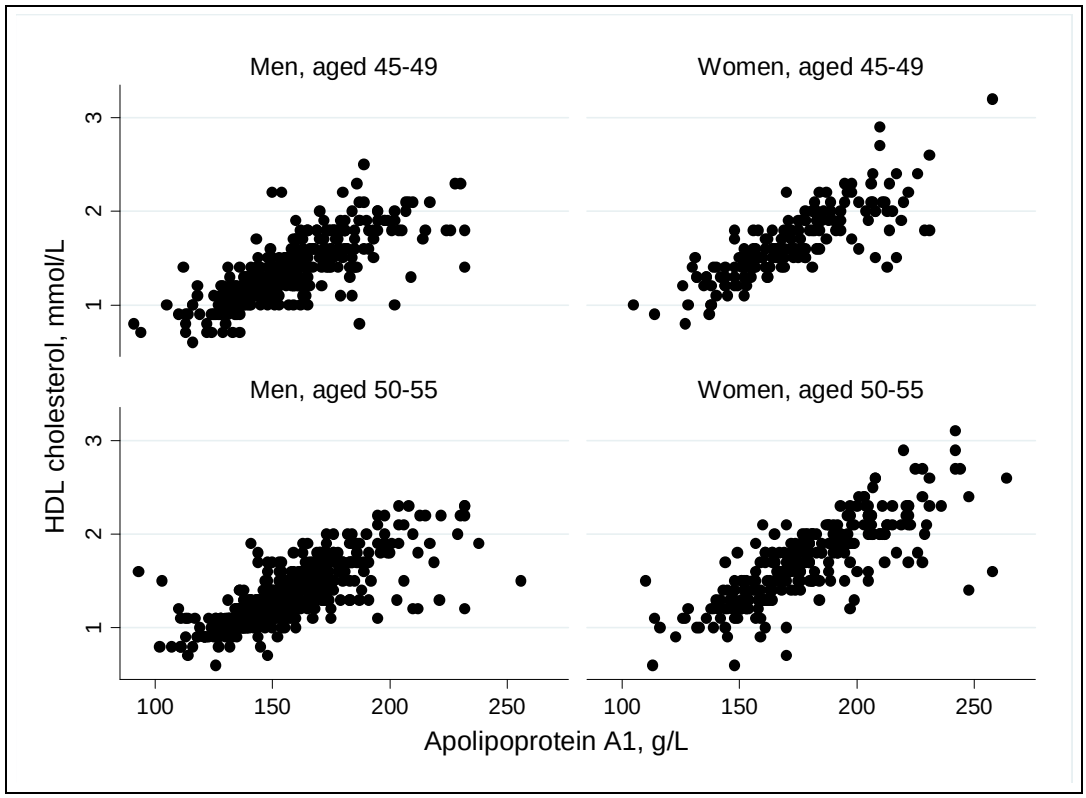


Figure 3.3 **HDL cholesterol against Apolipoprotein-A1 for 1,217 participants with both measurements at baseline in Whitehall II, according to age and gender**



Chapter 4: Estimating recent time trends in incidence of major coronary heart disease and type 2 diabetes in the UK using data from The Health Improvement Network and two cohort studies

4.1 Introduction

Chapter 2 highlighted the striking but divergent time trends in coronary heart disease (CHD) mortality and type 2 diabetes (T2DM) prevalence which have occurred in the UK in recent decades. The good news is that CHD mortality has been declining since the 1960s, and the CHD mortality rate is now roughly one-quarter of what it was in 1961[1]. In contrast the time trend in T2DM has been unfavourable; the combined evidence suggesting T2DM prevalence to have more than doubled since the 1980s[2-6]. As outlined in chapter 2, a step towards unpicking and understanding these time trends is to establish to what extent they reflect trends in incidence of these conditions. The existing literature suggests that congruous time trends in CHD[1, 2, 20-24] and T2DM incidence[4, 6, 25, 26] have indeed occurred. However, the data on time trends in incidence is limited, reflecting the difficulty in measuring incidence. There is a paucity of data particularly on more contemporary time trends from the 1990s to the present, and on trends within different socio-demographic groups, to ascertain whether some groups are experiencing greater changes in incidence than others.

The aim of this chapter is therefore to estimate recent time trends, particularly from the 1990s to the present, in incidence of major CHD and T2DM in the UK. This corresponds to objectives i) and ii) of the overall thesis objectives. Overall time trends, as well as time trends according to different socio-demographic characteristics (gender, age, UK region and socio-economic background) are described. Data from the Health Improvement Network (THIN) will primarily be used for the analyses.

The very large number of patients in this nationally representative database, with data on demographic characteristics and CHD and T2DM diagnoses, enables precise estimation of the time trends in CHD and T2DM incidence according to demographic characteristics. Incidence trends will also be estimated in the smaller British Regional Heart Study (BRHS) and Whitehall II cohorts (major CHD only for Whitehall II), to establish concordance between the different data sources. This will help to determine the extent to which the subsequent analyses in future chapters, using the rich risk factor data in these two cohorts to attempt to explain the time trends, may be representative and generalisable to the wider UK population.

Objectives

Estimate for men and women in the UK from the 1990s to the present:

1. The time trend in incidence of major CHD
2. The time trend in incidence of T2DM

overall and according to age, gender, socio-economic background and geographic region

The structure of this chapter is as follows: Section 4.2 details methods. Section 4.3 presents results specific to the first objective to estimate time trends in major CHD incidence, using THIN data. Section 4.4 presents results specific to the second objective to estimate time trends in T2DM incidence, using THIN data. In section 4.5 the time trends in major CHD and T2DM in the BRHS and Whitehall II cohorts are presented and compared with the estimates from THIN. The findings are then discussed in section 4.6.

4.2 Methods

4.2.1 Data sources

As explained in the previous section, the THIN database is principally used for these analyses, while the time trends will be also estimated in the BRHS (major CHD and T2DM) and Whitehall II (major CHD only) to assess the comparability between the data sources.

4.2.2 THIN Study sample

Trends in incidence of major CHD and T2DM were assessed over the 14 year period from 1 January 1995 to 31 December 2008, reflecting the earliest year that an adequate number of practices were first contributing data of acceptable completeness (see chapter 3, section 3.3.2, for details) and the latest complete year that data was available at the time of analysis. Two cohorts of patients in THIN were followed retrospectively for incident major CHD or incident T2DM over this time. To be included in the analyses, men and women had to be registered at a contributing THIN practice for at least some time between 1995 and 2008 (the time for which they could be followed-up for incident events). The patients also had to be at least 30 years old or less than 100 years old for some of that time (incidence of both conditions below the age of 30 is negligible and too few patients attained over 100 years of age). Patients were excluded if they were only temporarily registered or in a small number of cases, where their data was inconsistent (for example, a birth date after a death date). Whole practices were excluded if they had no data at all on social deprivation.

For the analyses of time trends in incidence of major CHD, patients with evidence of a history of major CHD prior to follow-up for incident events were excluded. For the

analyses of time trends in incidence of T2DM, patients with evidence of a history of any diabetes (T1DM or T2DM or diabetes unspecified) prior to follow-up for incident events, were excluded. Although patient data has only been fully captured in the THIN database from the early 1990s, historic data charting patient medical histories is available for many patients. Therefore it is possible to identify and exclude most prevalent cases. A previous study showed further that for patients who newly register at an existing contributing THIN practice, all previous medical history tends to be added to their records but often with an "event date" as the date of registration (or close to it), as opposed to the historic date that the diagnosis was made[324]. In this way such events may appear as new incident cases rather than prevalent cases. This can be seen from plots of incidence rates of diagnoses against time from registration, which show anomalously high incidence rates close to the registration date, if these events are assumed to have occurred at the given "event date"[324]. To avoid artificially inflating incidence rates, therefore, patients were followed for incident events only from a year after their registration date, and were excluded from analyses if they had a record of an event before this time (which would most likely be prevalent), or had less than one years worth of data from their registration date.

For the time trend in major CHD, patients with a history of stable or unstable angina (but no prior major CHD event) or who developed angina during the follow-up were retained for analysis. This is because developing angina does not preclude subsequently having a major CHD event. For the time trend in T2DM, participants who had a record of T1DM or a record of a complex or non-standard diabetes at any time before or during the follow-up were excluded. This is because the presence of another form of diabetes either precludes development of T1DM or, if transient, such

as gestational diabetes, these patients are likely to differ considerably in terms of their T2DM risk relative to the rest of the population. Non-standard diabetes cases leading to exclusion were: gestational diabetes, drug-induced diabetes, malnutrition related diabetes, secondary diabetes related to e.g. cystic fibrosis. A full list of Read codes denoting non-standard cases is given in the Appendix A.1. In addition, if the first new record relating to diabetes during the follow-up implied prevalent diabetes (for example it related to treatment of existing diabetes), the patient was excluded as a prevalent case. The flowcharts in figures 4.1 and 4.2 detail the numbers of patients included and excluded for the analyses of CHD incidence and of T2DM incidence respectively.

4.2.3 Follow-up

Patients were followed for incident major CHD or T2DM from a start date of the latest of: 1 January 1995, date practice began providing "acceptable quality" data (see chapter 3, section 3.3.2, for details – maximum of acceptable computer usage date and acceptable mortality rate date), date the patient had been registered at the practice for one year, and date the patient turned 30 years old. Patients were followed until an end date defined as the earliest of: 31 December 2008, date the patient left the practice, date the practice left THIN, date of death of the patient. Note that unlike traditional cohort studies, this analysis therefore involves an "open" cohort in the sense that patients do not all have the same baseline date but may enter and leave the cohort at different times.

4.2.4 Principal outcome as a first major CHD event

A first major CHD event was identified as the first occurring Read code (based on the associated "event date") in the patient medical records during the follow-up time relating to major CHD (see chapter 3, section 3.3.4, for details). Read codes used to define major CHD are listed in Appendix A.2 along with the frequencies with which they occurred in each calendar year. Included are codes corresponding to myocardial infarction (MI), NSTEMI, STEMI and non-specific MI. Unstable angina and non-specific acute coronary syndrome codes were excluded. The types of codes used vary over time as more codes are made available or recording preferences change. Trends in the incidences of different types of codes over time are shown in figure 4.3.

4.2.5 Principal outcome as a first diagnosis of T2DM

A first diagnosis of T2DM was identified principally as the first occurring Read code (based on the associated "event date") in the patient medical records during the follow-up time relating to a T2DM diagnosis (see chapter 3, section 3.3.4, for details). There were also a number of records related only to diabetes in general, without specifying type 1 or type 2. As outlined in chapter 3, section 3.3.4, since the participants were aged at least 30 years, any new non-specific diabetes record was assumed to refer to T2DM, and included as an incident T2DM case (provided there were no T1DM records anywhere else in the patient records). Of course we cannot rule out the possibility that some of these diabetes cases are late onset T1DM, particularly among the youngest patients, although the number of patients misclassified in this way is likely to be very small as to have little influence on the results. Records of insulin-dependent diabetes were also included, provided there were no other codes to indicate T1DM, as insulin may be indicated for T2DM. The

prevalences of the different Read codes for the incident T2DM cases in the cohort are given in Appendix A.3. Trends in the incidences of different types of codes over time are shown in figure 4.4.

4.2.6 Socio-demographic characteristics

Time trends in incidence of major CHD and T2DM were estimated according to each of the following socio-demographic characteristics: gender, age, socio-economic position, and residing country of the UK (England, Wales, Scotland, or Northern Ireland). Age was grouped into 5-year categories for the purposes of tabulating incidence rates by age, gender and calendar period, and grouped into 10-year categories for the purposes of estimating time trends by age-group. The oldest patients aged 80 and over were combined into a single group to avoid small categories. Socio-economic position was defined at area level using the Townsend score for social deprivation of local area of residence, grouped by quintiles (using the postal address record closest to start of follow-up if more than one record was found) as described in chapter 3, section 3.3.5.

4.2.7 Statistical methods

The choice of statistical methods used for the analysis was partially a pragmatic decision to overcome computational limitations. The vast size of the dataset prevented the patient data, stored separately for each practice, from being combined into a single dataset. Instead, for each practice in turn, and for each outcome in turn (an incident major CHD event or a new T2DM diagnosis), the total number of events and total person-years of follow-up for each combination of: calendar year, age group, gender, UK country and social deprivation quintile, were computed. The grouped

data was then combined into a single dataset and a Poisson regression model applied to this grouped data, regressing the total number of events on calendar year, adjusting for age and gender, to estimate the yearly change in the incidence of each outcome over the follow-up period. The log(total person-years) was used as an offset. Squared and cubic terms in calendar time were added to assess whether the log(incidence rate) increased linearly with time. Interactions between calendar time and gender, age-group, deprivation and UK country were added in turn to estimate trends within each demographic group.

General Practices contribute data to THIN over differing time periods so not all practices will be present throughout the follow-up period of interest (1995 to 2008), as illustrated in table 3.3 in chapter 3. Indeed only 72 practices contribute data in every year of the period. Any variation in major CHD or T2DM incidence rates between practices could therefore potentially confound the estimates of the time trends in these outcomes. To account for the potential clustering effect of general practice, random intercept multi-level Poisson models were used, with the different socio-demographic patient groups nested in practices.

Graphs of incidence rates against calendar year were also plotted, to visually examine the pattern of incidence over time. Incidence rates by 5-year age group, 5-year calendar period and gender were tabulated.

4.2.8 Analyses using BRHS and Whitehall II data

4.2.8.1 BRHS

The definitions of major CHD and T2DM used in the BRHS are given in chapter 3, section 3.2.4. To explore the secular time trends in the incidence of major CHD or T2DM some restructuring of the data was needed. The follow-up for each man was split into consecutive 5-year periods: 1980 to 1984; 1985 to 1989; 1990 to 1994; 1995 to 1999; 2000 to 2004 and 2005 to 2007. Within each period survival times were censored at death or end of the period, whichever came sooner, and men were excluded from the period if they had had an event before the period. The incidence of major CHD or T2DM in the different periods was then compared, adjusting for age, to assess secular trends over time. Specifically Cox proportional hazards regression applied to this split dataset, with calendar time (of start of period) as a covariate, was used to estimate the yearly change in the hazard of the outcome of interest (major CHD or T2DM) over the follow-up period. Age was used as the underlying time scale, with date of birth as a time origin, and age at start of each period as a delayed entry time to take account of left truncation. Use of an age time scale, as well as automatically adjusting for age[325], permitted calendar time to be entered into the model as a covariate so that the hazard of the outcome associated with calendar time could be estimated. Schoenfeld residuals were used to test the proportional hazards assumption[326]. The Cox models were stratified by the socio-demographic categories where this assumption was not met. Interactions between calendar time and country of Great Britain (England, Wales, Scotland), and socio-economic status (based on longest occupation held, in seven categories) were added to the Cox model. The follow-up for each man was then split further into 10-year age-bands, resulting in separate observations for each period/age-band combination for each man. An

interaction between age-band (as a categorical variable) and calendar time was added to the Cox model. Point estimates and 95% confidence intervals (CIs) of the incidence rate of each outcome within each 5 year period and 5 year age-band were computed from the doubly split dataset, and tabulated to enable comparison of the overall levels of incidence in each calendar period and age-band, with that obtained for men in THIN data. Note that incidence of first major CHD events was assessed only to 2004 (the most recent complete year of follow-up at time of analysis). As outlined in chapter 3, section 3.2.4, incident T2DM data with validated diagnosis dates were available from the 5-year follow-up in 1983-5 but were available only among survivors (to 1992) before 1990. Therefore T2DM incidence was primarily assessed in the periods from 1995 to 2007 (latest follow-up date for T2DM at time of analysis). In line with the analysis of THIN data, men with angina (either at baseline or during follow up) were retained for the major CHD analysis, unless they also developed major CHD. Men were included in the analysis of time trends in incidence of T2DM unless they had died or had a previous diagnosis of T2DM or T1DM before 1995.

To make as full use of the available data on T2DM as possible, and to attempt to explore trends in T2DM before 1995, the analyses of the time trends in T2DM were repeated including the period 1985 to 1994, that is to assess trends over the 23 year period between 1985 and 2007. Since T2DM incident data before 1992 was only available for survivors to at least 1992, to ensure a fair and unbiased estimate of the trend in incidence between 1985 and 2007, the analysis was carried out among that sub-group of men who survived to the end of the follow-up in 2007 only. In this way the men were treated in the same way throughout the follow-up period thus avoiding

bias in the estimate of the time trend. The disadvantage of this analysis of survivors is that it is uncertain how representative the time trend in this sub-group is of the wider population. To explore this issue, the time trend over just the later period between 1995 and 2007 among this sub-group was also estimated and then compared with the trend estimated for the full cohort of men in the original analyses to assess how closely the time trend among the survivors is likely to reflect that of the wider cohort.

4.2.8.2 Whitehall II cohort – incidence of major CHD only

Incident major CHD events (defined as detailed in chapter 3, section 3.4.4) were ascertained between 1985 and 2004. The same methods were used to estimate time trends in major CHD hazard as those used for the BRHS men. The follow-up for each participant was split into consecutive 5-year periods: 1985 to 1989; 1990 to 1994; 1995 to 1999; and 2000 to 2004. Then Cox proportional hazards regression applied to this split dataset, with calendar time (of start of period) as a covariate, was used to estimate the yearly change in the hazard of major CHD over the follow-up period, with censoring and age time-scale as for the BRHS. Interactions between calendar time and gender, and between calendar time and socio-economic status (based on Civil Service employment grade, in three categories[327]) were added to the Cox model, and, after further splitting of the dataset into 5-year age-bands, an interaction between calendar time and age-band was also added. Residing location was not considered as all participants were London-based. Tabulations of incidence rates by age, gender and calendar period were made as above using the doubly-split dataset.

Again, participants with angina (either at baseline or during follow up) were retained for analysis, unless they also developed major CHD.

4.2.9 Secondary analyses to further assess comparability between data sources

A key difference between the analyses of the different data sources, is that the time trends estimates from regression of THIN data are based on yearly incidence rates, while (reflecting the smaller sizes of the cohorts), the time trends estimates from the regression models of BRHS and Whitehall II were necessarily based on 5-yearly incidence rates. A second difference is that Poisson models were used for the THIN data (reflecting the necessity to group the data), while Cox's model was used for the cohort data (avoids assuming fixed incidence rates with time from start of each period). Secondary analyses were carried out i) on THIN data, grouping the data into 5-year periods as for the cohorts and ii) on BRHS and Whitehall II data, using Poisson models, to investigate more closely the comparability between the different data sources.

4. 3 Results - Time trend in incidence of major coronary heart disease: The Health Improvement Network

There were 2,927,137 patients aged between 30 and 100 years old eligible for inclusion in the analyses of incidence of major CHD between 1995 and 2008, from 434 general practices. Exclusions are detailed in the flow chart in figure 4.1. There were 1,421,694 (49%) men and 1,505,443 women. A total of 36,459 first major CHD events occurred during 17,236,482 person-years of follow-up between 1 January 1995 and 31 December 2008 corresponding to an overall event rate of 2.12 events per 1000 person years (95% CI 2.09 to 2.14). Among men, 22,834 major CHD events occurred during 8,268,407 person-years of follow-up, corresponding to an event rate of 2.76 events per 1000 person years (95% CI 2.73 to 2.80). Among women 13,625 major CHD events occurred during 8,968,075 person-years of follow-up, corresponding to

an event rate of 1.52 events per 1000 person years (95% CI 1.49 to 1.55). Table 4.1 presents the major CHD incidence rate for men and women by age and 5-year calendar period (1995-1999, 2000-2004 and 2005-2008). Among men, declines over calendar time in the incidence rate within each age group can be seen (looking down each column). However for the youngest age groups (under 40 years), where incidence rates are already less than 1 per 1000 person-years in 1995-1999, the differences between calendar periods are modest. Among women, declines in the incidence rate over time are seen in age groups above 55 years. Under 55 years, again where incidence rates are already less than 1 per 1000 person-years in 1995-1999, the incidence rates appear to have remained relatively constant over time. As expected, incidence is lower among women throughout and increases with age. Figure 4.5, which make use of the large number of patients contributing to each calendar year, to plot yearly incidence rates for men and women respectively, shows further that the decline is reasonably steady over time, except for a relatively large fall from 1995 to 1996, particularly among men.

Table 4.2 presents incidence rates of major CHD averaged over the first three years (1995 to 1997) and last three years of the study period (2006-2008), and the absolute changes in incidence between these two periods, according to demographic groups. Overall, incidence fell from 3.05 events per 1000 person years (95% CI 2.96 to 3.15) in 1995-1997 to 1.73 (95% CI 1.70 to 1.76) in 2006-2008, corresponding to an absolute decline of 1.32 events per 1000 person years (95% CI 1.22 to 1.42). Despite larger absolute declines among older age groups, the strong positive age gradient in incidence persisted over the study period. Incidence among men was roughly double that for women in both 1995 to 1997 and 2006 to 2008 and the absolute decline

among men was also almost double that for women. A deprivation gradient in incidence was apparent in both 1995 to 1997 and 2006 to 2008, with incidence rising with increasing quintile of Townsend score of area deprivation. A reverse gradient was seen for the absolute decline in incidence, with the greatest absolute decline in the most deprived quintile. Incidence of major CHD was highest in Scotland and Northern Ireland in 1995 to 1997, compared to England and Wales, and remained so in 2006 to 2008. Similar absolute declines in incidence occurred in England, Wales and Scotland; the absolute decline in Northern Ireland was slightly greater.

From multi-level random intercept Poisson regression (table 4.3), the average annual percentage decline in the rate of major CHD over the course of the follow-up from 1995 to 2008 was 4.88% (95% CI 4.59 to 5.18), adjusting for age and gender, corresponding to a total relative decline over 14 years from 1995 to 2008 of 50% (95% CI 48 to 53). A squared term in calendar year was not significant (p=0.8) reflecting the apparently steady and reasonably linear decline over time as observed in figure 4.5. Men experienced a slightly larger average annual age-adjusted relative decline than women: 4.92% (95% CI 4.55 to 5.29) compared with 4.79% (95% CI 4.30 to 5.27), but this difference was not statistically significant (p=0.8). Thus, although the larger absolute decline in men suggests incidence to have improved most in men, the relative declines suggest instead that men and women have benefited similarly. This reflects the higher incidence rate among men initially. Due to the similar relative declines, the gender inequality in incidence has persisted. There was some variation in the trend in major CHD incidence by age ($p<0.001$ for interaction between age group and calendar year). The largest declines occurred among the 60-69 and 70-79 year age groups (average annual relative declines of 6.55%, 95% CI 5.97 to

7.13, and 6.36%, 95% CI 5.82 to 6.89 respectively). Relatively modest relative declines (between 2.5% and 2.9% per annum) occurred among those over 80 years and under 50 years, in line with the observed age-gender specific incidence rates in Table 4.1. The rate of decline in major CHD incidence fell with increasing quintile of area deprivation (defined using the Townsend score), p=0.007 for deprivation-calendar year interaction. In order of increasing deprivation from least deprived to most deprived quintile, the average annual percentage declines in incidence of major CHD were: 5.51% (95% CI 4.91 to 6.11), 5.15% (95% CI 4.54 to 5.76), 4.98% (95% CI 4.34 to 5.62), 4.80% (95% CI 4.15 to 5.44), and 3.69% (95% CI 2.93 to 4.45). This pattern is converse to the trend in absolute declines, as the least deprived quintiles saw the least absolute declines. This again reflects that the most deprived areas had higher incidence rates initially. The gradient in the relative declines has led to persistence in the deprivation inequality in incidence. Incidence of major CHD appeared to decline slightly faster in Wales and Scotland (average annual age-gender adjusted relative declines of 5.45%, 95% CI 4.16 to 6.73, and 5.28%, 95% CI 4.11 to 6.44, respectively), than in England (4.90%, 95% CI 4.58 to 5.22) and Northern Ireland (4.07%, 95% CI 2.22 to 5.89), although these regional differences were not significant (p=0.5).

4.4 Results - Time trend in incidence of type 2 diabetes: The Health Improvement Network

There were 2,853,030 patients aged between 30 and 100 years old eligible for inclusion in the analyses of incidence of T2DM between 1995 and 2008, from 434 general practices. Exclusions are detailed in the flow chart in figure 4.2. There were 1,393,366 (49%) men and 1,459,664 women. A total of 80,896 patients developed

T2DM during 16,637,711 person-years of follow-up between 1 January 1995 and 31 December 2008 corresponding to an overall incidence rate of 4.86 events per 1000 person years (95% CI 4.83 to 4.90). 44,383 men developed T2DM during 8,030,195 person-years of follow-up, corresponding to an incidence rate of 5.53 events per 1000 person years (95% CI 5.48 to 5.58). 36,513 women developed T2DM during 8,607,516 person-years of follow-up, corresponding to an incidence rate of 4.24 events per 1000 person years (95% CI 4.20 to 4.29). Table 4.4 presents the T2DM incidence rates for men and women by age and 5-year calendar period (1995-1999, 2000-2004 and 2005-2008). Among both men and women up to the age of 60 years, incidence of T2DM appears to have risen across all three periods. Among men and women aged over 60 years, incidence in 2000-2004 was higher than in 1995-1999, but incidence in 2005-2008 was more or less the same as in 2000-2004. Incidence increased with age up to 74 years, and was lower in women. As most new cases occur among the older age groups, the pattern among the older age groups (of an increase in incidence only initially, followed by relatively constant incidence rates) has greater influence on the overall time trends, presented in figure 4.6, which plots overall yearly incidence rates for all men and women respectively, regardless of age. In line with the incidence rates in the table 4.4, according to the figure 4.6, between 1995 and 1998-1999 a modest increase in incidence of T2DM was generally seen, among both men and women. After 1998-1999 incidence appears to have increased at a faster rate until around 2002. Finally, from about 2002 to the end of the follow-up in 2008, the incidence rate appeared to remain relatively constant.

Table 4.5 presents incidence rates of T2DM averaged over the first three years (1995 to 1997) and last three years of the study period (2006-2008), and the absolute

changes in incidence between these two periods, according to demographic groups. Overall, incidence rose from 3.15 events per 1000 person years (95% CI 3.07 to 3.23) in 1995-1997 to 5.25 (95% CI 5.19 to 5.31) in 2006-2008, corresponding to an absolute increase of 2.10 events per 1000 person years (95% CI 2.00 to 2.20), larger than the absolute decline in major CHD incidence in the same population. Larger absolute increases occurred among the older age groups, such that incidence remained higher in the older age groups. A larger absolute increase occurred in men, than in women, and since incidence was already higher in men in 1995-1997, this resulted in a greater absolute difference in incidence between men and women in 2006-2008. A deprivation gradient in incidence was apparent in both 1995-1997 and 2006-2008, with incidence rising with increasing quintile of Townsend score of area deprivation. There was no clear trend in the absolute change in incidence by deprivation quintile, although the most deprived quintile experienced a larger absolute increase in incidence relative to the other deprivation quintiles. Incidence of T2DM was highest in Scotland in 1995-1997, compared to England, Wales and Northern Ireland, and remained so in 2006-2008. Similar absolute increases in incidence occurred in Wales, Scotland and Northern Ireland; the absolute increase in England was slightly smaller.

From multi-level random intercept Poisson regression (table 4.6), the average annual percentage increase in the incidence of T2DM over the course of the follow-up from 1995 to 2008 was 3.60% (95% CI 3.83 to 5.18), adjusting for age and gender, corresponding to a total relative increase over 14 years from 1995 to 2008 of 64% (59 to 69). Squared and cubed terms in calendar year were significant ($p<0.001$) reflecting varying rates of change in incidence over the period, as observed in figure 4.6. Men experienced a slightly larger average annual age-adjusted relative increase

than women: 3.89% (95% CI 3.58 to 4.2) compared with 3.34% (95% CI 3.00 to 3.68), ($p=0.02$ for interaction between gender and calendar year), in line with the larger absolute change in incidence in men, and resulting in a widening of the gender inequality in incidence. The rate of increase in T2DM incidence was greater in younger age groups (up to 59 years), reflecting the pattern seen in Table 4.4 ($p<0.001$ for age-calendar year interaction). Average annual relative increases of 5.02% (95% CI 3.87 to 6.19) and 5.49% (95% CI 4.82 to 6.17) occurred in the 30-39 and 40-49 year age groups. Among those aged 80 years and over, the corresponding figure was 2.51% (95% CI 1.81 to 3.21). Since incidence is lower in younger age groups, this suggests that the younger age groups may be catching up with the older age groups in terms of incidence; that is, new cases of T2DM are being increasingly identified at younger ages. As for the absolute changes, the average annual age-adjusted relative increase in incidence was highest in the most deprived deprivation quintile: 4.99% (95% CI 4.40 to 5.58) ($p<0.001$ for deprivation- calendar year interaction). In the other deprivation quintiles, the average annual relative increase ranged from 3.12% to 3.86%. This suggests a widening inequality, with T2DM incidence in the most deprived quintile even higher relative to the other quintiles than previously. In relative terms, T2DM incidence rose fastest in Northern Ireland (average annual age-gender adjusted relative increase of 4.84, 95% CI 3.22 to 6.49) and slowest in Wales (2.65, 95% CI 1.68 to 3.63), although the differences were not significant ($p=0.1$). Similar relative increases occurred in England and Scotland of 3.62 (95% CI 3.37 to 3.87) and 3.66 (95% CI 2.69 to 4.63). The higher rate of increase in T2DM incidence in Northern Ireland has meant that overall T2DM incidence in this constituent country has gone from being initially lower than in the other constituent countries, to on par with the other countries by the end of the period.

4.5 Results – Comparison with British Regional Heart Study and Whitehall II cohort

4.5.1 Major CHD incidence

4.5.1.1 BRHS overall incidence rates

Of the 7735 men recruited, 981 experienced a definite or possible MI before 1 January 1980 (the start of the follow-up period of interest) and so were excluded from this analysis. Of the remaining 6754 men, 1240 were recorded as having a first MI over 135,721 person-years of follow-up between 1 January 1980 and 31 December 2004 giving an overall event rate of 9.14 events per 1000 person-years, (95% CI 8.64 to 9.65). Incidence rates by 5-year age group and period (table 4.7) were broadly consistent with those among men in THIN (for those periods and age-groups covered by both data sources), except that incidence in THIN was lower in the very oldest age groups.

4.5.1.2 Whitehall II overall incidence rates

Of 10,308 participants recruited, one had no follow-up data and 35 reported an MI before baseline and so were excluded from analysis. The remaining 10,272 participants included 6,860 (67%) men and 3,412 women. A total of 382 first major CHD events occurred during 155,309 person-years of follow-up between 1 January 1985 and 31 December 2004; 307 major CHD events occurred among men during 105,508 person-years of follow-up and 48 major CHD events occurred during 49,800 person-years of follow-up among women. The overall incidence rates were 2.46 events per 1000 person-years (95% CI 2.22 to 2.72) among all participants, 2.91 (95% CI 2.60 to 3.25) among men and 1.51 (95% CI 1.20 to 1.89) among women. Again,

incidence rates by gender, and 5-year age group and calendar period (tables 4.8 and 4.9), are consistent with those in THIN.

4.5.1.3 Time trends in major CHD incidence in the different studies

Table 4.10 presents the average annual relative declines in major CHD hazard in the BRHS and Whitehall II cohorts, estimated from Cox regression analyses, adjusted for age and gender, overall and according to demographic group. The estimates are presented alongside the corresponding estimates of the relative declines in major CHD incidence in THIN for comparison.

There was no evidence of departure from the proportional hazards assumption of the Cox regression in the BRHS analyses. However, in Cox regression analyses of the Whitehall II cohort, the proportional hazards assumption was not met for gender so all models were stratified by gender.

The average annual decline in major CHD hazard in the Whitehall II cohort was 4.24% (95% CI 1.92 to 6.51), adjusting for age and gender, corresponding to a 20-year fall over 20 years from 1985 to 2004 of 58% (95% CI 32 to 74). This is consistent with the average annual decline in major CHD incidence of 4.88% observed in THIN from 1995-2008; the figure of 4.88% is included in the CI for the Whitehall II figure. Adjusting for age, the hazard rate of major CHD in the BRHS cohort fell on average by 3.3% (95% CI 2.1 to 4.5, $p<0.001$) per annum, corresponding to a fall of 57% (95% CI 42% to 68%) over the 25-year follow-up period from 1980 to 2004. This is a smaller average annual decline than that observed in THIN; the CI excludes 4.88%. However, in further analyses of the BRHS,

restricting the time period to 1985-2004 (matching that in Whitehall II), the average annual decline rose to 4.06% (95% CI 2.64 to 5.46), a figure more consistent with that of Whitehall II and THIN, suggesting that the relative decline in major CHD has been greater in more recent years.

The estimates of the decline in major CHD hazard in the BRHS and Whitehall II according to demographic group in Table 4.10 should be interpreted with caution as the estimates are very imprecise (wide CIs) due to the small numbers within each group. That said, reassuringly, the overall patterns across demographic groups observed in THIN are generally replicated in the two cohorts, including the increasing rates of decline in major CHD with falling deprivation, the slightly smaller rate of decline in men (Whitehall II), and the faster decline in Wales compared to England and Scotland (BRHS). The findings for age group are less consistent with THIN. However due to the ageing of the cohorts, not all age groups are present in the analyses for the whole time-period (as illustrated in tables 4.7, 4.8 and 4.9), and thus within each cohort, the time trends by age correspond to different time-periods and so may not be directly comparable.

Secondary analyses, designed to make the analyses of the different data sources as comparable as possible, were carried out. In particular, using grouped Poisson regression for the BRHS and Whitehall II cohorts (instead of Cox regression), and modelling calendar time in 5-year periods in the THIN regression models (instead of in years). Further the THIN analyses were restricted to those aged 40 to 70 years to match the age-range of the cohorts more closely. These alterations made little difference to the results.

4.5.2 T2DM incidence

4.5.2.1 BRHS overall incidence rates – all men

6016 of the 7735 men initially recruited in 1978-1980 were included in the present analyses. The remainder had died (1373, 18%), or had a diagnosis of diabetes, type 1 or type 2, (346, 4%) prior to the start of the follow-up period on 1 January 1995. Of 6016 men, 526 developed T2DM over 62,043 person-years of follow-up between 1 January 1995 and 31 December 2007 giving an overall event rate of 8.48 events per 1000 person-years, (95% CI 7.78 to 9.23). Incidence rates by 5-year age group and period (table 4.11) were broadly consistent with those among men in THIN.

4.5.2.2 BRHS overall incidence rates – survivors

The analyses were repeated considering incidence of T2DM from 1985 to 2007, but among only those men who had survived to the end of the follow-up in 2007, to ensure a fair comparison between time periods given the nature of the data on incidence of T2DM prior to 1995 (available for survivors only), as detailed in section 4.2.8.1. A total of 3949 men survived to 2007 so were included in the analysis. Of these men, 524 developed T2DM over 86,489 person-years of follow-up between 1 January 1985 and 31 December 2007 giving an overall event rate of 6.06 events per 1000 person-years, (95% CI 5.56 to 6.60). The incidence rates of T2DM by 5-year age group and 5-year calendar period are shown in table 4.12. The incidence rates for the latter three periods 1995-1999, 2000-2004 and 2005-2007 agree closely with those for the full cohort, and for THIN men.

4.5.2.3 Time trends in incidence of T2DM in the different studies

Table 4.13 presents the average annual relative increases in T2DM hazard in the BRHS, among all men and among survivors only, estimated from Cox regression analyses, adjusted for age, overall and according to demographic group. The estimates are presented alongside the corresponding estimates in THIN for comparison. There was some evidence of departure from the proportional hazards assumption of the Cox regression for constituent country so results are stratified by country.

Adjusting for age, the hazard rate of T2DM among all men in the BRHS cohort increased on average by 5.3% (95% CI 2.7 to 8.0, $p<0.001$) per annum, corresponding to almost a doubling in the hazard, that is an increase of 96% (95% CI 41% to 173%) over the 13-year follow-up period from 1995 to 2007. Considering survivors only, over the extended period from 1985 to 2007, the average annual increase in the hazard of T2DM, adjusting for age, was 7.69% (95% CI 5.51 to 9.92), corresponding to a four and a half fold increase over the whole 23-year period. This is a larger relative increase than for the whole cohort. However, in further analyses of the survivors, restricted to the same period of 1995 to 2007 as for the whole cohort, the hazard rate of T2DM increased in this survivor sub-group on average by 5.3% (95% CI 2.3 to 8.4, $p<0.001$) per annum. This is very similar to the time trend in T2DM observed over this period for the whole cohort, indicating that the discrepancy relates to the different time-periods (with a faster relative increase in the 1980s) rather than a difference between survivors and the whole cohort. This suggests that the findings on incidence prior to 1995 in this group of survivors may be extended to the rest of the cohort too.

The estimate of an average annual increase of 5.3% in the BRHS between 1995 and 2007 is larger than that in THIN from 1995 to 2008 (3.6%). However, the discrepancy may be explained by the observed "flattening" of the time trend in incidence in the most recent years, which appears to exert increasing influence on the overall time trend estimates with every additional year included. In further analyses, restricting the period by just one year in THIN to 1995-2007 (to match that of the BRHS analysis), the average annual increase rises to 4.35% (95% CI 4.08 to 4.61). Restricting further to 1995-2006, the average annual increase is 5.37% (95% CI 5.05 to 5.69), emphasizing the increasing influence of the flattening of the time trend on the overall trend estimate.

Again, the patterns in the time trend in relation to the different demographic characteristics are largely consistent across the data sources. All three data sources show that T2DM incidence increased at a broadly similar rate in the 50-59, 60-69 and 70-79 year old age groups, while the rate of increase in T2DM incidence is greatest in the most deprived area (THIN) and lowest socio-economic status (BRHS). Wales experienced the smallest rate of increase in T2DM incidence compared with England and Scotland according to all three data sources.

Secondary analyses, designed to make the analyses of the different data sources as comparable as possible, using grouped Poisson regression (BRHS and Whitehall II), and modelling calendar time in 5-year periods (THIN) made little difference to the results.

4.6 Discussion

4.6.1 Summary of main findings

Analysis of data from the THIN primary care database indicates that over the 14 year period from 1995 to 2008, incidence of major CHD has fallen on average by 4.88% per annum, adjusting for age and gender. This corresponds to an overall relative decline of 50%. The fall has been reasonably steady over this period, and represents an absolute fall in incidence of 1.32 fewer events per 1000 person years. Over the same period, incidence of T2DM has risen, with an average annual age-gender adjusted relative increase of 3.60%, corresponding to a total relative increase of 64% and an absolute increase of 2.10 more events per 1000 person years, thus a larger absolute change than for major CHD. Unlike the trend in major CHD, the rate of increase in incidence in T2DM appears to vary considerably over the period; slow from 1995 to 1998-1999, faster from 1999 to 2003 and then limited beyond 2003. Overall incidence of both conditions was around 3 events per 1000 person years in 1995. T2DM incidence rose to over 5 events per 1000 person years in 2008, while major CHD incidence fell to 1.75 events per 1000 person years.

There was some variation in the time trends in incidence of major CHD and of T2DM by demographic characteristics. For both conditions, there was a deprivation inequality with more favourable trends (a faster relative decline in major CHD and a slower relative increase in T2DM) occurring in more affluent areas. Slightly faster relative changes in both CHD and T2DM occurred among men compared with women, although the differences were small. In terms of constituent country, the most favourable trends occurred in Wales (fastest relative fall in incidence of major CHD and slowest relative increase in incidence of T2DM) while the least favourable

trends occurred in Northern Ireland (slowest relative fall in incidence of major CHD and fastest relative increase in incidence of T2DM).

4.6.2 Strengths and limitations of analysis of THIN database

The key strengths of the THIN database analyses, particularly by comparison with the two cohorts, include the very large sample size and nationwide scope, including men and women of all ages across the UK, enabling precise estimates of national trends.

There are variations in incidence between different general practices and different practices contributed data at different time-points. However, multilevel models, including practice as a random effect, enabled adjustment for this potential confounding effect of practice on the time trends.

The broad lists of Read codes used to identify major CHD and T2DM ensured as far as possible that changes in the choices of Read codes used by GPs over time do not influence the time trend estimates. In terms of the types of Read codes used for major CHD, codes to identify specifically STEMI and NSTEMI events have been increasingly used since about 2002 (figure 4.3 and Appendix A.2). However, at the same time, use of a code for "MI not otherwise specified" and other more general MI codes has fallen, suggesting that rather than capturing more CHD events not previously recorded by use of these extra codes post 2002, GPs are using these more specific codes in place of the more general codes to record the same types of events. The steady time trend in major CHD incidence supports this. Regarding Read codes for T2DM, both codes specifically for T2DM, and codes for general diabetes were assumed to relate to T2DM as patients were aged over 30 years. As for major CHD,

over time there appears to have been a switch to from non-specific to specific codes, this time from codes for general diabetes to codes specifically for T2DM (figure 4.4 and Appendix A.3). It is possible that some of the general diabetes codes relate to T1DM, rather than T2DM. Since the general diabetes codes are used more frequently in earlier years, this would lead to overestimation of incidence rates particularly in earlier years and in turn underestimation of the rise in incidence over time. However, T1DM cases represent a small proportion of all diabetes cases in the population (~10%)[9], and the vast majority of new cases among the over 30s are T2DM. Therefore, the impact of inclusion of T1DM cases is likely to be minimal. Indeed, the incidence rates and the time trend in T2DM estimated, correspond closely to those observed in the BRHS, and to other data sources (once analyses are restricted to the same time-period).

Individual-level data on socio-economic status is not available. However the area-level Townsend deprivation score in THIN is arguably a good proxy for individual socioeconomic status as it is based on areas of only a small number (~150) of households such that misclassification is unlikely. The comparability between the results by Townsend deprivation score in THIN and by occupational socio-economic status in BRHS and Whitehall II supports this.

The THIN database is subject to certain limitations reflecting that the data is routinely collected and not obtained specifically for research purposes. Patient data in THIN are accrued only from registration at the practice and when computerised records of patient visits were available, rather than from birth. Some major CHD events and T2DM records occurring before the patient registered or patient data was captured on

computer may be undetected. As a result it is not always possible to ascertain if a major CHD event or T2DM diagnosis during the follow-up is truly incident. However, it has been shown that major historical diagnoses (including major CHD or T2DM) do tend to be recorded at registration; diagnoses recorded close to the registration date in THIN are most likely records of patient history rather than new incident events[324]. Moreover, T2DM, as a chronic condition, generally necessitates regular monitoring (at least once a year), such that 99.7% of T2DM records in THIN occur less than one year before the next record, a consistent finding across all calendar years. Allowing a year after registration before following up patients for incident events (and excluding patients with an event during that year as prevalent cases), thus ensures as far as possible that all events captured are new incident cases[324]. The chance of including recurrent events is highest in the earlier calendar years, with less prior patient data, leading to possible overestimation of incidence in early years. However, incidence of both major CHD and T2DM is broadly comparable to that in the two cohorts and in other data (see section 4.6.4), thus the impact is likely to be very modest.

A second potential limitation specific to the analyses of major CHD incidence, is that fatal CHD events, where a patient dies and cause of death is cited as CHD, may not be coded as Read codes and so not captured in THIN. The incidence rates in THIN and the BRHS and Whitehall II are broadly comparable. However, incidence in the oldest age groups in THIN (over 70 years), among whom a greater proportion of events are fatal, does appear to be lower than that in the cohorts, suggesting that some fatal events are missed. To explore the data further, events were broken down into the proportion fatal (death within 30 days) and non-fatal. Compared with the BRHS over

the overlapping time-period, the proportions of fatal events in each age group were indeed lower in THIN. Since studies suggest case fatality rates to also have fallen over time (see chapter 2, section 2.2.2.2), the impact of missing some fatal events will likely be underestimation of the decline in major CHD incidence (a greater proportion of events in the early years will be fatal and so missed, leading to greater underestimation of incidence in these years and so underestimation of the decline over time). However the decline observed in THIN was if anything greater than that observed in the two cohorts, suggesting the impact to be minimal.

4.6.3 Comparisons with the analyses of BRHS and Whitehall II cohort data

The time trend estimates from the BRHS and Whitehall II cohorts, both overall and by demographic group, were generally consistent with the findings in THIN, when the differing time-periods covered were taken into account. This is reassuring and supports the validity and generalisability of the BRHS and Whitehall II analyses in subsequent chapters to explain the time trends seen.

The time trend estimates from the BRHS and Whitehall II cohorts extend over earlier calendar years, from the 1980s onwards, showing further that the fall in incidence of major CHD and rise in incidence of T2DM occurred over this earlier period too.

Comparing the findings for the time trend in major T2DM among the whole BRHS cohort with the "survivor" cohort over the overlapping time-period 1995 to 2004, the results were broadly consistent, lending support to use of the findings from the survivor cohort over the earlier time-period, for which data for the full cohort was not available, and in the analyses in subsequent chapters.

The BRHS and Whitehall II cohorts are similar data sources and so share similar strengths: established dedicated cohort studies with (near) complete and accurate follow-up for cardiovascular diseases. Indeed follow-up has been maintained for 98% of surviving men in the BRHS, with similarly high figures for Whitehall II. Moreover, the methods used to identify participants with major CHD events have been consistent over the follow-up period in both the BRHS and Whitehall II. The analysis of time trends in T2DM using the whole BRHS cohort was restricted to that period when ascertainment methods were also consistent (review of GP records). For the analysis limited to BRHS "survivors", over an extended period, the methods of ascertainment were not consistent (retrospective self-report before 1990 versus later use of GP records). However, any self-reported T2DM diagnosis in the questionnaire before 1990 prompted the researchers to go back to the GP records to confirm the diagnosis and date of diagnosis. Thus any self-reported diagnosis may be taken as a true doctor-diagnosis, consistent with diagnoses after 1990; that is, the false-positive rate will be negligible. It is possible that diabetes cases may have been missed where patients have not reported T2DM (false-negatives). The likely impact of the use of self-report before 1990 would therefore be to underestimate the incidence of T2DM in the earliest periods (1985-1989 and 1990-1994). The result of this bias would be overestimation of the increase in incidence of T2DM over time. That said, the possible underestimation of diabetes cases and subsequent bias is likely to be small as previous studies have shown questionnaire self-report of diabetes to agree closely with medical records, and in particular, have a high specificity (thus corresponding low false negative rate)[328-331].

The two data sources share the same possible limitation of using cohorts to estimate time trends (as opposed to repeated cross-sections of a population), that of the ageing of the cohort over time. Since risk of major CHD increases with age, any residual confounding by age would have led to underestimation of the favourable decline in incidence. Adjustment was made for current age at each time-period to take account of ageing, and although it remains possible that the effects of calendar time and age have not been fully disentangled, the residual confounding is likely to be minor. The comparability of the results with THIN supports this.

4.6.4 Comparison with other published data

4.6.4.1 Decline in incidence of major CHD

A previous BRHS analysis reported a consistent decline of 3.5% per annum between 1978 and 2000[20]; a separate analysis of THIN data reported consistent declines by country of up to 4.6% per annum between 1996 and 2005[24]; the modest variations in the sizes of the declines in incidence can be accounted for by the different time-periods covered. Note that the THIN data analyses were published after the initial drafting of this thesis, and did not consider trends by deprivation.

Referring back to chapter 2, section 2.2.2.1, those studies using other data sources which considered major CHD incidence trends over time-periods coinciding at least in part with the time-period covered (1980 to 2008) reported estimates of the average annual changes ranging from a modest 1.4% decline in men and a 0.2% *increase* in women in Glasgow between 1985 and 2004, to a decline of 4.6% among men in Belfast between 1983 and 1993 (WHO MONICA)[22]. Separate studies in Scotland report intermediate sized declines of 3.5% between 1990 and 2000[21] and 2.7-2.8%

between 1986 and 2008[1]. However, no studies consider time trends over the exact same periods as covered here, making direct comparison difficult, as the relative declines are in part influenced by the initial rate of incidence which varies depending on the start year. Moreover, all these previous studies were limited to a single city or region of the UK.

The OXMIS study estimated time trends in major CHD from 1966-7 to 1994-5[23], that is over a calendar period predominately prior to calendar periods considered here. Smaller average annual relative declines in age-standardised incidence of 1.2% in men and 0.3% in women aged 30 to 69 years in Oxfordshire were observed, suggesting a smaller rate of decline in earlier years. Although again since the declines are estimated relative to the incidence rate initially, and incidence in 1966-7 was that much greater than at the start of the periods considered in the present analyses, the absolute changes may not be dissimilar.

The similarity of the time trends by gender in the present analyses is in line with findings from Scotland of similar average annual declines of 2.7% and 2.8% among men and women respectively between 1986 and 2008[1]. The smaller declines in women relative to men reported in the WHO MONICA and OXMIS studies could reflect the earlier time period; the similar trends by gender observed in the present analysis may suggest therefore that women are now catching up with men in terms of improving CHD incidence. No studies from other data sources have considered time trends in incidence by socio-economic status.

4.6.4.2 Rise in incidence of T2DM

A separate analysis of THIN data reported a trend of 5.2% per annum in T2DM incidence between 1996 and 2005[6]; this is consistent with the observed trend in the current analysis of 5.37%, when limited to a similar period 1995-2006. The smaller increase of 3.6% per annum observed for the whole period from 1995 to 2008 reflects the "flattening" of the trend in the most recent years, as shown in section 4.4. Notably in line with the present analysis, a figure in the paper also shows a jump in incidence in 1999-2000 followed by a tailing off towards the end of the follow-up, although the authors do not remark on this. The THIN data analyses were published after the initial drafting of this thesis, and did not consider trends by deprivation or country.

Referring to chapter 2, section 2.3.2.1, three previous studies using other data sources estimate time trends in diabetes incidence over time-periods coinciding at least in part with the time-period covered (1985 to 2008)[4, 25, 26]. The average annual increases in incidence estimated in these studies were 5.2% and 6.3% among men and women respectively in the nationwide General Practice Research Database (GPRD)[25] between 1996 and 2006; 6.3% in Tayside, Scotland between 1993 and 2004 (DARTS Clinical Information System data)[4]; and 4.8% in the GPRD again, over an earlier period from 1994 to 1998[26]. These estimates are consistent with the findings in the present analysis, once the "flattening" of the trend beyond 2004 is taken into account. The two GPRD studies both showed similar trends by gender in line with the present study findings. No previous studies were found which examine the temporal trend in T2DM in the most recent years from 2005 onwards so it was not possible to verify the apparent lack of increase in T2DM in this period. Also no studies considered trends in major CHD or T2DM incidence according to socio-economic status or country.

4.6.5 Interpretation of findings

4.6.5.1 Is the decline in major CHD incidence a true epidemiological change in the population?

The various analyses using the different data sources suggest a fall in the incidence of major CHD from 1980 to 2008. An important question however is whether this apparent fall in incidence is a true epidemiological shift in incidence in the population, that is, fewer people experiencing a major CHD event, reflecting changes in the risk profile in the population or improved primary preventive treatments. As discussed in chapter 2, section 2.5.1, the alternative is that the trend is (in some part) an artefact of changes in factors such as the methods used to identify cases in the current analysis, case ascertainment (that is, the proportion of all major CHD events occurring that are known and do not go undiagnosed), changes in diagnostic criteria and, for fatal CHD events, which may be ascertained from death certificates, changes in the coding of cause of death.

It was outlined in chapter 3 that for major CHD, within each study the same methods have been used throughout the follow-up to capture major CHD cases as recorded in the GP records, and therefore changes in the method used within each study to identify major CHD events cannot account for the time trend in major CHD events seen. Given the nature of major CHD events, normally with evident serious manifestations, case ascertainment (that is, the proportion of all major CHD events occurring that are known and do not go undiagnosed) is unlikely to be a major issue, unlike for T2DM which can go undiagnosed. A major change in the diagnosis of MI occurred in 2000, with the introduction of the measurement of cardiac troponins as the new reference standard for diagnosing myocardial injury[87], compared with the prior

World Health Organisation (WHO) definition of acute MI of unequivocal electrocardiogram (ECG) changes and/or unequivocal enzyme changes[88, 89]. The likely impact of the introduction of the use of troponins is an increased sensitivity, with more events classed as major CHD events which might not have been previously classed as such[90-92]. This in turn would lead to, if anything, underestimation of the decline in major CHD incidence, particularly when comparing the periods before and after 1999, thus does not help to explain the decline observed. The steady trend seen over the whole period, with no obvious discontinuity around 1999 suggests further that the diagnostic change has had limited impact. In terms of fatal events, it was shown above that not all fatal events are captured in THIN, and of those that are, only a proportion will likely have been identified only from the death certificate, and then coded as Read codes. Thus any changes in the coding of cause of death on the death certificates (using the International Classification of Diseases (ICD) coding system) is unlikely to have much impact. For the BRHS and Whitehall II analyses, ICD coding changes could have greater influence. As detailed in Chapter 2, section 2.5.1, the main changes over the period of study (1980 to 2008) were over the period 1984-92 when direct causes of death could be coded less often, while more secondary causes could be coded more often, and in 2001 when ICD-9 was replaced by ICD-10. Previous studies however suggest that both these changes have had minimal impact on CHD mortality trends[332, 333]. Janssen et al[333] considered the impact of the coding rule change between 1984 and 1992; a 1% increased mortality rate was observed immediately after the coding rule change, but it could not be ruled out as being an outlying estimate and this small discontinuity is unlikely to have had a dramatic influence on the observed trends, especially since the decline in mortality was greatest from the 1980s onwards. Griffiths et al[332] then considered the impact on the decline in

CHD mortality of the most recent (and considerable) ICD-revision in 2001. The findings were that there was little difference in CHD mortality rates under the different coding systems (ratio comparing the two rates = 1.005) such that the influence on the time trends in CHD mortality is likely to be minimal.

Finally, one study suggested that the introduction of the Quality and Outcomes Framework (QOF) for managing CHD patients in General Practice in 2003 may have had the impact of GPs reviewing and verifying records, leading to the removal of incorrect (false positive) CHD codes, since fewer events were found in a more recent download of GP data compared to an earlier pre-QOF version[334]. If incidence trends are computed comparing different data downloads, this could lead to spurious declines in incidence; however as the same data download of THIN was used for all calendar years in the present analysis, this observation is unlikely to influence the present observed CHD incidence trends estimates. Ultimately, this all implies that the decline observed may be a real epidemiological change, reflecting risk factor trends and treatment changes, rather than induced by a change in diagnostic criteria.

4.6.5.2 Is the rise in T2DM incidence a true epidemiological change in the population?

The different data sources showed an increase in incidence of T2DM at least from the mid 1980s to the early 2000s, although no significant increase in incidence was observed beyond the early 2000s. The year-on-year analysis of THIN data showed further an apparent "jump" in incidence around 1999. Again a key question is whether the pattern in incidence observed reflects true epidemiological changes in the proportion of the population developing T2DM over calendar time, or whether the

pattern is in some part an artefact of changes in diagnostic criteria, case ascertainment, health policy and so forth. Methods employed in the analysis of THIN data for capturing T2DM diagnoses were consistent throughout the follow-up, and while methods in the BRHS did differ (self report versus later review of GP records), this is unlikely to have had a substantial influence on the trends estimates as explained in section 4.6.3.

Diagnostic criteria for diabetes changed in the late 1990s, with the publishing of new criteria from the American Diabetes Association in 1997[93] and then from WHO in 1999[94]. As outlined in chapter 2, section 2.5.1, the key difference in these new criteria, compared with the existing WHO criteria used before this time[95], was the greater emphasis on the use of fasting glucose (as opposed to previous criteria based mainly on post-load glucose measurements) along with a reduced diagnostic fasting glucose threshold to indicate diabetes of 7.0 mmol /l rather than 7.8 mmol/l previously. The change in the type of measurements taken, from use of post-load glucose measurements to fasting glucose has been shown to lead to different patients being identified as having T2DM, but, the impact of the change in criteria on prevalence and incidence rates is not fully resolved, with studies having different conclusions[335-339]. In studies in the US[335, 337, 338] prevalence estimates were lower using the new criteria, compared to the old, implying if anything, the changing criteria may lead to underestimation of the rise in T2DM. This was because, in these populations, it was more common for patients to have above threshold levels of post-load glucose but not fasting glucose, rather than vice-versa. For example, in the US NHANES population, of all T2DM cases identified using either criteria, 41% met just the old post-load criteria compared with 14% meeting just the new fasting glucose

criteria and 44% meeting both criteria[338]. This study also estimated prevalence of T2DM at different time-points using first the existing criteria throughout, and then the new criteria throughout. It found that whether the new or old criteria were used, prevalence had increased over time. Conversely, some studies in the UK and Europe[336, 339] suggest that the new diagnostic criteria may have led to an increase in the number of patients diagnosed with T2DM, who might previously not have been identified as such, and therefore may explain some of the increase in T2DM incidence and prevalence over time. This is because in these populations, it was more common for patients to have above threshold levels of fasting glucose but not post-load glucose, rather than vice-versa. For example, in the UK, out of all T2DM cases identified by either criteria, 42% met just the new fasting glucose criteria, while 18% met just the old post-load glucose criteria and 40% met both, a pattern that persisted stratifying by ethnic group[336].

Recommendations on cardiovascular prevention from the late 1990s[97] and the introduction of QOF for managing diabetes patients in General Practice in 2004 may have increased awareness of T2DM and so increased T2DM ascertainment. Studies have investigated the impact of QOF on management of patients with T2DM with mixed findings[340-342], but the impact of QOF on case-ascertainment or incidence is unclear. Studies estimating case-ascertainment of T2DM in the UK together suggest that ascertainment stood at around 50% between the 1980s[343] and 2000[344], but could have increased to over 80% in 2004-2005[345, 346] (post QOF). However as the estimates at the different time points come from different studies on different sections of the UK population, a direct comparison may not be fair. Moreover, the 2004-2005 estimate, from a report by the National Diabetes Audit, is calculated from a predicted

overall diabetes prevalence, based on prevalence observed from surveys carried out more than 20 years ago and assuming T2DM incidence has remained constant since, and may appreciably underestimate the extent of undiagnosed disease, if incidence of T2DM has in fact risen. Morgan *et al* consider the issue from an alternative perspective, in their paper on changes in complications of T2DM[71]. They found that T2DM patients in 2004 had fewer complications than patients in 1996, and argued that this could be indicative of improved case-ascertainment, as more T2DM patients with less severe symptoms may have been identified through routine screening, rather than as a result of the occurrence of a complication. Incidence of T2DM remained constant or even appeared to decline after the implementation of QOF, so QOF does not appear to explain rising T2DM incidence. Instead, the introduction of QOF appears to have led to a change in coding, with a fall in the use of general diabetes codes after 2002 (figure 4.4). This is supported by Calvert *et al*, who also noted a change over time from general diabetes codes to specific diabetes codes, reflecting the codes used to define diabetes in QOF rules[340].

The change in diagnostic criteria and introduction of cardiovascular prevention recommendations do coincide with the "jump" in incidence in 1999 so increased ascertainment arising from the recommendations and/or the changing diagnostic criteria may help to explain some of the rising incidence at this point. That said, according to the BRHS analysis, incidence of T2DM has been increasing well before 1999 so the change in diagnostic criteria and cardiovascular recommendations are unlikely to completely explain the rise in incidence.

To summarise, before around 1999, there appeared little in the way of changes in diagnostic criteria or policy that could have influenced incidence rates of T2DM, thus before 1999 it appears that the increase may be a true epidemiological trend reflecting changes in the risk profile of the British population. After 1999, the situation is less clear and it is possible that the true incidence rates in the more recent calendar years have been influenced to some extent by changing diagnostic criteria and policy recommendations leading to changes in case-ascertainment. Alternatively, T2DM incidence may still be increasing at a background steady rate beyond 1999, and the changes in diagnostic criteria and policy are simply affecting when the new cases are identified. That is, without the changes, we would still see a steady rise in incidence, rather than the jump in 1999.

4.6.5.3 Relation to trends in mortality of CHD and prevalence of T2DM

The findings from this chapter suggest that, at least from the 1980s onwards, the decline in mortality from CHD may be partially explained by a fall in incidence of major CHD events, that is fewer people experiencing a major CHD event in the first place. Similarly the rise in prevalence of T2DM, at least from the mid 1980s until the late 1990s, may be seen to reflect at least in part a rise in incidence of T2DM, that is an increase in the number of patients developing T2DM. The apparent rise in incidence beyond 1999 to the early 2000s may also explain the observed rise in prevalence over this later period, but the extent to which the increase in incidence, and therefore prevalence, over this time is a true epidemiological increase in the numbers of patients developing T2DM as opposed to reflections of increased case ascertainment and diagnostic criteria changes, remains uncertain.

That is not to say that changes over time in survival, particularly case fatality following a major CHD event or relative mortality of diabetic patients compared with the general population, could not also be contributing, if favourable time trends in these events have also occurred. There is a lack of data on T2DM prevalence trends beyond 2005 (see chapter 2, section 2.3.1) so it is unknown whether prevalence has continued to increase in the last five years. It may be that prevalence has also remained constant in line with the trend in incidence in the most recent years. Alternatively, if prevalence has continued to increase, a continued rise in prevalence over this time may instead be more likely to reflect an improvement in relative mortality.

4.6.5.4 Impact of variations in trends by socio-demographic group

This chapter presents previously little reported trends in incidence of major CHD and T2DM according to different socio-demographic characteristics. In particular, more favourable trends occurred in less deprived groups: the rate of decline in major CHD appeared faster while the rate of increase of T2DM was slower among those in more professional/ senior employment grades compared with more junior grades or unskilled occupations and in less deprived areas compared with more deprived areas. Since incidence of both major CHD and T2DM was initially greater among more deprived groups, the more favourable trends suggest a widening socio-economic inequality in terms of T2DM and CHD incidence rates.

The finding of more a favourable trend in incidence of major CHD with increasing socio-economic position, and a possible resultant widening socio-economic inequality in incidence, reflects findings from previous studies showing more favourable trends

in CHD mortality with increasing socio economic position, both in the BRHS[61] and in other data sources[54, 59, 60]. Similarly the more favourable trend in incidence of T2DM with increasing socio-economic position reflects previous study findings showing more favourable trends in T2DM prevalence with increased socio-economic position in the BRHS[3]; few other studies have considered time trends in prevalence by socio-economic status. This highlights the correspondence between trends in major CHD incidence and mortality and between trends in T2DM incidence and prevalence.

The apparent similarity in the rate of increase in T2DM and rate of decline of major CHD by gender has resulted in men remaining at higher risk of both these conditions. Regarding the trends by constituent country, the least favourable trends in both major CHD and T2DM incidence (i.e. smallest relative decline in major CHD, and greatest relative increase in T2DM) occurred in Northern Ireland, while the most favourable trends occurred in Wales. Given the variations in the absolute incidence rates at the start of the analyses, the effect of the differing time trends has generally been an attenuation of the differences in incidence between the different countries.

The least favourable relative changes in incidence of T2DM and major CHD occurred in the youngest age groups. This is concerning as it is these age groups which will influence the future prevalence and burden of disease. For major CHD, this reflects the observed flattening of the decline in CHD mortality in younger groups[52-54].

4.6.6 Chapter conclusions/ post-script

In this chapter it has been shown that incidence of major CHD events has declined since the 1980s among most demographic groups (although some groups have seen

larger declines than others). It seems likely therefore that a decline in incidence of major CHD has made an important contribution to the decline in mortality from CHD. It was also shown that in contrast to the favourable trend in major CHD, incidence of T2DM has risen, at least between the mid 1980s and early 2000s. Therefore it is reasonable to suppose that the rise in T2DM incidence has made an important contribution to the rise in prevalence of T2DM.

In the subsequent results chapters 5, 6, 7, and 8, the reasons for the rise in major CHD incidence and fall in T2DM incidence will be explored. In particular the roles of concurrent time trends in risk factors and preventive treatment will be investigated. This in turn will shed further light on the factors leading to the fall in CHD mortality and rise in T2DM prevalence, and help to unravel further whether the T2DM incidence trends are true epidemiological changes or not.

Table 4.1 **Rates of incidence of major CHD per 1000 person-years by age, gender and calendar period: THIN database**

Men	***Age, years***										
	30-34	*35-39*	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80+*
Incidence rate per 1000 person-years (95% CI)											
1995-1999	0.12	0.37	0.73	1.65	2.63	4.26	5.64	7.37	9.34	11.46	11.64
	(0.08 to 0.19)	(0.29 to 0.47)	(0.61 to 0.88)	(1.46 to 1.86)	(2.39 to 2.90)	(3.90 to 4.64)	(5.20 to 6.11)	(6.84 to 7.94)	(8.69 to 10.03)	(10.63 to 12.37)	(10.77 to 12.58)
2000-2004	0.08	0.32	0.72	1.53	2.38	3.33	4.68	5.80	7.22	8.61	10.29
	(0.06 to 0.11)	(0.28 to 0.38)	(0.64 to 0.80)	(1.41 to 1.66)	(2.23 to 2.54)	(3.14 to 3.52)	(4.43 to 4.94)	(5.50 to 6.11)	(6.85 to 7.61)	(8.15 to 9.10)	(9.79 to 10.81)
2005-2008	0.08	0.25	0.66	1.27	1.99	2.58	3.52	3.95	5.13	6.03	8.12
	(0.06 to 0.12)	(0.20 to 0.30)	(0.59 to 0.74)	(1.16 to 1.38)	(1.85 to 2.14)	(2.42 to 2.74)	(3.32 to 3.73)	(3.71 to 4.20)	(4.83 to 5.46)	(5.65 to 6.43)	(7.69 to 8.57)

Women	***Age, years***										
	30-34	*35-39*	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80+*
Incidence rate per 1000 person-years (95% CI)											
1995-1999	0.04	0.08	0.21	0.29	0.59	1.42	2.00	3.33	4.78	6.06	7.87
	(0.02 to 0.08)	(0.05 to 0.14)	(0.15 to 0.30)	(0.21 to 0.38)	(0.48 to 0.73)	(1.22 to 1.64)	(1.75 to 2.27)	(3.00 to 3.69)	(4.38 to 5.22)	(5.57 to 6.59)	(7.39 to 8.38)
2000-2004	0.03	0.06	0.18	0.31	0.57	0.96	1.61	2.49	3.57	4.92	6.51
	(0.02 to 0.05)	(0.04 to 0.08)	(0.15 to 0.23)	(0.26 to 0.37)	(0.50 to 0.65)	(0.87 to 1.07)	(1.47 to 1.76)	(2.31 to 2.69)	(3.34 to 3.81)	(4.63 to 5.23)	(6.24 to 6.80)
2005-2008	0.03	0.05	0.14	0.32	0.56	0.70	1.03	1.70	2.45	3.62	5.85
	(0.02 to 0.06)	(0.04 to 0.08)	(0.11 to 0.18)	(0.27 to 0.38)	(0.49 to 0.64)	(0.62 to 0.79)	(0.93 to 1.14)	(1.55 to 1.86)	(2.26 to 2.66)	(3.37 to 3.89)	(5.59 to 6.12)

Table 4.2 **Major CHD incidence rates in 1995-1997 and 2006-2008 and absolute changes in incidence between the two periods, overall and by demographic group**

	Major CHD incidence rate in 1995-1997, 95% CI	Major CHD incidence rate in 2006-2008, 95% CI	Absolute change in incidence, 95% CI
Overall	3.05 (2.96 to 3.15)	1.73 (1.70 to 1.76)	-1.32 (-1.42 to -1.22)
By Demographic group			
Age, years			
30-39	0.14 (0.10 to 0.19)	0.11 (0.10 to 0.14)	-0.02 (-0.07 to 0.02)
40-49	0.76 (0.67 to 0.87)	0.58 (0.54 to 0.62)	-0.19 (-0.29 to -0.08)
50-59	2.27 (2.09 to 2.47)	1.45 (1.38 to 1.52)	-0.82 (-1.02 to -0.62)
60-69	4.87 (4.57 to 5.19)	2.40 (2.30 to 2.50)	-2.47 (-2.79 to -2.14)
70-79	8.44 (7.99 to 8.91)	4.01 (3.85 to 4.17)	-4.43 (-4.92 to -3.94)
80+	10.26 (9.60 to 10.97)	6.58 (6.33 to 6.85)	-3.68 (-4.41 to -2.95)
Sex			
Men	3.98 (3.83 to 4.15)	2.26 (2.21 to 2.32)	-1.72 (-1.89 to -1.55)
Women	2.22 (2.11 to 2.34)	1.23 (1.19 to 1.27)	-0.99 (-1.11 to -0.87)
Townsend quintile of area deprivation			
1 (least deprived)	2.36 (2.21 to 2.52)	1.38 (1.33 to 1.45)	-0.97 (-1.14 to -0.81)
2	2.83 (2.65 to 3.03)	1.68 (1.61 to 1.76)	-1.15 (-1.35 to -0.94)
3	3.18 (2.97 to 3.42)	1.77 (1.67 to 1.86)	-1.42 (-1.66 to -1.17)
4	3.76 (3.50 to 4.02)	2.05 (1.94 to 2.16)	-1.71 (-1.99 to -1.43)
5 (most deprived)	4.01 (3.70 to 4.34)	2.24 (2.13 to 2.36)	-1.77 (-2.10 to -1.43)
UK Country			
England	3.05 (2.95 to 3.15)	1.70 (1.66 to 1.74)	-1.34 (-1.45 to -1.24)
Wales	2.77 (2.41 to 3.20)	1.49 (1.34 to 1.66)	-1.28 (-1.70 to -0.86)
Scotland	3.32 (2.84 to 3.88)	2.01 (1.85 to 2.19)	-1.31 (-1.85 to -0.77)
Northern Ireland	3.72 (2.97 to 4.65)	2.13 (1.93 to 2.35)	-1.58 (-2.44 to -0.73)

Table 4.3 **Major CHD rate ratio per annum increase in calendar time between 1995 and 2008, and corresponding percentage decline in incidence, overall and by demographic group**

	Major CHD Rate ratio per annum increase in calendar time, 95% CI	% decline in major CHD incidence per annum*, 95% CI	p-value†
Overall	0.951 (0.948 to 0.954)	**4.88 (4.59 to 5.18)**	
By Demographic group			
Age, years			
30-39	0.971 (0.947 to 0.996)	**2.89 (0.40 to 5.32)**	
40-49	0.975 (0.964 to 0.986)	**2.48 (1.36 to 3.58)**	
50-59	0.960 (0.952 to 0.967)	**4.04 (3.31 to 4.77)**	
60-69	0.934 (0.929 to 0.940)	**6.55 (5.97 to 7.13)**	
70-79	0.936 (0.931 to 0.942)	**6.36 (5.82 to 6.89)**	
80+	0.973 (0.966 to 0.979)	**2.74 (2.12 to 3.36)**	**<0.001**
Sex			
Men	0.951 (0.947 to 0.955)	**4.92 (4.55 to 5.29)**	
Women	0.952 (0.947 to 0.957)	**4.79 (4.30 to 5.27)**	**0.8**
Townsend quintile of area deprivation			
1 (least deprived)	0.945 (0.939 to 0.951)	**5.51 (4.91 to 6.11)**	
2	0.949 (0.942 to 0.955)	**5.15 (4.54 to 5.76)**	
3	0.950 (0.944 to 0.957)	**4.98 (4.34 to 5.62)**	
4	0.952 (0.946 to 0.959)	**4.80 (4.15 to 5.44)**	
5 (most deprived)	0.963 (0.956 to 0.971)	**3.69 (2.93 to 4.45)**	**0.007**
UK Country			
England	0.951 (0.948 to 0.954)	**4.90 (4.58 to 5.22)**	
Wales	0.945 (0.933 to 0.958)	**5.45 (4.16 to 6.73)**	
Scotland	0.947 (0.936 to 0.959)	**5.28 (4.11 to 6.44)**	
Northern Ireland	0.959 (0.941 to 0.978)	**4.07 (2.22 to 5.89)**	**0.5**

Note: From multilevel Poisson models, adjusted for age and sex, with random intercepts to adjust for practice variation. *Calculated from rate ratios (RR) as 100*(1-RR). †p-value for interaction between calendar year and demographic factor, to assess for a difference in the time trends according to each category of the demographic factor

Table 4.4 **Rates of incidence of T2DM per 1000 person-years by age, gender and calendar period: THIN database**

Men	***Age, years***										
	30-34	*35-39*	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80+*
Incidence rate per 1000 person-years (95% CI)											
1995-1999	0.33	0.72	1.53	2.32	3.53	5.06	6.93	7.44	7.94	7.56	5.84
	(0.26 to 0.43)	(0.60 to 0.86)	(1.34 to 1.74)	(2.09 to 2.57)	(3.24 to 3.84)	(4.68 to 5.49)	(6.44 to 7.45)	(6.90 to 8.01)	(7.34 to 8.58)	(6.89 to 8.30)	(5.24 to 6.51)
2000-2004	0.65	1.24	2.34	3.88	5.63	7.79	10.45	12.70	12.98	11.61	8.67
	(0.57 to 0.73)	(1.14 to 1.34)	(2.19 to 2.49)	(3.68 to 4.08)	(5.39 to 5.87)	(7.50 to 8.09)	(10.07 to 10.84)	(12.25 to 13.18)	(12.47 to 13.51)	(11.07 to 12.18)	(8.21 to 9.15)
2005-2008	0.71	1.47	2.80	4.46	6.66	7.94	10.41	12.49	12.59	11.82	8.46
	(0.63 to 0.80)	(1.36 to 1.59)	(2.65 to 2.96)	(4.26 to 4.67)	(6.40 to 6.93)	(7.65 to 8.24)	(10.06 to 10.78)	(12.04 to 12.96)	(12.09 to 13.12)	(11.26 to 12.40)	(8.02 to 8.92)
Women	***Age, years***										
	30-34	*35-39*	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80+*
Incidence rate per 1000 person-years (95% CI)											
1995-1999	0.37	0.59	1.08	1.36	2.37	3.48	4.63	5.52	6.40	6.43	5.19
	(0.29 to 0.48)	(0.49 to 0.73)	(0.92 to 1.26)	(1.19 to 1.56)	(2.13 to 2.63)	(3.16 to 3.83)	(4.24 to 5.05)	(5.08 to 5.99)	(5.92 to 6.91)	(5.92 to 6.98)	(4.80 to 5.62)
2000-2004	0.51	0.91	1.53	2.47	3.60	4.98	7.56	8.97	10.07	9.12	7.32
	(0.45 to 0.59)	(0.83 to 1.01)	(1.41 to 1.65)	(2.32 to 2.64)	(3.41 to 3.80)	(4.75 to 5.22)	(7.24 to 7.89)	(8.61 to 9.36)	(9.66 to 10.49)	(8.72 to 9.55)	(7.03 to 7.63)
2005-2008	0.47	1.00	1.66	2.84	4.09	5.32	6.97	8.93	10.17	9.44	7.14
	(0.40 to 0.54)	(0.91 to 1.10)	(1.54 to 1.78)	(2.68 to 3.01)	(3.88 to 4.30)	(5.09 to 5.56)	(6.68 to 7.26)	(8.57 to 9.31)	(9.75 to 10.6)	(9.01 to 9.89)	(6.85 to 7.45)

Table 4.5 **T2DM incidence rates in 1995-1997 and 2006-2008 and absolute changes in incidence between the two periods, overall and by demographic group**

	T2DM incidence rate in 1995-1997 (95% CI)	T2DM incidence rate in 2006-2008 (95% CI)	Absolute change in incidence (95% CI)
Overall	3.15 (3.07 to 3.23)	5.25 (5.19 to 5.31)	2.10 (2.00 to 2.20)
By Demographic group			
Age, years			
30-39	0.46 (0.39 to 0.55)	0.96 (0.90 to 1.01)	0.49 (0.40 to 0.59)
40-49	1.39 (1.26 to 1.54)	2.95 (2.86 to 3.04)	1.55 (1.39 to 1.72)
50-59	3.45 (3.23 to 3.70)	5.99 (5.85 to 6.14)	2.54 (2.26 to 2.81)
60-69	5.84 (5.50 to 6.19)	9.27 (9.07 to 9.48)	3.43 (3.03 to 3.83)
70-79	6.60 (6.20 to 7.02)	10.7 (10.5 to 11.0)	4.13 (3.64 to 4.63)
80+	5.31 (4.83 to 5.83)	7.46 (7.18 to 7.75)	2.16 (1.59 to 2.73)
Sex			
Men	3.44 (3.29 to 3.59)	6.06 (5.97 to 6.16)	2.63 (2.45 to 2.80)
Women	2.82 (2.69 to 2.95)	4.49 (4.41 to 4.57)	1.67 (1.52 to 1.82)
Townsend quintile of area deprivation			
1 (least deprived)	2.39 (2.24 to 2.55)	4.34 (4.24 to 4.45)	1.95 (1.76 to 2.14)
2	2.86 (2.68 to 3.06)	4.79 (4.67 to 4.91)	1.92 (1.69 to 2.15)
3	3.04 (2.83 to 3.27)	5.32 (5.19 to 5.46)	2.28 (2.02 to 2.54)
4	4.08 (3.81 to 4.36)	6.04 (5.88 to 6.20)	1.96 (1.65 to 2.28)
5 (most deprived)	4.14 (3.82 to 4.47)	7.06 (6.85 to 7.28)	2.93 (2.54 to 3.32)
UK Country			
England	3.11 (3.01 to 3.21)	5.18 (5.12 to 5.25)	2.08 (1.95 to 2.20)
Wales	3.02 (2.63 to 3.46)	5.46 (5.21 to 5.72)	2.44 (1.96 to 2.93)
Scotland	3.44 (2.95 to 4.01)	5.79 (5.56 to 6.03)	2.35 (1.77 to 2.92)
Northern Ireland	2.83 (2.19 to 3.67)	5.26 (4.93 to 5.60)	2.42 (1.62 to 3.23)

Table 4.6 **T2DM rate ratio per annum increase in calendar time between 1995 and 2008, and corresponding percentage increase in incidence, overall and by demographic group**

	T2DM Rate ratio per annum, 95% CI	% increase in T2DM incidence per annum*, 95% CI	p-value†
Overall	1.036 (1.034 to 1.038)	**3.60 (3.37 to 3.83)**	
By Demographic group			
Age, years			
30-39	1.050 (1.039 to 1.062)	**5.02 (3.87 to 6.19)**	
40-49	1.055 (1.048 to 1.062)	**5.49 (4.82 to 6.17)**	
50-59	1.043 (1.038 to 1.048)	**4.32 (3.83 to 4.81)**	
60-69	1.029 (1.025 to 1.033)	**2.91 (2.49 to 3.33)**	
70-79	1.034 (1.029 to 1.039)	**3.39 (2.93 to 3.86)**	
80+	1.025 (1.018 to 1.032)	**2.51 (1.81 to 3.21)**	**<0.001**
Sex			
Men	1.039 (1.036 to 1.042)	**3.89 (3.58 to 4.20)**	
Women	1.033 (1.030 to 1.037)	**3.34 (3.00 to 3.68)**	**0.02**
Townsend quintile of area deprivation			
1 (least deprived)	1.034 (1.030 to 1.039)	**3.43 (2.96 to 3.91)**	
2	1.031 (1.026 to 1.036)	**3.12 (2.63 to 3.60)**	
3	1.039 (1.034 to 1.044)	**3.86 (3.36 to 4.35)**	
4	1.035 (1.030 to 1.040)	**3.52 (3.02 to 4.03)**	
5 (most deprived)	1.050 (1.044 to 1.056)	**4.99 (4.40 to 5.58)**	**<0.001**
UK Country			
England	1.036 (1.034 to 1.039)	**3.62 (3.37 to 3.87)**	
Wales	1.027 (1.017 to 1.036)	**2.65 (1.68 to 3.63)**	
Scotland	1.037 (1.027 to 1.046)	**3.66 (2.69 to 4.63)**	
Northern Ireland	1.048 (1.032 to 1.065)	**4.84 (3.22 to 6.49)**	**0.1**

Note: From multilevel Poisson models, adjusted for age and sex, with random intercepts to adjust for practice variation. *Calculated from rate ratios (RR) as 100*(1-RR). †p-value for interaction between calendar year and demographic factor, to assess for a difference in the time trends according to each category of the demographic factor

Table 4.7 **Rates of incidence of major CHD per 1000 person-years by age and calendar period: British Regional Heart Study men**

		Age group, years								
		40-44	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80-84*
Number of person-years of follow-up										
	1980-1984	3013.7	8307.8	8199.9	7882.4	5056.8				
	1985-1989		3050.1	8109.0	7852.4	7321.5	4426.2	114.0		
Calendar	*1990-1994*			2940.4	7751.3	7214.9	6445.9	3704.3	94.4	
period	*1995-1999*				2818.9	7294.8	6551.6	5492.1	2891.3	67.1
	2000-2004					2627.0	5956.1	5022.3	3744.7	1627.3
Number of incident major CHD events										
	1980-1984	7	28	54	58	55				
	1985-1989		10	55	59	90	64	1		
Calendar	*1990-1994*			21	35	72	74	67	1	
period	*1995-1999*				18	43	56	80	51	4
	2000-2004					16	58	63	68	32
Incidence rate per 1000 person-years (95% CI)										
	1980-1984	2.32 (1.11, 4.87)	3.37 (2.33, 4.88)	6.59 (5.04, 8.60)	7.36 (5.69, 9.52)	10.88 (8.35, 14.17)				
	1985-1989		3.28 (1.76, 6.09)	6.78 (5.21, 8.83)	7.51 (5.82, 9.70)	12.29 (10.00, 15.11)	14.46 (11.32, 18.47)	NA		
Calendar period	*1990-1994*			7.14 (4.66, 10.95)	4.52 (3.24, 6.29)	9.98 (7.92, 12.57)	11.48 (9.14, 14.42)	18.09 (14.24, 22.98)	NA	
	1995-1999				6.39 (4.02, 10.14)	5.89 (4.37, 7.95)	8.55 (6.58, 11.11)	14.57 (11.70, 18.13)	17.64 (13.41, 23.21)	
	2000-2004					6.09 (3.73, 9.94)	9.74 (7.53, 12.60)	12.54 (9.80, 16.06)	18.16 (14.32, 23.03)	19.66 (13.91, 27.81)

Notes: NA = not applicable: too few participants in this age group and period for reliable estimation of incidence rate; Trends in incidence over time can be seen by looking down each age-group column

Table 4.8 **Rates of incidence of major CHD per 1000 person-years by age and calendar period: Whitehall II men**

		Age group, years							
		35-39	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*
Number of person years of follow-up									
Calendar period	*1985-1989*	4450.9	5796.5	4006.1	3985.3	1559.6			
	1990-1994	1202.0	8597.3	8776.0	6503.5	5976.2	1422.6		
	1995-1999		1092.1	7770.0	7929.1	5797.5	5302.9	1229.8	
	2000-2004			954.6	6686.5	6527.7	4770.9	4297.8	867.0
Number of incident major CHD events									
Calendar period	*1985-1989*	0	8	7	19	13			
	1990-1994	0	6	12	21	28	11		
	1995-1999		3	18	20	22	26	7	
	2000-2004			2	13	22	25	23	1
Incidence rate per 1000 person-years (95% CI)									
Calendar period	*1985-1989*	0	1.38 (0.69, 2.76)	1.75 (0.83, 3.67)	4.77 (3.04, 7.47)	8.34 (4.84, 14.35)			
	1990-1994	0	0.70 (0.31, 1.55)	1.37 (0.78, 2.41)	3.23 (2.11, 4.95)	4.69 (3.23, 6.79)	7.73 (4.28, 13.96)		
	1995-1999		2.75 (0.89, 8.52)	2.32 (1.46, 3.68)	2.52 (1.63, 3.91)	3.79 (2.50, 5.76)	4.90 (3.34, 7.20)	5.69 (2.71, 11.94)	
	2000-2004			2.10 (0.52, 8.38)	1.94 (1.13, 3.35)	3.37 (2.22, 5.12)	5.24 (3.54, 7.75)	5.35 (3.56, 8.05)	1.15 (0.16, 8.19)

Table 4.9 **Rates of incidence of major CHD per 1000 person-years by age and calendar period: Whitehall II women**

		Age group, years							
		35-39	*40-44*	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*
Number of person-years of follow-up									
Calendar period	*1985-1989*	1752.1	2401.4	2251.6	2603.8	1075.9			
	1990-1994	459.0	3210.2	3715.7	3522.1	3846.2	927.9		
	1995-1999		415.1	2850.5	3302.2	2954.8	3167.4	753.8	
	2000-2004			370.9	2404.5	2672.2	2280.8	2375.8	483.3
Number of incident major CHD events									
Calendar period	*1985-1989*	0	2	0	3	4			
	1990-1994	1	0	2	10	5	1		
	1995-1999		0	2	1	8	9	3	
	2000-2004			0	1	3	5	14	1
Incidence rate per 1000 person-years (95% CI)									
Calendar period	*1985-1989*	0	0.83 (0.21, 3.33)	0	1.15 (0.37, 3.57)	3.72 (1.40, 9.91)			
	1990-1994	2.18 (0.31, 15.47)	0	0.54 (0.13, 2.15)	2.84 (1.53, 5.28)	1.30 (0.54, 3.12)	1.08 (0.15, 7.65)		
	1995-1999		0	0.70 (0.18, 2.81)	0.30 (0.04, 2.15)	2.71 (1.35, 5.41)	2.84 (1.48, 5.46)	3.98 (1.28, 12.34)	
	2000-2004				0.42 (0.06, 2.95)	1.12 (0.36, 3.48)	2.19 (0.91, 5.27)	5.89 (3.49, 9.95)	2.07 (0.29, 14.69)

Table 4.10 **Average annual age-gender-adjusted percentage declines in incidence of major CHD between 1980 and 2008 in the different data sources, overall and according to socio-demographic characteristics**

British Regional Heart Study, 1980 to 2004		Whitehall II cohort, 1985 to 2004		The Health Improvement Network, 1995 to 2008	
	Average annual decline in hazard (95% CI), %		*Average annual decline in hazard (95% CI), %*		*Average annual decline in rate (95% CI), %*
Overall	3.30 (2.14, 4.46)	**Overall**	4.24 (1.92, 6.51)	**Overall**	4.88 (4.59 to 5.18)
Age group, years		**Age group, years**		**Age group, years**	
40-49	3.75 (-11.9, 17.2)	40-49	-2.10 (-9.22, 4.57)	40-49	2.48 (1.36 to 3.58)
50-59	2.35 (-0.23, 4.86)	50-59	5.60 (2.89, 8.23)	50-59	4.04 (3.31 to 4.77)
60-69	3.57 (2.10, 5.02)	60-69	3.18 (-3.10, 9.07)	60-69	6.55 (5.97 to 7.13)
70-79	3.24 (0.20, 6.19)			70-79	6.36 (5.82 to 6.89)
		Gender		**Gender**	
		Men	4.35 (1.80, 6.84)	Men	4.92 (4.55 to 5.29)
		Women	3.72 (-1.99, 9.12)	Women	4.79 (4.30 to 5.27)
Socio-economic status		**Employment grade**		**Townsend quintile**	
I Professional	5.33 (0.37, 10.1)	Civil Service grades 1-7	5.16 (1.79, 8.41)	1 (least deprived)	5.51 (4.91 to 6.11)
II Intermediate	3.42 (0.87, 5.91)	Executive officer	4.10 (1.11, 7.00)	2	5.15 (4.54 to 5.76)
III Skilled non-manual	4.41 (0.46, 8.20)	Clerical	2.46 (-2.62, 7.28)	3	4.98 (4.34 to 5.62)
III Skilled manual	3.32 (1.55, 5.05)			4	4.80 (4.15 to 5.44)
IV Semi-skilled	1.78 (-1.66, 5.11)			5 (most deprived)	3.69 (2.93 to 4.45)
V Unskilled	1.40 (-3.99, 6.51)				
[Armed forces	1.36 (-5.45, 7.74)]*				
Constituent country				**Constituent country**	
England	2.94 (1.65, 4.21)			England	4.90 (4.58 to 5.22)
Wales	6.61 (0.42, 12.4)			Wales	5.45 (4.16 to 6.73)
Scotland	4.79 (1.58, 7.89)			Scotland	5.28 (4.11 to 6.44)

*Socio-economic status in the BRHS listed in decreasing order with the exception of armed forces, which forms a distinct group of mixed status

Table 4.11 **Rates of incidence of T2DM per 1000 person-years by age and calendar period: British Regional Heart Study men**

		Age group, years						
		55-59	*60-64*	*65-69*	*70-74*	*75-79*	*80-84*	*85-89*
Number of person-years of follow-up								
Calendar period	*1995-1999*	3028.5	7803.1	7327.5	6325.5	3288.8		
	2000-2004		2799.6	6943.1	6196.6	4780.5	2211.6	
	2005-2007			2229.3	3599.7	2872.9	1949.8	571.7
Number of incident T2DM diagnoses								
Calendar period	*1995-1999*	18	54	45	46	20		
	2000-2004		21	69	70	44	18	
	2005-2007			26	50	21	18	6
Incidence rate per 1000 person-years (95% CI)								
Calendar period	*1995-1999*	5.94 (3.74, 9.43)	6.92 (5.30, 9.04)	6.14 (4.59, 8.23)	7.27 (5.45, 9.71)	6.08 (3.92, 9.43)		
	2000-2004		7.50 (4.89, 11.5)	9.94 (7.85, 12.58)	11.30 (8.94, 14.28)	9.20 (6.85, 12.37)	8.14 (5.13, 12.92)	
	2005-2007			11.66 (7.94, 17.13)	13.89 (10.53, 18.33)	7.31 (4.77, 11.21)	9.23 (5.82, 14.65)	10.50 (4.72, 23.36)

Table 4.12 **Rates of incidence of T2DM per 1000 person-years by age and calendar period: British Regional Heart Study men who have survived to 2007 (end of follow-up)**

		Age group, years								
		45-49	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*80-84*	*85-89*
Number of person-years of follow-up										
Calendar period	*1985-1989*	2580.7	6598.7	5280.0	3502.2	1441.1				
	1990-1994		2628.0	6570.2	5262.5	3484.6	1429.6			
	1995-1999			2587.1	6427.1	5138.5	3414.4	1392.8		
	2000-2004				2512.4	6175.2	4907.6	3265.3	1346.6	
	2005-2007					2147.4	3458.5	2645.9	1685.1	499.2
Number of incident T2DM diagnoses										
Calendar period	*1985-1989*	3	19	9	6	2				
	1990-1994		5	21	23	11	4			
	1995-1999			13	38	34	18	10		
	2000-2004				17	60	62	36	14	
	2005-2007					25	49	21	18	6
Incidence rate per 1000 person-years (95% CI)										
Calendar period	*1985-1989*	1.16 (0.37, 3.60)	2.88 (1.84, 4.51)	1.70 (0.89, 3.28)	1.71 (0.77, 3.81)	1.39 (0.35, 5.55)				
	1990-1994		1.90 (0.79, 4.57)	3.20 (2.08, 4.90)	4.37 (2.90, 6.58)	3.16 (1.75, 5.70)	2.80 (1.05, 7.46)			
	1995-1999			5.02 (2.92, 8.65)	5.91 (4.30, 8.13)	6.62 (4.73, 9.26)	5.27 (3.32, 8.37)	7.18 (3.86, 13.34)		
	2000-2004				6.77 (4.21, 10.88)	9.72 (7.54, 12.51)	12.63 (9.85, 16.2)	11.03 (7.95, 15.28)	10.40 (6.16, 17.55)	
	2005-2007					11.64 (7.87, 17.23)	14.17 (10.71, 18.75)	7.94 (5.17, 12.17)	10.68 (6.73, 16.95)	NA

Table 4.13 **Average annual age-gender-adjusted percentage increases in incidence of T2DM between 1985 and 2008 in the different data sources, overall and according to socio-demographic characteristics**

British Regional Heart Study - all men, 1995 to 2007		**British Regional Heart Study - survivors, 1985 to 2007**		**The Health Improvement Network, 1995 to 2008**	
	Average annual increase in hazard (95% CI), %		*Average annual increase in hazard (95% CI), %*		*Average annual increase in rate (95% CI), %*
Overall	5.33 (2.70, 8.02)	**Overall**	7.69 (5.51, 9.92)	**Overall**	3.60 (3.37 to 3.83)
Age group, years		**Age group, years**		**Age group, years**	
				30-39	5.02 (3.87 to 6.19)
				40-49	5.49 (4.82 to 6.17)
		50-59	6.30 (-1.48, 14.7)	50-59	4.32 (3.83 to 4.81)
60-69	5.83 (1.42, 10.4)	60-69	8.38 (5.37, 11.5)	60-69	2.91 (2.49 to 3.33)
70-79	5.16 (1.81, 8.61)	70-79	7.33 (3.78, 11.0)	70-79	3.39 (2.93 to 3.86)
				Gender	
				Men	3.89 (3.58 to 4.20)
				Women	3.34 (3.00 to 3.68)
Socio-economic status		**Socio-economic status**		**Townsend deprivation quintile**	
I Professional	5.07 (-2.44, 13.2)	I Professional	6.98 (2.47, 11.7)	1 = least deprived	3.43 (2.96 to 3.91)
II Intermediate	2.57 (-2.08, 7.44)	II Intermediate	3.98 (0.83, 7.23)	2	3.12 (2.63 to 3.60)
III Skilled non-manual	3.44 (-3.89, 11.3)	III Skilled non-manual	7.40 (2.88, 12.1)	3	3.86 (3.36 to 4.35)
III Skilled manual	6.86 (3.01, 10.9)	III Skilled manual	9.68 (6.98, 12.5)	4	3.52 (3.02 to 4.03)
IV Semi-skilled	7.70 (0.10, 15.9)	IV Semi-skilled	7.76 (3.00, 12.7)	5 = most deprived	4.99 (4.40 to 5.58)
V Unskilled	16.5 (4.97, 29.4)	V Unskilled	14.7 (8.52, 21.3)		
[Armed forces	-5.97 (-17.8, 7.54)]*	[Armed forces	4.9 (-3.34, 13.9)]*		
Constituent country		**Constituent country**		**Constituent country**	
England	4.65 (1.84, 7.53)	England	7.36 (5.01, 9.77)	England	3.62 (3.37 to 3.87)
Wales	-0.74 (-14.3, 14.9)	Wales	1.90 (-10.2, 15.7)	Wales	2.65 (1.68 to 3.63)
Scotland	6.31 (-0.97, 14.1)	Scotland	11.3 (4.75, 18.3)	Scotland	3.66 (2.69 to 4.63)

*Socio-economic status in the BRHS listed in decreasing order with the exception of armed forces, which forms a distinct group of mixed status

Figure 4.1 **Flowchart illustrating derivation of THIN cohort for analysis of time trend in major CHD incidence**

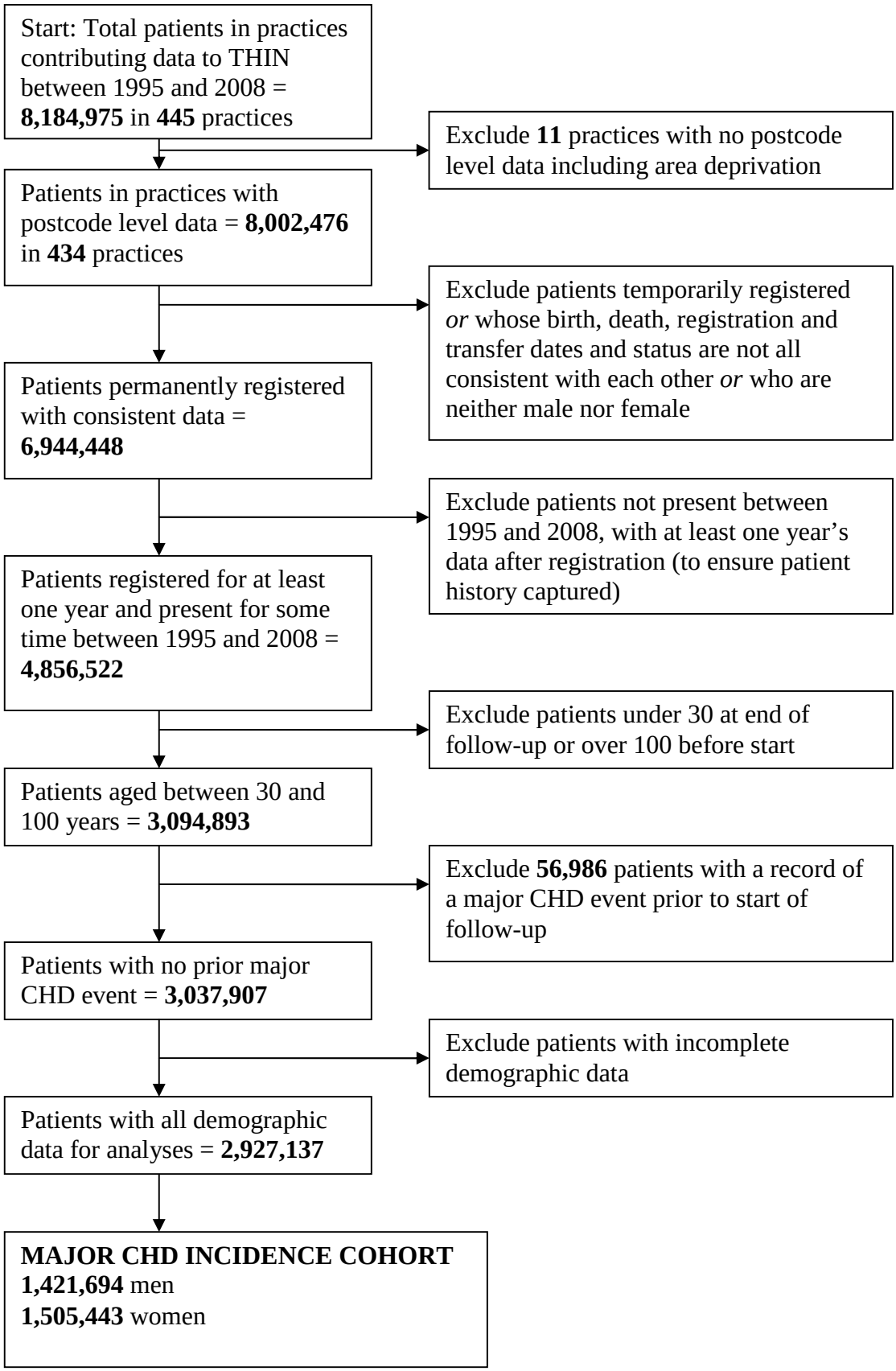


Figure 4.2 **Flowchart illustrating derivation of THIN cohort for analysis of time trend in T2DM incidence**

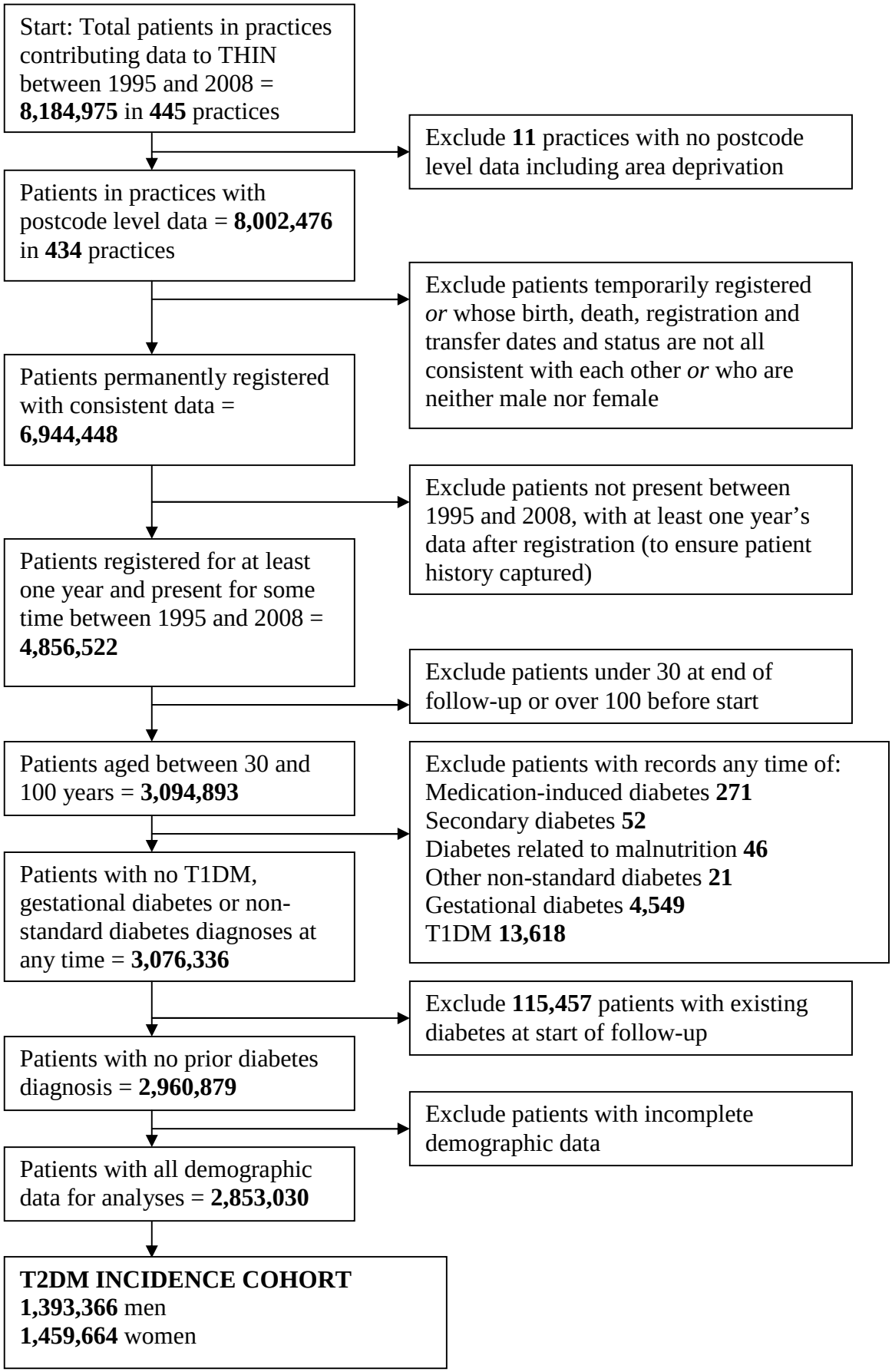
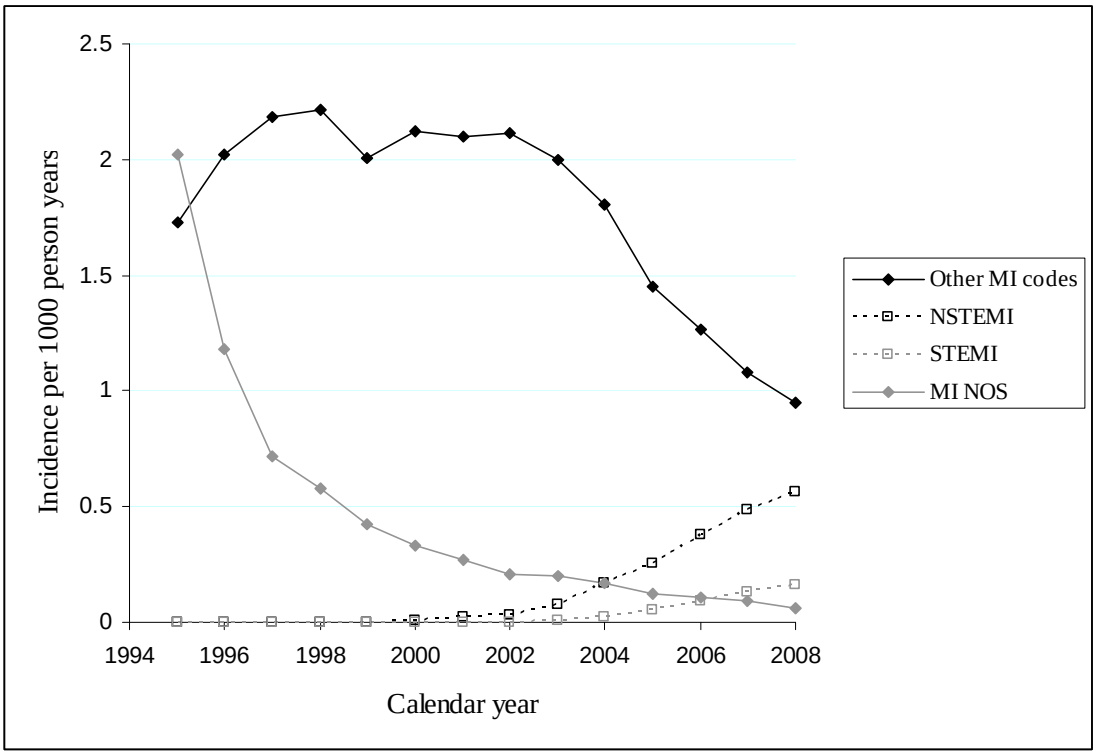


Figure 4.3 **Trends over calendar time in use of different types of Read codes for incident major CHD among patients aged 30 years and over in the THIN database**



NOS = Not otherwise specified

Figure 4.4 **Trends over calendar time in use of different types of Read codes for incident diabetes among patients aged 30 years and over (therefore assumed to be T2DM) in the THIN database**

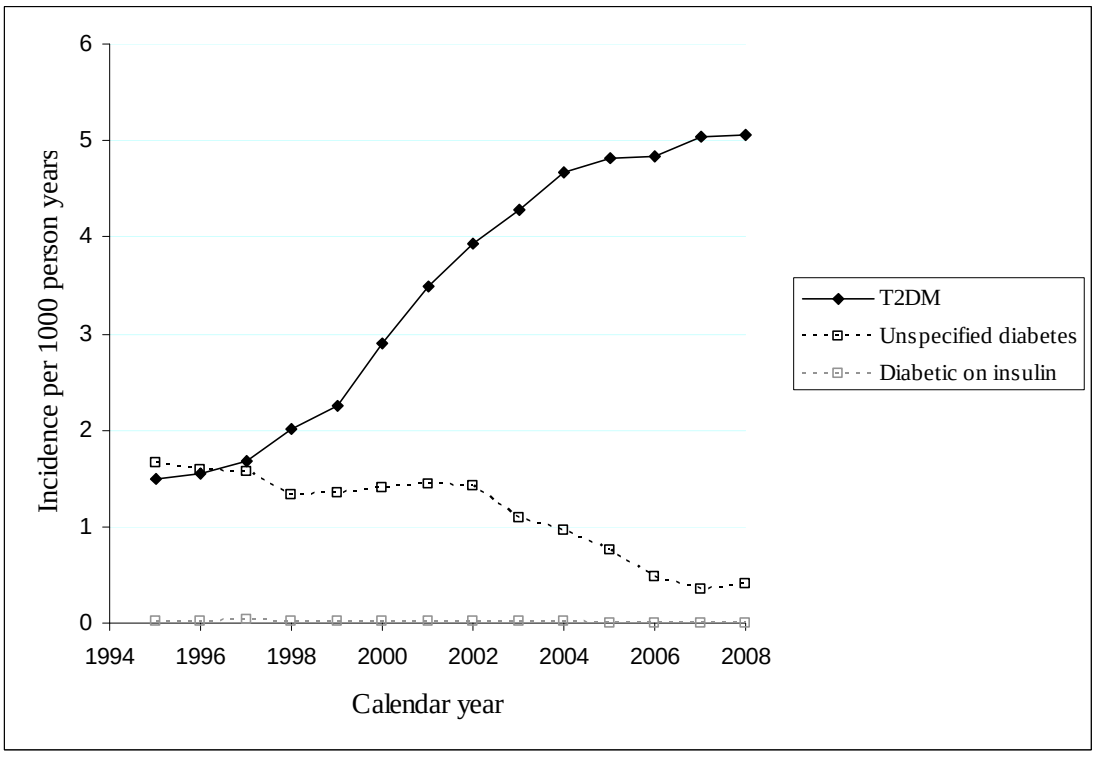


Figure 4.5 **Time trend in the rate of incidence of major CHD per 1000 person-years by gender: THIN database**

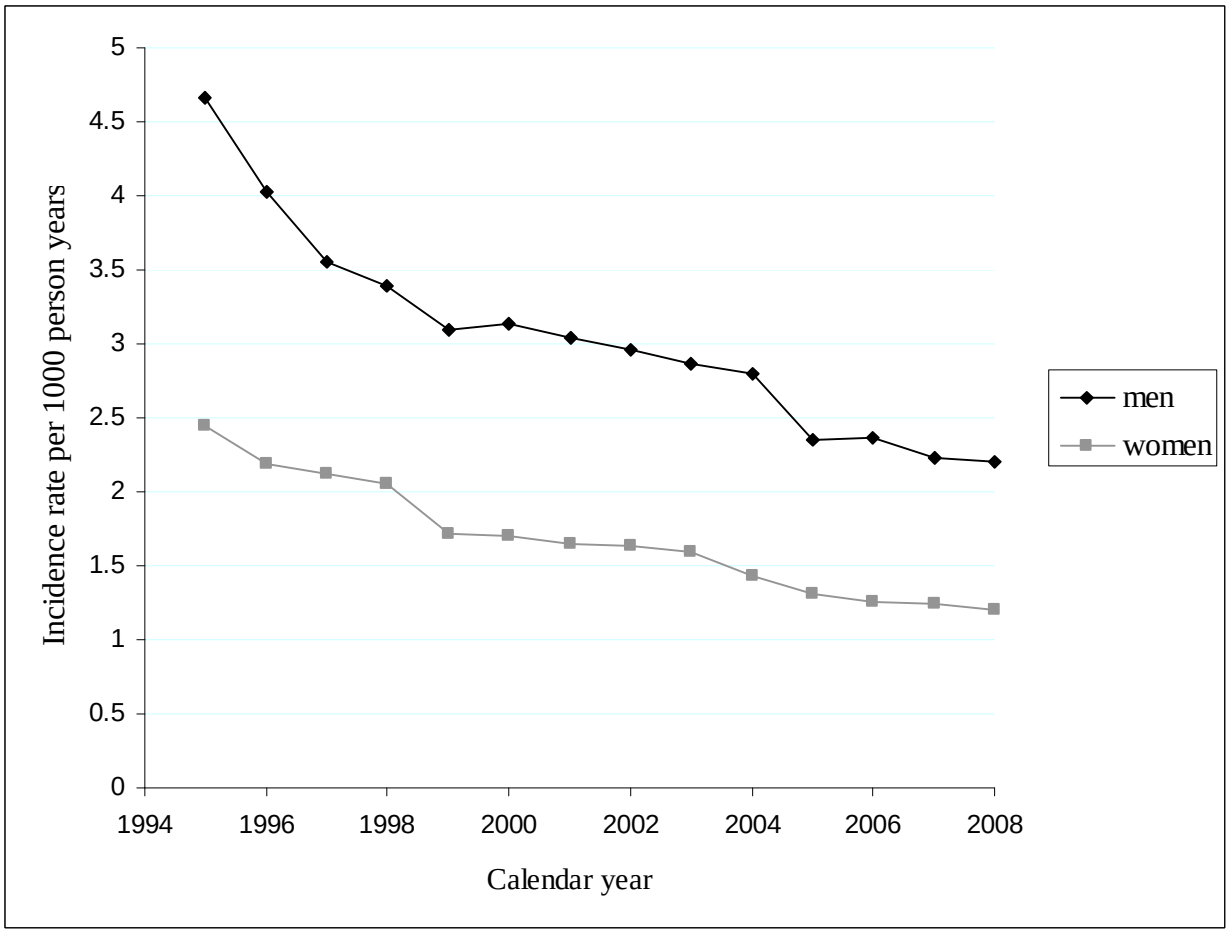
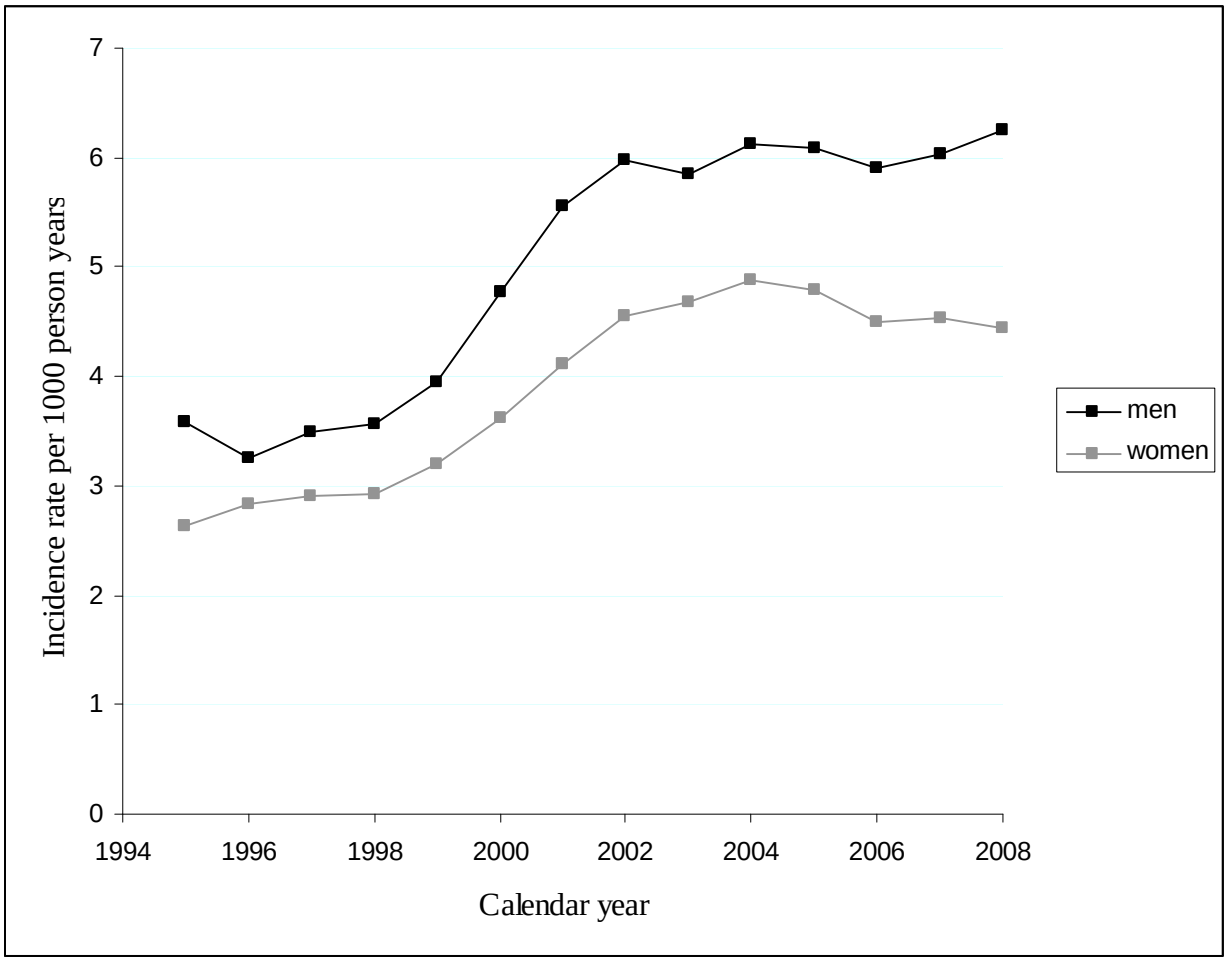


Figure 4.6 **Time trend in the rate of incidence of T2DM per 1000 person-years by gender: THIN database**



Chapter 5: Analysing the role of trends in aetiological exposures in the time trend in major coronary heart disease incidence in the British Regional Heart Study

5.1 Introduction

In chapter 4 it was shown that considerable favourable secular time trends in incidence of major coronary heart disease (CHD) have occurred in the UK in recent decades, contributing to an overall decline in CHD mortality rates. In particular in the British Regional Heart Study (BRHS) cohort, a 57% decline in the incidence of major CHD over 25 years from 1980 to 2004 was observed, adjusting for age.

Understanding the reasons for the favourable time trend in CHD incidence may help to inform future efforts to reduce CHD further, both in the UK and in other locations. As shown in chapter 2, table 2.1, few studies worldwide have been able to examine the contribution of changes in lifestyle factors or interventions, either individually or in combination, to time trends in CHD *incidence*[13, 17, 298]. The one previous study incorporating sections of the UK population, was based on aggregate data and thus subject to limitations of ecological analyses[13]. It also included only two cities (Belfast and Glasgow), which may not be representative of the wider UK population, and focus was on explaining variations in major CHD trends between populations rather than within populations. The aim of this chapter is therefore to explore the reasons for the decline in major CHD incidence in the UK population. Specifically, the principal objectives are to estimate secular trends in established aetiological exposures and then to quantify the extent to which the decline in incidence of major CHD may be attributable to the secular trends in these exposures. Data from the representative BRHS will be used, enabling an individual-level analysis combining individual aetiological exposure levels with CHD outcomes, to look at trends over 25 years from

1978 in British men. This corresponds to objective iii)a) of the overall thesis objectives.

Objectives

1. To estimate the secular time trends in major CHD aetiological exposures in British men over 25 years since 1978
2. To quantify the contribution of the trends in the aetiological exposures to time trends to the decline in incidence of major CHD over this time

The structure of this chapter is as follows: Section 5.2 details methods specific to this section, including statistical methods. Section 5.3 presents results related to the first objective, to estimate secular time trends in major CHD aetiological exposures. Section 5.4 presents results related to the second objective, to quantify the contribution of the trends in the aetiological exposures to the decline in incidence of major CHD. Finally, section 5.5 provides a discussion and interpretation of the findings of the chapter.

5.2 Methods

5.2.1 Data source

Analyses in this chapter are carried out using the BRHS, described in detail in chapter 3. As outlined in chapter 3, section 3.2.9, the BRHS is particularly suitable for this analysis as CHD outcomes and risk factors levels have been concurrently monitored over an extended period. Moreover a marked decline in incidence of major CHD was demonstrated in the previous chapter 4, and the men recruited to the BRHS cohort are

socially and geographically representative of men of the same age across Britain, at least at recruitment in 1978-80. Follow-up data up to 31 December 2004 was used for this analysis, as this was the most recent data available when the analysis was carried out. This enables exploration of time trends over a quarter of a century. Questionnaire/ examination data up to and including the examination at 20 years follow-up in 1998-2000 were used.

5.2.2 Principal outcome of a first major CHD event

The principal outcome was a first major CHD event, defined as death with CHD as the cause or a non-fatal myocardial infarction (MI), over the 25 year period between baseline (1978-80) and 31 December 2004. Diagnosis methods are outlined in chapter 3, section 3.2.4.

5.2.3 Aetiological exposures

The risk factors considered as potential contributory factors to the CHD trends were those lifestyle and clinical factors with strong evidence for a potentially causal association with major CHD identified in chapter 2, section 2.5.2.1, and for which repeated measurements are available in the BRHS. Specifically, the risk factors considered were: cigarette smoking, systolic blood pressure (SBP), non-HDL cholesterol (difference between total cholesterol and HDL cholesterol), HDL cholesterol, alcohol consumption, physical activity, and BMI. Strong associations between each of these risk factors and CHD have been established, as outlined in chapter 2, section 2.5.2.1. Diet and diabetes were also identified as major aetiological exposures, but repeated data on diet was not available, while the role of diabetes is considered separately in chapter 9. Methods of ascertainment of each risk factor, and

categorisations, are detailed in chapter 3, section 3.2.5. Risk factor data over the 20 year period from baseline (1978-80) to the 20-year follow-up examination (1998-2000) were considered. Cigarette smoking status, alcohol consumption, physical activity level and BMI data were available at each questionnaire time-point during the follow-up, that is, at baseline (1978-1980), at 5 years (1983-5), in 1992, in 1996 and at 20 years (1998-2000). Physical activity data was not collected at 5 years, and was instead imputed as the "average" of levels at baseline and in 1992 (see chapter 3, section 3.2.7). SBP, HDL and non-HDL cholesterol measurements were made at the two physical examinations at baseline and at 20 years.

5.2.4 Statistical methods

As outlined in section 5.1, the main aim of this chapter is to explore and estimate the secular time trends in the major coronary risk factors and the role that these time trends have played in the decline in major CHD hazard. Key to addressing this aim is the availability of repeated risk factor data at the different questionnaire/ examination time-points in the BRHS. We can compare the risk factor levels in different questionnaires at different time-points. A crucial point is that when comparing risk factor levels at different time-points, we are not concerned with within-person changes. Rather, we compare risk factor levels among men of a certain age at one time-point with men who reach that same age at a different time point. Figure 5.1 serves to illustrate this, showing the age range of the men at each questionnaire time-point. Because the age-range of the men at recruitment was wide, spanning twenty years, from aged 40 to 60 years, there is considerable overlap in age between the different time-points. Consider for example the youngest men at recruitment who were 40 years old at say the latter part of the 1978-1980 recruitment period, that is

recruited in 1980. At the five year follow-up in 1985 they were 45 years old and so their risk factor and major CHD risk in 1985 may be compared with that at baseline of other men aged 45 at baseline. Similarly, at the next follow-up date in 1992, they were aged 52 years. And so on up to the 20 year follow-up in 2000 when, now aged 60, their risk factor data and major CHD risk in 1998-2000 may be compared with that of the eldest men who were already approaching 60 years at baseline. Importantly, by comparing men of the same age at the different time-points, rather than looking at within-man changes, we are able to disentangle the "effect" of calendar time from the effect of aging. For example, SBP tends to rise with age[347] thus looking at within-man changes, any potential secular decline in SBP over calendar time would likely be masked by the within-man rise with age.

To explore the secular between-time-point risk factor and major CHD trends some restructuring of the data is needed. The follow-up for each man was split into five consecutive periods, each of approximately five years, separated by the different questionnaires/ examination time-points. Specifically the five periods were: period 1 from 1978-80 to 1983-5; period 2 from 1983-5 to 1992; period 3 from 1992 to 1996; period 4 from 1996 to 1998-2000 and period 5 from 1998-2000 to 2004. Each period is then treated as if corresponding to a separate individual, such that each of the 7735 men in the BRHS now contribute up to five "pseudo-individuals", depending on length of follow-up of each man: if a man dies or is lost to follow-up or experiences a major CHD event, the man contributes to periods only up to and including the period in which the death, CHD event or censoring occurs. Thus these men will correspond to fewer than five new pseudo-individuals and there will be fewer pseudo-individuals in the later periods. Each of these new pseudo-individuals has a "baseline" as the date

of the questionnaire at the start of the relevant period, and "baseline" risk factor levels as the risk factor levels in that questionnaire. Each pseudo-individual is followed-up for major CHD for approximately five years, to the date of the next questionnaire. The date of end of follow-up for each pseudo-individual is the minimum of the following: date of major CHD event, date of non-CHD death, date of loss to follow-up, date of next questionnaire. For the final period, starting at the latest questionnaire/ examination used in this analysis in 1998-2000, and for which there is no questionnaire to mark the end of the period, the date of end-of follow-up is the minimum of: date of major CHD event, date of death, date of loss to follow-up and 31 December 2004. Grouping pseudo-individuals at each period, we obtain five "sub-cohorts", each followed-up for approximately five years from "baseline", at different calendar periods, which are then compared to assess secular trends over time. From a data handling point of view, splitting up the data in this way results in one large dataset, with each row representing a different pseudo-individual, such that each of the original 7735 men in the BRHS may have up to five rows of data. An illustration of the dataset is shown below (not actual data):

ID of man	pseudo-individual	Pseudo-baseline qu'naire	Start date of follow-up for pseudo-individual	End date of follow-up for pseudo-individual	Outcome (major CHD event) for pseudo-individual	Date of Outcome	Pseudo-baseline smoking	Pseudo-baseline BMI	…
123456	A1	1978-80	01-Jun-79	01-Jun-84	0		current	25.1	
123456	A2	1983-85	01-Jun-84	15-Oct-92	0		current	25.3	
123456	A3	1992	15-Oct-92	10-Apr-96	0		current	26.0	…
123456	A4	1996	10-Apr-96	01-Jun-99	0		ex	26.2	
123456	A5	1998-2000	01-Jun-99	31-Dec-04	0		ex	26.2	
123457	B1	1978-80	08-May-80	08-May-85	0		current	28.2	
123457	B2	1983-85	08-May-85	15-Oct-92	0		current	28.5	…
123457	B3	1992	15-Oct-92	21-Feb-94	1	21-Feb-94	current	29.0	
									…
123458	C1	1978-80	17-Mar-78	17-Mar-83	0		never	27.3	
123458	C2	1983-85	17-Mar-83	07-Jan-87	0		never	28.2	
…	…	…	…	…	…	…	…	…	…
…	…	…	…	…	…	…	…	…	…

The first five rows represent five pseudo-individuals derived from the first man (ID 123456), who survived until the very end of the follow-up on 31 December 2004, without having a major CHD event. The next three rows represent three pseudo-individuals derived from the second man (ID 123457), who had a major CHD event on 21 February 1994, after which he no longer contributes to the study. The next two rows represent two pseudo-individuals derived from a third man (ID 123458) who died on 7 January 1987, of non-CHD causes, without having a major CHD event.

Simple cross-tabulations of each of the risk factors according to five-year age groups and questionnaire/ examination time-point were carried out to enable an initial exploration of how risk factor levels have changed over calendar time in the cohort. Formal estimates of population-averaged changes over time in each risk factor, per annum and over the 20-years from baseline (1978-80), were obtained from regression modelling in this expanded dataset of the each risk factor on calendar time, with use of generalised estimating equations (GEEs) with robust standard errors to take account of dependency between repeated measures for each man. For each pseudo-individual, the variable "calendar time" was computed as the time in years from the very start of the study, at the first recruitment in 1978, to the date of the start of the follow-up for each pseudo-individual. The coefficient of calendar time thus corresponded to the per annum risk factor change, while multiplying the coefficient by 20 gave an estimate of the 20 year changes. Age at the "baseline" for each pseudo-individual (that is, at the date of the questionnaire at the start of the period to which the pseudo-individual belongs) was included as a covariate (along with all significant powers) to adjust for age and thereby isolate the effect of calendar time from the effect of cohort aging. Specifically, population-averaged trends in the odds of being a

current smoker, the odds of being least moderately physically active and the odds of being a regular drinker over time were obtained from logistic regression with GEEs. Linear regressions with GEEs were used to give estimates of the population-averaged age-adjusted mean trends in each of the continuous variables (BMI, SBP, HDL and non-HDL cholesterol).

The contribution of each risk factor trend to the decline in major CHD hazard was assessed by comparing Cox proportional hazards regression models of incident major CHD on "calendar time" in this expanded dataset of pseudo-individuals, with and without adjustment for the risk factor at the pseudo-baseline for each pseudo-individual. Age was used as the underlying time scale in these time-dependent Cox regressions, with date of birth as a time origin, and age at the date of the "baseline" for each pseudo-individual as a delayed entry time to take account of left truncation. Use of an age time scale, as well as automatically adjusting for age[325], also permitted calendar time to be entered into the model as a covariate so that the change in the hazard of major CHD with calendar time could be estimated. Follow-up time and major CHD incidence were defined using the start and end dates and outcome for each pseudo-individual defined above. Schoenfeld residuals were used to test the proportional hazards assumption[326]. Robust standard errors were used to account for the dependency between the different pseudo-individuals corresponding to the same man.

The proportion of the decline in major CHD hazard statistically explained, or attributable to, the risk factor trend is given by the expression $(\beta_0-\beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in a Cox regression model with just calendar time as a

covariate, and β_1 is the coefficient of calendar time in a Cox regression model adjusting additionally for the risk factor(s)[348]. This is the percentage attenuation of the calendar time coefficient in the presence of the risk factor(s). Bias-corrected bootstrap re-sampling was used to give an approximate 95% confidence interval (CI) for this estimate[349]. Physical activity, alcohol consumption and cigarette smoking were entered into models as categorical class variables. BMI, SBP, non-HDL cholesterol and HDL cholesterol were continuous. As data on SBP, non-HDL cholesterol and HDL cholesterol were only available at the study baseline in 1978-80 and at 20 years in 1998-2000, to eliminate bias all models incorporating these variables included only data from the first period (with 1978-80 as the pseudo-baseline) and the last period (with 1998-2000 as the pseudo-baseline). In the above expression coefficients of calendar time from these models were compared with the coefficient from a separate unadjusted model also using this restricted follow-up data. Squared terms in the continuous risk factor variables were included where significant (non-HDL cholesterol and SBP).

The above methods to estimate the percentage of the decline in major CHD explained by the risk factor trends, correspond to those used by Hu *et al* to investigate the decline in major CHD in a cohort of women in the US[17], as outlined in chapter 2, section 2.7.1. The chief difference is that Hu *et al* use logistic regression to compare the risk of major CHD in different periods, as opposed to the hazard of major CHD from Cox regression (reflecting that the outcome in the study by Hu *et al* was ascertained at intervals rather than continuously). Hu *et al* note the correspondence between their pooled logistic regression analysis and time-dependent Cox regression[350]. However, use of Cox regression is arguably a more powerful approach,

as participants are included until the date of their event or exit from the study, rather than only if they survive to the end of the relevant period (which is the case for computation of risks in logistic regression which does not take into account person time).

5.2.5 Participants included in analysis

All study men were included except those who had had a major CHD event before baseline (n=952). Men who had a major CHD event during follow up were excluded from the analyses of major CHD incidence after the time of their event. These men were also excluded after the time of their event from the GEE regression analyses of changes in risk factors so that the changes in the risk factors estimated from the GEE analyses corresponded to changes among the disease-free population that may therefore influence the trend in the hazard of a first major CHD event. Men with angina (either at baseline or during follow up) were retained for analysis, unless they also developed a major CHD event. Men missing data on any risk factor in a questionnaire time-point were excluded from that time-point and the associated follow-up, but included at other time points. Men missing some risk factor data in all time-points were excluded from the analyses altogether (n=106).

Table 5.1 shows the numbers of men included in each questionnaire time-point (and the associated subsequent follow-up period), which corresponds to the numbers of men with no prior major CHD event and complete risk factor data at that time point. 6,751 men contributed risk factor data at at least one time-point and so could be included in the main analyses to explain the major CHD time trends. Since follow-up for major CHD was maintained for >98% of surviving men, the fall in the numbers of

men contributing over time reflects the loss of those who had a major CHD event, died or who did not provide risk factor information (by not responding to the questionnaire or attending the examination), rather than loss to follow-up.

5.3 Results - Time trends in major coronary risk factors

Table 5.2 shows the distribution of the major coronary risk factors at each questionnaire time-point among the study men, by 5-year age group. The secular time trends in each risk factor may be seen by looking down each age-group column. There was a clear decrease over time in the proportion of men who were cigarette smokers within each age group. Indeed, from logistic regression with GEEs, the age-adjusted population-averaged odds of being a current cigarette smoker declined by 73% (95% CI 68 to 78, $p<0.001$) between baseline and the 20-year follow-up. There was no significant evidence of a change over this time in the proportion of men who regularly drink, after adjusting for age ($p=0.2$, from logistic regression with GEEs). Physical activity levels increased slightly, with the age-adjusted population-averaged odds of being at least moderately active at 20 years follow-up being 1.91 (95% CI 1.62 to 2.24, $p<0.001$) times that at baseline. Over the 20-years, age-adjusted mean BMI increased significantly by 1.89kg/m^2 (95% CI 1.61 to 2.18, $p<0.001$), from linear regression with GEEs. For example, between baseline and the 1996 questionnaire (an average time of 17 years into the study), among 55-59 year olds mean BMI increased from 25.4kg/m^2 to 27.2kg/m^2. Among 60-64 year olds mean BMI increased from 26.1kg/m^2 at 5 years follow-up to 27.3kg/m^2 at 20 years follow-up (a period of 15 years). The secular time trends in SBP, HDL and non-HDL cholesterol are not easily ascertained from the Table 5.2, as these risk factors were only measured at two time points 20 years apart with non-overlapping age ranges. However, linear regression

with GEEs gave an estimate of an age-adjusted fall in mean SBP of 7.2mmHg (95% CI 4.9 to 9.5, p<0.001) over the 20 years. Similarly, from linear regression with GEEs, it was estimated that mean HDL cholesterol levels increased by 0.15mmol/L (95% CI 0.12 to 0.19, p<0.001), adjusting for age, and mean non-HDL cholesterol levels fell by 0.30mmol/L (95% CI 0.18 to 0.41, p<0.001), adjusting for age.

5.4 Results - Analysis of relation of trends in risk factors to trends in major coronary heart disease incidence

Among the 6,751 men included in the main analysis, adjusting for age, the hazard rate of major CHD fell by 3.8% (95% CI 2.6 to 5.0, p<0.001) per annum, corresponding to a fall of 62% (95% CI 48 to 72) over 25 years from baseline. This is very close to the 57% estimate in chapter 4, section 4.5.1.3; the very modest difference reflecting primarily the exclusion of non-responders (no risk factor data) in later years. Estimates of the proportions of the decline in the hazard of major CHD over time attributable to each risk factor time trend, derived using the technique outlined in section 5.2.4, are presented in table 5.3. The largest single contribution was that of the fall in cigarette smoking, which in isolation statistically explained 23% (bootstrap 95% CI 15 to 34) of the observed 62% decline in the hazard of major CHD over the 25 years from baseline. The fall in mean SBP explained 13% (bootstrap 95% CI 6 to 54) of the decline in hazard, the rise in mean HDL cholesterol explained 12% (bootstrap 95% CI 5 to 42) and the fall in mean non-HDL cholesterol explained 10% (bootstrap 95% CI 4 to 32). Physical activity explained a borderline significant part of the decline (5%, bootstrap 95% CI 0 to 11). Alcohol consumption had little impact (1% explained). The rise in mean BMI was adverse (-7% of the decline in major CHD explained, 95% bootstrap CI -13 to -3), and, in the absence of changes in the

other risk factors, would have been expected to lead to an increase, rather than a decline, in the hazard of major CHD over time.

Taken together, the four factors which, singly, accounted for statistically significant reductions in major CHD hazard (cigarette smoking, SBP, non-HDL cholesterol and HDL-cholesterol) could explain 46% (bootstrap 95% CI 23 to 164) of the decline. This figure is less than the sum of the individual contributions reflecting that the risk factors are not independent from each other. The interpretation of the CI, with an upper bound greater than 100%, is that the data are consistent (at the 95% confidence level) with the risk factors explaining at least 23% of the decline in the hazard of major CHD and at most an even greater decline than that observed. The addition of physical activity and alcohol intake made little difference to this estimate (44%, bootstrap 95% CI 22 to 149). There was no evidence of departure from the proportional hazards assumption of the Cox regression.

The effect of adjustment for the (non-significant) laboratory measurement differences in blood lipid measurements described in chapter 3, section 3.2.6, would be to reduce the mean 20 year increase in the HDL cholesterol level from 0.16 mmol/L to 0.10 mmol/L, while leaving the decrease in non-HDL cholesterol levels unchanged at 0.28 mmol/L. On this basis, the contribution of HDL cholesterol to the observed decline in MI hazard would be reduced from 12% to 7% (bootstrap 95% CI 3 to 29), while that of non-HDL cholesterol levels would remain unchanged at 10%. The overall combined contribution of the four major risk factors (smoking, blood pressure, non-HDL, HDL cholesterol and physical activity) would be reduced from 46% to 43%.

5.5 Discussion

5.5.1 Summary of main findings

Of the 62% decline in the hazard of major CHD in this cohort of British men over 25 years from 1978-80 to 2004, 46% could be explained by a combination of time trends in the major coronary risk factors over this time: a fall in the number of cigarette smokers (most powerful of all), a decrease in the mean SBP among the cohort, an increase in mean HDL cholesterol and a decrease in mean non-HDL cholesterol. Physical activity and alcohol consumption had relatively little impact. The rise in mean BMI was counterproductive and, in the absence of changes in other risk factors, would have been expected to lead to an increase, rather than a decline, in the incidence of major CHD.

5.5.2 Comparison with other studies

In terms of the risk factor trends seen, the overall decline in SBP is consistent with cross-sectional routine data for England reported in the Health Survey for England 1998[351] and with SBP trends observed in Glasgow, Scotland (WHO MONICA)[245], (mean fall of 4.5mmHg over an overlapping 10-year period between 1986 and 1995 compared with our figure of 7.6mmHg over 20 years). Data on long-term trends in cholesterol in the UK is limited, particularly for HDL cholesterol, although a separate Health Survey for England report on cardiovascular disease and risk factors[352] highlighted a significant decline in the prevalence of total cholesterol levels exceeding 5mmol/L between 1994 and 2006. The same report suggested that between 2003 and 2006 the prevalence of HDL cholesterol levels below 1mmol/L had increased in men, contrary to our findings, which may be explained by the more recent time period, short (3 year) follow-up and large age–range covering all ages, as opposed to middle

to older age only. The Office for National Statistics General Household survey reported a consistent decline in smoking prevalence in Great Britain from 47% among men aged 50-59 years and 36% among men aged 60 or over in 1978 to 27% among men aged 50-59 years and 16% among men aged 60 or over in 2000[353]. Data from the Health Survey for England[73], showed a comparable increase in BMI levels; mean BMI in men aged 55-64 years increased from 27.1kg/m2 in 1993 to 27.9kg/m2 in 2000. Health Survey for England data also showed the proportion of men and women meeting government recommended physical activity levels to have risen slightly from 32 to 36% in men in England from 1997 to 2003, the slight increase consistent with that observed among the BRHS men over that period. The negligible change in alcohol consumption among the BRHS men reflects national data over a concurrent period[353].

Few studies have looked directly at how time trends in risk factors correspond to time trends in *incidence* of major CHD, and just one other study, by Hu *et al.*, in a US population, used individual data (US Nurses Health Study)[17] and may be directly compared with the chapter findings. In that study, outlined in chapter 2, section 2.7.1, (which did not measure blood pressure or blood lipids) decreased smoking prevalence accounted in isolation for 42% of the decline in CHD, changes in diet (particularly a decrease in saturated fat, an increase in fibre) accounted for 52% and an increase in post-menopausal hormone use accounted for 29%. In the presence of an adverse change in BMI, 68% of the decline in incidence could be explained by combined changes in smoking, diet and post-menopausal hormone use. The larger percentage of 68% of the decline explained by the risk factors may reflect the quality of exposure assessment, and the influence of diet on a range of risk factors (including blood

pressure and cholesterol). As outlined in chapter 2, section 2.5.2.2, the protective effect of hormone replacement therapy is uncertain in the light of more recent evidence that post-menopausal hormone use increases CHD risk[170-173]; discounting hormone replacement therapy would bring the combined percentage explained closer to our estimate. The WHO MONICA Project, based on aggregate data, suggested that cigarette smoking, SBP and total cholesterol together explained approximately 38% of the variation in coronary event rates from the mid-1980s to the mid-1990s in men in 27 different populations, including Belfast and Glasgow[13]. The individual contribution of cigarette smoking was 20%, that of total cholesterol was 19% and that of SBP was 6%, figures broadly consistent with the findings in the present study. Note that in the WHO MONICA project, a different approach was adopted to that of Hu *et al* and that employed in this study; risk factor levels were used to explain variation between populations rather than variations in MI risk over time within a single population. The IMPACT project used aggregate data to examine the influence of different factors on the decline in CHD *mortality* in England[15] and Scotland[12] in recent decades. The IMPACT project found that 52% of the decline in CHD mortality in England between 1981 and 2000 could be accounted for by major risk factor changes, with the decline in cigarette smoking accounting for 44% and changes in blood pressure and total cholesterol accounting for close to 10% each[15]. Similar proportions were observed in Scotland, with respect to the CHD mortality decline between 1975 and 1994 (56% for all major factors, 36% for cigarette smoking and 6% each for blood pressure and total cholesterol)[12]. These results correspond well with the results from the present analysis in showing the relative importance of the risk factors (in terms of the relative sizes of percentage contributions) to be the same. None of these studies looked at the contribution of HDL cholesterol.

This analysis is distinct from studies assessing the more familiar "population attributable risk fraction" (PARF) of major CHD for given risk factors[143, 354]. In studies of PARF, the objective is to assess the degree to which overall risk of major CHD in a population is attributable to risk factors. In this study the objective is instead to assess the degree to which the *trend over time* in major CHD risk in the population is attributable to risk factor trends; in particular how much of the favourable decline in major CHD may be attributable to risk factor improvements. As well as a difference in the interpretation of the findings, the key difference in the modelling is that overall risk of major CHD in a PARF calculation may be attributed to a combination of modifiable risk factors, such as adiposity, and static risk factors, such as genetics, while in contrast, trends over time in major CHD may be attributed to only modifiable risk factors, which have changed over time in the cohort, thus the relative contribution of factors may differ. Since the trends in major CHD may be attributed only to modifiable risk factors, the analysis may arguably be considered to have more immediate public health implications in terms of identifying ways to reduce underlying risk of major CHD in a population. For comparison, the INTERHEART study computed PARFs for (non-fatal) MI for men in Western Europe as smoking 39%, exercise 38%, alcohol 14%, hypertension 21%, abdominal obesity 69% and lipids (combined) 37%[143]. Broadly speaking these figures concord with the present findings, in particular the important roles of smoking, hypertension and lipids.

5.5.3 Strengths and limitations

This cohort is socially and geographically representative of British men of the same age range, with the exception of ethnic minority groups. The representativeness is substantiated by the observation in chapter 4, section 4.6.3, that the trends in major

CHD incidence are consistent with those estimated in THIN and Whitehall II, and other data sources, while mirroring trends in CHD mortality. Moreover, as detailed in the previous section 5.5.2, the trends seen in risk factors in this cohort are consistent with routine data for the UK.

A key strength is the relating of risk factor changes to coronary events within the same population of individuals, avoiding the limitations of ecological analyses predominantly used to study time trends[258]. Comparability between the risk factor measurements at different time points is also very important in this analysis. As detailed in chapter 3, sections 3.2.5 and 3.2.6, behavioural risk factor levels have been recorded frequently and using consistent methods of ascertainment on each occasion. Adjustment of the 20 year SBP measurements ensured comparability between the two time-points. In subsidiary analyses adjusting for the non-significant systematic differences between the baseline and 20-year lipid measurement techniques, the conclusions did not change.

In this analysis the estimates of the risk factor trends, the major CHD time trend, and the roles of the risk factors in the CHD time trend, are based on those who provided risk factor information after baseline (through responding to questionnaires after baseline and/ or attending the follow-up examination), rather than the whole study population. The potential for survival or response biases needs consideration. The most likely impact would be overestimation of the favourable trends observed in both the risk factors and major CHD incidence, due to the healthy participant effect. However, the similarity between the major CHD incidence trend estimates in the BRHS in chapter 4, section 4.5.1.3 (whole cohort) and in the BRHS in this chapter

(responders with risk factor data) suggests any such bias would be limited. In addition, to explore the potential response or survivor effects on the risk factor trends in this cohort, baseline levels of the risk factors among those who attended the 20-year examination have been compared with levels among non-attendees[355]. The differences between the baseline levels were generally small to negligible (mean differences of 0.1kg/m^2, 0mmol/l, 2.4mmHg and 1.2mmHg for BMI, total cholesterol, SBP and DBP respectively), especially when compared with the overall changes over time, suggesting that response or survivor effects were unlikely to have had a dramatic influence on the observed trends (and therefore the contribution to the major CHD decline). One exception is cigarette smoking; non-attendees were significantly more likely to be cigarette smokers at baseline than attendees (prevalence of 47% versus 32%), which may have led to overestimation of the smoking decline (and therefore contribution to major CHD decline), although again, the difference between the non-attendees and attendees is still small compared with the change in prevalence over time.

The limited (two point) data on blood pressure and cholesterol necessitated restriction of the follow-up time to the first five years and the last five years only to analyse the contribution of these risk factors. The effect of using this restricted dataset on the results was investigated by comparing estimates of the contribution of smoking, alcohol consumption and physical activity computed using this restricted data with the reported estimates for these risk factors computed from the full dataset. In all cases, the contributions estimated from the limited dataset (17% for smoking, 0.2% for alcohol, 2% for physical activity) were slightly smaller than the estimates from the full dataset. This suggests that use of this limited data may if anything have led to

underestimation of the contributions of blood pressure and cholesterol, assuming a similar pattern. Physical activity imputed at Q5 (see chapter 3, section 3.2.7) could lead to an induced trend in physical activity, however the likely influence on the physical activity results is small as the observed trend in physical activity was in any case modest.

Analyses have been based on the assumption that the effects of risk factor levels on CHD outcomes occur within the time between consecutive questionnaires (approximately five years). This could lead to underestimation of the effects of a risk factor trend, if there is a lag time of more than five years before the benefits of a risk factor change are realised. However, there is evidence that substantial benefits from smoking cessation, changes in blood lipids and changes in blood pressure are realised within five years[356-358]. The effects of regression dilution[144], which could influence both the extent of risk factor changes over time, and the estimates of risk factor associations with MI risk, have also not been taken into account; this could influence estimates of risk factor contributions in either direction. Overall statistical power and precision of the analysis are limited, and bootstrap CIs are therefore wide, although in the main informative. The cohort comprises older, mainly white, British men; generalisability of the results of both analyses to other populations (women, younger men, different ethnic groups or different countries) is uncertain. In chapter 6, trends in major CHD incidence are analysed in the Whitehall II cohort, comprising men and women, providing the opportunity to validate the findings in men in the BRHS in this chapter with an external dataset, as well as to investigate how the results vary for women.

5.5.4 Interpretation of findings

In this cohort of older British men, half the decline in major CHD incidence may be attributed to modest favourable time trends in cigarette smoking, blood lipids (HDL and non-HDL cholesterol) and blood pressure.

According to the results, an appreciable proportion of the decline in major CHD incidence remains unexplained. Changing diagnostic criteria for major CHD was ruled out as a possible explanation for the observed major CHD decline in chapter 4, section 4.6.5.1. It remains possible that this unexplained decline is also accounted for by changes in the risk factors evaluated in this analysis (reflecting imprecision in the analysis leading to underestimation of the risk factor contributions). Alternatively, although several major cardiovascular risk factors have been considered, trends in other risk factors, outlined in chapter 2, section 2.5.2.1, could be influential. These include particularly diabetes (predominantly T2DM) and aspects of diet. Given that T2DM incidence is rising, and T2DM is associated with an increased risk of major CHD, T2DM trends will not help to explain the decline in major CHD incidence. Rather, the rising T2DM will more likely have limited the decline in major CHD, as for BMI. The relationship between the trends in T2DM and in major CHD is explored in chapter 9. Diet was not measured longitudinally in this study population so it was not possible to consider the influence of this factor on the time trends. It is likely that diet operates on CHD risk at least in part through changing blood pressure and blood lipid levels, and through BMI. However it may also have some independent influence. In the Whitehall II cohort certain aspects of diet were measured at repeated intervals, therefore enabling exploration of the role of diet when the analyses are carried out on this cohort in chapter 6.

The unexplained portion of the decline could also reflect other risk factors such as psychosocial factors, and stress[122-126], provided favourable time trends in these factors have occurred. Life course influences[134-139] could be important too, if birth cohort effects are operating. Previous studies suggest that period, rather than cohort effects dominate the CHD trends[52, 145-147], which would suggest limited impact of early life/ life course influences, however further research is needed to confirm this. Increasing availability of early treatment, particularly revascularization, for angina (especially unstable angina) may play a role, although in chapter 2, section 2.5.2.2, it was noted that the evidence for revascularisation as a primary prevention measure for a major CHD event is weaker than for the effectiveness of revascularisation as secondary prevention[168]. Moreover, the relative low occurrence in the population of revascularisations as primary prevention suggests that the impact of revascularisations may be modest at best. Indeed data from the Minnesota Heart Survey suggest increased numbers of coronary artery bypass grafts (CABGs) in the Minnesota population explained a modest 6% of the decline in CHD mortality over 14 years[292]; since this includes CABGs following a major CHD event, the figure for explaining CHD incidence trends is likely to be lower. Increasing use of evidence-based medications (primarily statins[152-155] and anti-hypertensive drugs[156-160], as outlined in chapter 2, section 2.5.2.2) may be likely to influence major CHD incidence primarily through changing blood pressure and blood lipid levels in primary prevention at least[153, 160]. The analyses presented here do not distinguish between improvements in blood pressure and blood lipids due to lifestyle changes and those due to medication use. In chapter 7, the role of increasing use of evidence-based medications in the

favourable trends in these risk factors (and by extension, in the CHD decline) will be explored.

The rise in population BMI during the past 25 years in the UK has almost certainly reduced the scale of the decline in CHD that has occurred, though its effects have been outweighed by the favourable changes in cigarette smoking, blood lipids and blood pressure. The potential for further reductions in CHD in the UK population through cigarette smoking is constrained by the already low remaining cigarette smoking prevalence. However, the changes in blood pressure and particularly in blood lipids that have so far occurred are modest. Population-wide changes in these factors, particularly through population-wide dietary changes, still have considerable potential for further reductions in CHD risk.

5.5.5 Chapter conclusions/ postscript

The key finding of this chapter is that approximately half of the 25-year decline in major CHD among older British men may be explained by favourable time trends in smoking prevalence, SBP and HDL and non-HDL cholesterol. Questions remain. First, does the "unexplained" portion of the decline reflect imprecision in the analysis or other unmeasured contributing factors? Second, have risk factor trends contributed to a decline in major CHD in women in a similar way? In chapter 6, analogous analyses are carried out in the Whitehall II cohort of London-based men and women of a similar age. This will provide the opportunity to compare results for women and to verify the findings in men, as a step towards establishing whether the results for the BRHS cohort are due to imprecision or chance, or a true finding. The Whitehall II cohort will be particularly useful for verifying the roles of blood pressure and lipids

which are measured more frequently in this cohort than in the BRHS. Moreover, the role of diet will be explored. A further consideration is the role of preventative medications, particularly anti-hypertensive drugs and statins. Chapter 7 explores the extent to which the favourable trends in blood pressure and blood lipids may be explained by increased medication use, and so by extension, how medication use may have contributed to the major CHD incidence decline.

Table 5.1 **Men included in the analyses by age and questionnaire time-point**

Surviving men with no history of MI prior to questionnaire time-point

	Age group, years								
	40-44	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*All men*
Baseline (1978-80)	1,708	1,696	1,676	1,703					6,783*
5 years (1983-85)		1,639	1,633	1,594	1,569				6,435
13 years (1992)			399	1,474	1,382	1,255	827		5,337
17 years (1996)				660	1,369	1,227	1,045	468	4,769
20 years (1998-2000)					1,199	1,122	917	643	3,881

Men with additionally complete data on smoking, physical activity, alcohol and BMI (included in main time trend analysis)†

	Age group, years								
	40-44	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*All men*
Baseline (1978-80)	1,689	1,667	1,653	1,668					6,677
5 years (1983-85)		1,537	1,511	1,456	1,403				5,907
13 years (1992)			353	1,298	1,166	992	641		4,450
17 years (1996)				560	1,170	990	785	341	3,846
20 years (1998-2000)					1,071	1,002	770	533	3,376

Men with additionally complete data on SBP, total cholesterol, HDL cholesterol (included in the time trend analysis restricted to first + last 5 yrs of follow-up)‡

	Age group, years								
	40-44	*45-49*	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*All men*
Baseline (1978-80)	1,625	1,594	1,585	1,599					6,403
20 years (1998-2000)					1,015	946	723	498	3,182

*The number 6,783 is slightly greater than the 6,754 men in the analyses in chapter 4 as the present analysis begins from study entry in 1978, while the analysis in chapter 4 began in 1980 and thus excludes those men with a major CHD event between 1978 and 1980. †Total number of men in main time trend analysis (number of men with complete data on smoking, physical activity, alcohol and BMI in at least one time-point = **6,751**. This is greater than the number of men in any one time-point as different men may have complete data in different time-points. ‡Total number of men in time trend analysis restricted to first+last 5 years of follow-up (number of men with complete data on smoking, physical activity, alcohol and BMI and SBP and lipids in at least one time-point = **6,544**. Note: Only men contributing to 2+ time-points could contribute to the GEE analyses of risk factor trends so total men contributing may be slightly lower for these analyses (data at two or more time-points are needed for GEE modelling).

Table 5.2 **Smoking, alcohol consumption, physical activity, BMI, SBP, HDL cholesterol, non-HDL cholesterol by age group and follow-up time**

		Age group, years															
		40-44		*45-49*		*50-54*		*55-59*		*60-64*		*65-69*		*70-74*		*75-79*	
No. of current smokers (%)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	626	**(36.7)**	703	**(41.6)**	731	**(43.7)**	687	**(40.4)**								
	1983-85 (5 years)			479	**(29.6)**	535	**(33.2)**	533	**(33.9)**	460	**(29.9)**						
	1992 (~13 years)					88	**(22.2)**	279	**(19.0)**	280	**(20.3)**	236	**(18.9)**	131	**(15.9)**		
	1996 (~17 years)							104	**(15.9)**	206	**(15.3)**	196	**(16.2)**	149	**(14.4)**	51	**(11.1)**
	1998-2000 (20 years)									157	**(13.1)**	151	**(13.5)**	116	**(12.7)**	57	**(8.9)**
No. of regular drinkers (%)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	1229	**(72.0)**	1213	**(71.6)**	1162	**(69.4)**	1173	**(69.0)**								
	1983-85 (5 years)			1049	**(64.9)**	1023	**(63.1)**	885	**(56.3)**	908	**(59.2)**						
	1992 (~13 years)					250	**(65.8)**	904	**(64.1)**	742	**(57.1)**	667	**(55.6)**	437	**(55.6)**		
	1996 (~17 years)							424	**(67.1)**	885	**(67.4)**	697	**(59.5)**	577	**(58.6)**	250	**(55.8)**
	1998-2000 (20 years)									789	**(67.0)**	723	**(65.5)**	516	**(57.8)**	359	**(57.5)**
No. of men with at least moderate physical activity* (%)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	768	**(45.4)**	675	**(40.3)**	583	**(35.2)**	555	**(33.2)**								
	1983-85 (5 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1992 (~13 years)					169	**(43.3)**	659	**(45.8)**	587	**(44.2)**	500	**(44.4)**	297	**(39.5)**		
	1996 (~17 years)							268	**(42.4)**	548	**(41.7)**	482	**(42.1)**	325	**(35.2)**	126	**(30.6)**
	1998-2000 (20 years)									590	**(50.7)**	556	**(50.9)**	405	**(46.1)**	228	**(37.4)**
Mean Body mass index, kg/m^2 (sd)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	**25.27**	(3.13)	**25.43**	(3.13)	**25.57**	(3.20)	**25.49**	(3.24)								
	1983-85 (5 years)			**26.05**	(3.30)	**26.09**	(3.16)	**26.19**	(3.20)	**26.10**	(3.21)						
	1992 (~13 years)					**26.88**	(3.64)	**26.74**	(3.51)	**26.53**	(3.25)	**26.52**	(3.28)	**26.24**	(3.31)		
	1996 (~17 years)							**27.21**	(3.48)	**27.05**	(3.85)	**26.93**	(3.46)	**26.53**	(3.55)	**26.06**	(3.33)
	1998-2000 (20 years)									**27.27**	(3.81)	**27.09**	(3.69)	**26.79**	(3.68)	**26.22**	(3.54)

* Corresponds to men judged to have moderate, moderately vigorous or vigorous activity levels (as opposed to inactive, occasional or light)

Table 5.2 *continued* **Smoking, alcohol consumption, physical activity, BMI, SBP, HDL cholesterol, non-HDL cholesterol by age group and follow-up time**

		Age group, years															
		40-44		*45-49*		*50-54*		*55-59*		*60-64*		*65-69*		*70-74*		*75-79*	
Mean Systolic blood pressure, mmHg (sd)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	**138.7**	(17.2)	**141.9**	(19.5)	**144.5**	(19.7)	**148.1**	(21.6)								
	1983-85 (5 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1992 (~13 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1996 (~17 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1998-2000 (20 years)									**144.5**	(22.8)	**148.1**	(23.4)	**151.7**	(24.1)	**155.5**	(26.1)
Mean HDL cholesterol, mmol/L (sd)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	**1.16**	(0.24)	**1.14**	(0.24)	**1.15**	(0.26)	**1.17**	(0.26)								
	1983-85 (5 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1992 (~13 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1996 (~17 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1998-2000 (20 years)									**1.33**	(0.34)	**1.30**	(0.33)	**1.31**	(0.33)	**1.37**	(0.35)
Mean non-HDL cholesterol, mmol/L (sd)																	
Questionnaire time-point (follow-up)	1978-80 (baseline)	**5.07**	(1.06)	**5.19**	(1.06)	**5.11**	(1.00)	**5.18**	(1.02)								
	1983-85 (5 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1992 (~13 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1996 (~17 years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	1998-2000 (20 years)									**4.73**	(1.07)	**4.76**	(1.07)	**4.63**	(1.05)	**4.49**	(1.13)

Table 5.3 **Fall in the hazard of a first major CHD event per annum and over 25 years. Percentage of this fall explained by the risk factors from Cox regression analyses with time-dependent covariates**

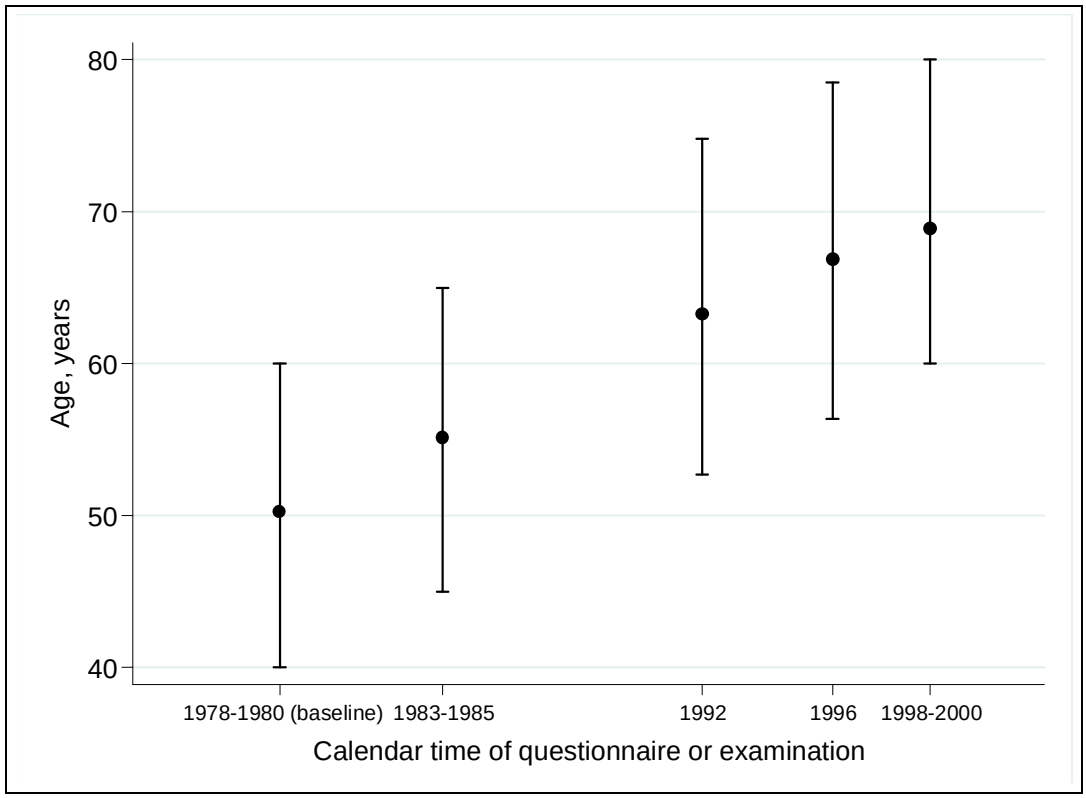
Cox model	Risk factors adjusted for	Coefficient for calendar time, β	Fall in hazard of major CHD per annum, % (95% CI)	p-value	Corresponding fall in hazard over 25 years, %*	% of the observed decline in hazard explained by the risk factor(s)†, (95% CI)
A	**No adjustment**	**-0.0385**	**3.78 (2.6, 5.0)**	**<0.001**	**61.8**	
	Individual risk factors - compared with model A					
B	Smoking (current/ex/never)	-0.0297	2.93 (1.7, 4.1)	<0.001	52.4	**22.9 (15.2, 34.0)**
C	Physical activity (inactive/occasional/light/moderate/ moderately vigorous/vigorous)	-0.0365	3.59 (2.4, 4.8)	<0.001	59.9	**5.2 (0.3, 10.7)**
D	Alcohol consumption (never/occasional/light/moderate/heavy)	-0.0381	3.74 (2.5, 4.9)	<0.001	61.4	**1.1 (-1.8, 4.5)**
E	BMI, kg/m2 (continuous)	-0.0413	4.04 (2.8, 5.2)	<0.001	64.4	**-7.1 (-13.0, -3.1)**
A2	**No adjustment, restricted follow-up (first five years and last five years only)§**	-0.0492	4.80 (1.4, 8.1)	0.007	70.8	
	Individual risk factors - compared with model A2					
F	HDL cholesterol, mmol/L (continuous)	-0.0432	4.22 (0.8, 7.6)	0.02	66.0	**12.3 (5.1, 42.3)**
G	Non-HDL cholesterol, mmol/L (continuous)	-0.0445	4.36 (0.9, 7.7)	0.01	67.2	**9.5 (4.2, 31.5)**
H	SBP, mmHg (continuous)	-0.0426	4.17 (0.7, 7.5)	0.02	65.5	**13.4 (5.5, 53.9)**
	Combinations of risk factors - compared with model A2					
J	Smoking, HDL cholesterol, non-HDL cholesterol, SBP	-0.0265	2.62 (-1.0, 6.1)	0.2	48.5	**46.1 (22.9, 163.6)**
K	Smoking, HDL cholesterol, non-HDL cholesterol, SBP, physical activity, alcohol	-0.0275	2.71 (-0.9, 6.2)	0.1	49.7	**44.1 (21.7, 149.1)**

* Corresponding fall in hazard over 25 years =100% × [1- exp(β × 25)]

† For smoking, alcohol, physical activity and BMI, % of the observed decline in hazard over 25 years explained by the risk factor = 100% × $(\beta_0 - \beta_1)/\beta_0$ where β_0 is the coefficient for calendar time in the model only adjusting for age (model A) and β_1 is the coefficient for calendar time in the model adjusting additionally for the risk factor. For SBP, HDL cholesterol and non-HDL cholesterol and all risk factors combined, β_0 is the coefficient for calendar time in the restricted model only adjusting for age (model A2) and β_1 is the coefficient in the model adjusting additionally for the risk factor(s).

§ Separate unadjusted model using restricted follow-up data to enable a valid comparison with models incorporating blood pressure and cholesterol as data on these variables were only available at limited time-points

Figure 5.1 **Mean age and age range of men in the British Regional Heart Study over the course of the follow-up**



Key: Points = mean age; capped bars = age range (maximum age to minimum age)

Chapter 6: Analysing the role of trends in aetiological exposures in the time trend in major coronary heart disease incidence in the Whitehall II cohort

6.1 Introduction

In the previous chapter 5, it was shown that 46% of the decline in incidence of major CHD in the British Regional Heart Study (BRHS) cohort of middle-aged British men could be attributed to favourable time trends in cigarette smoking, systolic blood pressure (SBP) and both non-HDL and HDL cholesterol. However important questions remain. It is unknown whether similar patterns are present in British women. Moreover, a similar analysis has not been previously carried out in the UK, probably reflecting the paucity of studies with the necessary repeated data on CHD incidence and risk factors. Thus the findings in the previous chapter need validation, in particular the role of lipids and SBP, as data on these factors was infrequently ascertained in the BRHS cohort. The aim of this chapter is therefore to estimate the contribution of risk factor changes to recent trends in the incidence of major CHD in the Whitehall II cohort of British men and women. The Whitehall II cohort comprises men and women similar in age to the BRHS men, and followed-up over an overlapping time-period. Regular clinical measurements are available in the Whitehall II cohort (at three separate time-points as opposed to the two examinations in the BRHS). Thus, the Whitehall II cohort should be suitable for addressing the above issues raised, that is, validation of the BRHS findings, as well as analysing trends in British women. The main drawback is the confinement of the Whitehall II cohort to one single regional geographic location (London), such that the findings from Whitehall II may not be representative of Britain as a whole, hence the use of the nationally representative BRHS cohort primarily. That said, the comparability

between the estimates of the decline in major CHD incidence from the BRHS and Whitehall II, when restricted to the same time-period (as shown in chapter 4, section 4.5.1.3), suggests that the findings from Whitehall II may be more widely applicable.

Objective

To estimate the secular time trends in major coronary risk factors (smoking, blood pressure, lipid levels, body mass index, physical activity, alcohol consumption and ietary factors) and the contribution of the risk factor time trends to the decline in incidence of major CHD over 20 years among men and women in the Whitehall II cohort.

a) For the whole cohort
b) According to gender
c) According to employment grade

The structure of this chapter is as follows: Section 6.2 details methods specific to this section, including statistical methods. Results are given in section 6.3 and section 6.4. Section 6.5 provides a discussion and interpretation of the findings of the chapter.

6.2 Methods

6.2.1 Data source

The Whitehall II study was detailed in chapter 3, section 3.4. To recap, the cohort comprises 10,308 men and women recruited between 1985-1988, aged 35-55 years, from London civil service departments. Risk factor measurements (including physical measurements and blood assays) were available at three phases during the follow-up for this analysis: at phase 1 (baseline, 1985-8), phase 3 (1991-3), and phase 5 (1997-

9). The men and women were followed for incident major CHD up to phase 7 (2002-4).

6.2.2 Principal outcome of a first major CHD event

The principal outcome was a first major CHD event, defined as a fatal CHD or non-fatal MI, between baseline (1985-1988) and 2002-4 (end of phase 7), (mean follow-up of 15.4 (SD 4.2) and 9.0 (SD 4.5) years for patients who were censored, and who experienced the outcome respectively). As outlined in chapter 3, section 3.4.4, fatal CHD was identified from flagging with the National Health Service Central Registry. Nonfatal MIs were ascertained from self-report in the questionnaires up to phase 7, with subsequent confirmation according to the MONICA criteria.

6.2.3 Coronary risk factors

In line with the analysis in chapter 5, the following risk factors were considered: Cigarette smoking, alcohol consumption, physical activity, body mass index (BMI), HDL cholesterol and non-HDL cholesterol, and systolic blood pressure. In addition data on some elements of diet were available; in particular, frequency of fruit and vegetable consumption, type of milk regularly consumed and type of bread regularly consumed. Methods of ascertainment of each risk factor and categorisations are detailed in chapter 3, section 3.4.5. Data on all risk factors was available at all three phases 1, 3 and 5 (although for some participants, HDL cholesterol at phase 1 was an estimate, based on apolipoprotein levels, as described in chapter 3, section 3.4.6). Thus risk factor trends over an approximately 12 year period from 1985-1988 to 1997-1999 could be estimated.

6.2.4 Statistical methods

Cox regression was used initially to estimate associations between each risk factor at phase 1 and subsequent hazard of major CHD over the whole follow-up to 2004 (that is, ignoring initially the secular trends). This initial Cox regression was carried out to confirm whether associations between the risk factors and major CHD did indeed exist to justify inclusion in the main analyses prior to computing attributable proportions, particularly for the dietary factors for which associations with CHD are less well established. All risk factors except type of milk were significantly associated (positively or negatively) with hazard of major CHD. Therefore milk was not included in the main analyses.

The statistical methods used to estimate both time trends in the coronary risk factors and the proportion of the decline in incidence of major CHD explained by each risk factor are the same as those used in chapter 5 for the BRHS cohort (see section 5.2.4). That is, as in chapter 5, the follow-up for each participant was split into consecutive periods, each of approximately five years, separated by the different examination phases: a first period from phase 1 to phase 3; a second from phase 3 to phase 5 and a third from phase 5 to phase 7. Each period is treated as if corresponding to a separate individual, and forms a separate row of data. Each of these "pseudo-individuals" has a "baseline" as the date of the examination at the start of the relevant period, and "baseline" risk factor levels as the risk factor levels at that examination. Each pseudo-individual is followed-up for major CHD from their baseline to the minimum of: date of major CHD event, date of death, date of loss to follow-up, date of next phase. The major CHD incidence and risk factor levels between pseudo-individuals in different periods are then compared to assess secular trends over time. In particular, age-

adjusted secular time trends among men and women from phases 1 to 5 in the risk factors were estimated from regression of the risk factor on calendar time (of start of period), in this split dataset, adjusted for age and stratified by gender and using generalised estimating equations (GEEs) with robust standard errors to take account of dependency between repeated measures for each participant. Logistic models were fitted for percentage change in prevalence of being a current cigarette smoker, having at least medium physical activity levels, consuming alcohol over recommend limit, usually eating white bread, and usually eating fruit and vegetables at least twice daily; and linear models for time trend in mean BMI, SBP, HDL and non-HDL cholesterol. Cox regression on this split dataset, was used to estimate the time trend in the hazard of major CHD, again using robust standard errors to account for dependency between repeated observations for each participant. Age was used as the underlying time scale. The extent to which the secular time trends in each of the risk factors statistically explained the trend in hazard of major CHD were again estimated by the expression $(\beta_0-\beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in a Cox regression model with just calendar time as a covariate, and β_1 is the coefficient of calendar time in a Cox regression model adjusting additionally for the risk factor(s)[348]. Bias-corrected bootstrap resampling gave an approximate 95% confidence interval (CI) for this estimate. Squared terms in the continuous risk factors (BMI, SBP and HDL and non-HDL cholesterol) were added to the models to test for non-linearity; squared-terms for HDL and non-HDL cholesterol were significant and so retained in the final models. The Cox regression analyses were first and foremost applied to men and women combined, adjusting for gender. Further analyses were carried out to estimate risk factor contributions to the decline in major CHD in men and women separately, however these analyses should be considered exploratory, as a means to investigate

whether there are potentially differences between men and women, as power for these stratified analyses is low (low numbers of events, particularly for women).

Additional analyses were carried out among all participants stratified by employment grade categorised as high (civil service grades 1 to 7), medium (civil service executives, including senior and higher) and low (clerical). Since this London-based cohort may not be representative of Britain as a whole, particularly in terms of socio-economic distribution (since the cohort are of a higher on average socio-economic position), one might hypothesize that the results for participants in the lower socio-economic groups reflect more closely the national picture. These further stratified analyses enable exploration of this hypothesis. These analyses were carried out on the participants as a whole, not simultaneously stratified by gender too, as the double stratification would have led to low numbers in each group and therefore very imprecise results. Again, these stratified analyses should be considered exploratory.

6.2.5 Participants included in analysis

Participants who had had an MI before baseline (phase 1) were excluded. Participants who had an MI during follow up were excluded from analyses of incidence of major CHD and risk factor trends after the time of their event. Participants who developed angina (either at baseline or during follow up) were retained for analysis, unless they also had an MI. Participants missing data on one or more risk factors in a particular phase were excluded from that phase and the associated follow-up, but included in other phases. Participants missing data in all phases were excluded from analyses altogether. Numbers of participants included in each phase are given in table 6.1.

6.3 Results – Time trends in the major coronary risk factors in Whitehall II

Of 10,308 participants recruited, one had no follow-up data, 35 reported having had an MI before baseline (prevalent cases), and 819 had missing data on ≥1 risk factor at all phases and were excluded from analysis. The remaining 9,453 participants included 6,379 (67%) men and 3,074 women. Risk factor levels by age and phase are presented in table 6.2 for men and table 6.3 for women. Considering first the favourable risk factor time trends, the proportion of men and women who were cigarette smokers declined between 1985-8 and 1997-9, although the decline was significant only among women. In men, the percentage change over the 12 years in the age-adjusted odds of being a current cigarette smoker was -9.2% (95% CI -20 to 3.6, p=0.2) (table 6.4). The corresponding figure among women was -37% (95% CI -45 to -27, p<0.001). Mean SBP fell in both sexes with a slightly larger decline observed in women. Age-adjusted changes in mean SBP over the period were -4.2mmHg (95% CI -5.0 to -3.4, p<0.001) and -6.2mmHg (95% CI -7.5 to -4.9, p<0.001) among men and women respectively. Average non-HDL cholesterol and HDL cholesterol levels also changed favourably. Age-adjusted mean HDL cholesterol levels rose by 0.13mmol/L (95% CI 0.11 to 0.15, p<0.001) and non-HDL cholesterol levels changed by -0.40mmol/L (95% CI -0.46 to -0.33, p<0.001) among men. Among women the corresponding figures were 0.08mmol.L (95% CI 0.04 to 0.11, p<0.001) for HDL cholesterol and -0.56 (95% CI -0.65 to -0.47, p<0.001) for non-HDL cholesterol, thus a slightly smaller rise in HDL than in men but a comparable fall in non-HDL. Fruit and vegetable consumption also changed favourably, with significant one-and-a-half-fold age-adjusted increases in the odds of consuming fruit and vegetables at least twice daily, among both men and women.

Certain risk factors did not change favourably over the period, either remaining relatively constant over the period or changing unfavourably. In particular, over the period, adjusting for age, mean BMI increased significantly, by 1.16kg/m^2 (95% CI 0.99 to 1.33, p<0.001) in men and by 0.78kg/m2 (95% CI 0.41 to 1.15, p<0.001) in women. Alcohol consumption increased by an average of 6.0 units per week (95% CI 5.2 to 6.8, p<0.001) among men and by 3.2 units per week (95% CI 2.6 to 3.9) among women, adjusting for age. Correspondingly, adjusting for age, the proportion of men and women who reported alcohol consumption over the recommended limit also increased significantly (6% percentage increase in men and 8% in percentage increase in prevalence in women). Physical activity levels decreased significantly in men; there was a 12% (95% CI 8.8 to 15) reduction in the proportion of men with at least moderate physical activity levels, adjusting for age. There was no significant change in physical activity levels among women (p=0.2 for the age-adjusted trend over time in odds of having at least moderate physical activity levels). Bread consumption did not alter substantially, with little change in the proportions of men and women reporting consumption of predominantly white bread, as opposed to other bread types.

6.4 Results - Analysis of relation of trends in risk factors to trends in major coronary heart disease incidence

Among this group of participants with available risk factor data, the observed decline in major CHD hazard was 6.51% (95% CI 3.22 to 9.68) per annum, adjusting for age and gender, or 74% (95% CI 48 to 87) over 20 years (table 6.5), higher than the 58% observed for the whole cohort. Estimates of the proportions of this decline in the hazard of a first major CHD event over time among all participants attributable to each risk factor change are presented in table 6.5. Four risk factor trends contributed

in isolation to the 74% decline in hazard of major CHD among all participants. Percentage contributions of these risk factors in order of size were: declining non-HDL cholesterol 34% (bootstrap 95% CI 20 to 76), rising HDL cholesterol 17% (bootstrap 95% CI 10 to 32), declining SBP 13% (bootstrap 95% CI 7 to 24), and declining cigarette smoking 6% (bootstrap 95% CI 2 to 14). Together they explained a total of 54% (95% bootstrap CI 34 to 105) of the decline (as before the upper bound of the CI indicates that the data are consistent at the 95% confidence level with the risk factors explaining a greater decline than that observed). The contribution of increased fruit and vegetable consumption did not reach statistical significance (7%, bootstrap 95% CI -1 to 20), the combined contribution with the four other risk factors being 56% (bootstrap 95% CI 34 to 112). Trends in physical activity, alcohol consumption and bread consumption had no notable impact. The rise in mean BMI was adverse, explaining -11% (bootstrap 95% CI -23 to -5) of the decline in major CHD hazard in isolation. The proportion of the decline explained by the risk factors combined reduced from 56% to 48% (bootstrap 95% CI 27 to 96) with additional adjustment for the adverse trend in BMI. This suggests that increasing BMI limited the scale of the CHD decline.

In chapter 4, section 4.5.1.3, it was shown that men and women in the cohort experienced similar declines in the hazard of major CHD. In this subgroup of participants with risk factor data, the declines, although larger than for the whole cohort, remained similar among men and women (73% and 82% respectively). The relative contributions of each of the risk factors to the CHD declines within each gender were broadly similar to each other and to that in the combined analysis (table 6.6). Exceptions were that among women, there was a smaller contribution from

HDL cholesterol compared with SBP and the proportion explained by cigarette smoking was not significant (although the point estimate was larger than for men). Further, among women, a negative impact of BMI was not as apparent. The percentage contribution of the five risk factors: HDL and non-HDL cholesterol, SBP, cigarette smoking and fruit and vegetable consumption, combined was similar among men and women (54%, bootstrap 95% CI 30 to 126, and 59%, 95% bootstrap CI 19 to 221 respectively).

The analysis stratifying by baseline employment grade, categorised as high (civil service grades 1 to 7), medium (civil service executives, including senior and higher) and low (clerical), is shown in table 6.7. The percentage decline in incidence of major CHD over 20 years among participants in the lowest employment grades was smallest (60.9%, 95% CI -60.5 to 90.5), followed by a marginally larger decline among those in the highest employment grades (66.6%, 95% CI 0.3 to 88.8), and with the largest decline occurring in those of intermediate employment grades (79.9%, 95% CI 51.3 to 91.7). The differences in the percentage decline in incidence of major CHD over 20 years in each employment grade were not significant (p=0.6). The relative contributions of the risk factors to the major CHD trends were similar for medium and high employment grades, with non-HDL cholesterol the greatest contributor, followed by HDL, SBP and a small contribution from smoking (table 6.7). For the low employment grade, the relative contributions differed somewhat. Non-HDL remained the greatest contributor, however smoking and SBP appeared to be more influential; smoking making a contribution comparable to that of HDL and SBP making a larger contribution than HDL.

There was no strong evidence of departure from the proportional hazards assumption of the Cox regressions tested using Schoenfeld residuals.

6.5 Discussion

6.5.1 Summary of main findings

Over half of the 74% decline in major CHD incidence over 20 years among participants with risk factor data (men and women combined) in the Whitehall II cohort could be attributed to a combination of favourable time trends in major risk factors, particularly non-HDL cholesterol, HDL cholesterol, SBP, and cigarette smoking. A borderline significant association of the CHD decline with increased fruit and vegetable consumption was also observed. Bread consumption, physical activity and alcohol consumption did not help to explain the decline in major CHD. Rising adiposity had an adverse impact, such that had other favourable risk factor trends not occurred, the unfavourable trend in BMI may have led to an increase in major CHD incidence over the follow-up.

6.5.2 Comparison between men and women in Whitehall II

In chapter 4, section 4.5.1.3, it was shown that over 20 years between 1985 and 2004 similar declines in hazard of major CHD occurred in men and women. In this chapter, results reveal that coronary risk factor time trends have had broadly comparable influences on the declines in men and women. In particular, the four major risk factors (non-HDL and HDL cholesterol, SBP and cigarette smoking) combined could explain a similar proportion (about half) of the declines in both men and women. While the estimated size of the potential contribution associated with each of the risk factors individually differed for men and women, the relative impact associated with

each risk factor was broadly comparable, with the exception that SBP was more influential than HDL cholesterol among women, while the reverse was true among men. The broad similarity in the potential influences of the risk factor trends on the CHD decline between men and women fits with previous research suggesting the associations of these particular risk factors with CHD to be similar among men and women[100, 103, 359]. The differences in the relative importance of SBP and HDL cholesterol likely reflect differing time trends in the risk factors: the observed greater decline in age-adjusted average SBP among women compared with men (fall of 6.2mmHg versus 4.2mmHg over 12 years), and the greater rise in age-adjusted average HDL among men compared with women (rise of 0.13mmol/L versus 0.08mmol/L over 12 years), rather than different strengths of association of the risk factors. There is a lack of national data on trends over this period in lipids so it is difficult to assess whether the differences in the trends in HDL between men and women observed in this cohort have also occurred in the British population as a whole. However Health Survey for England data[360] on mean SBP levels between 1993 and 1998, a period overlapping the phase 2 and phase 3 Whitehall II measurements, show SBP to have declined by 1 to 2mmHg more in women over this time compared with men, among participants of a similar age as those in Whitehall II at phases 2 and 3, in line with our findings. Specifically, declines between 1993 and 1998 in mean SBP were: 2mmHg and 2mmHg (men, aged 45-54 and 55-64 years respectively) and 3mmHg and 4mmHg (women, aged 45-54 and 55-64years respectively). Although rising adiposity was associated with an adverse impact on the trend in major CHD among men, this was not observed among women. This finding is somewhat counterintuitive given the similar influence of BMI in men and women[361] and the estimates of the trends in BMI; although women experienced a smaller age-

adjusted rise in mean BMI over the period, this rise was nevertheless significant and not unsubstantial (0.8kg/m^2 compared with 1.2kg/m^2 among men). Limitations in the analyses (detailed below), particularly the lack of power in the analyses for women, may explain the apparent limited influence of the rise in BMI in women.

6.5.3 Comparison between employment grade in Whitehall II

In chapter 4, section 4.5.1.3, a gradient in the trend in major CHD incidence by employment grade was observed, whereby the largest decline occurred among those in the most senior employment grades, while the smallest decline occurred in the most junior employments grades. This is in line with the deprivation gradients observed in THIN and BRHS. Due to smaller numbers of participants in the analyses in this chapter, the gradient did not persist, suggesting the influence of responder bias on the results. However, the analyses of the contributions of the risk factors do reveal some differences between the employment grades. For medium and high employment grades non-HDL cholesterol was the greatest contributor, followed by HDL, SBP and a small contribution from smoking. In contrast, for the low employment grade, smoking and SBP appeared to be more influential; particularly relative to HDL. While these results stratified by employment grade should be interpreted with caution due to the low numbers, leading to imprecise estimates, it is interesting to note that the results for the most junior employment grade reflect more closely the findings of the relative risk factor contributions in the BRHS (greater influence of smoking and SBP). This fits with the fact that the Whitehall II cohort as a whole is less deprived relative to the BRHS (which is more closely representative of the general population). This is because the recruitment sampling frame of men and women employed in London civil

service offices automatically led to the absence of manual labourers and unemployed individuals in the Whitehall II cohort.

6.5.4 Comparison of men in Whitehall II with the BRHS findings

The Whitehall II cohort comprises men of an overlapping age-range to the men in the BRHS, followed over a similar calendar period. The men in Whitehall II were aged 35-55 at recruitment in 1985-88. In comparison men in the BRHS were aged 40-60 at recruitment in 1978-80, and so were aged 45-70 in 1985-88. The considerable overlap in age suggests that useful comparison may be drawn between the analyses of the two cohorts. In chapter 4, 4.5.1.3, it was observed that the decline in incidence of major CHD among men in Whitehall II was comparable to that found in the BRHS over the same period (4.24% per annum versus 4.06% per annum). The results of the analysis of the Whitehall II men in this chapter, assessing the contribution of risk factor trends to the CHD decline, are also largely consistent with the analogous analysis of the BRHS men in chapter 5. A similar proportion of the decline in major CHD could be attributed to changes in cardiovascular risk factors among men in both cohorts (53% versus 46% in the BRHS). The same four risk factors were important in both cohorts (cigarette smoking, SBP and non-HDL and HDL cholesterol), and the same risk factors that had little impact (alcohol consumption and physical activity) or were counterproductive (BMI). However, there are certain differences between the findings from the two cohorts. The relative impacts of the four key risk factors differed, with non-HDL cholesterol and HDL cholesterol explaining the largest portion of the decline in major CHD in the present cohort, compared with cigarette smoking having the greatest influence in the BRHS. Indeed these four risk factors, in order of size of contribution, are essentially reversed (to recap, contributions of

smoking, SBP, HDL cholesterol and non-HDL cholesterol in the BRHS were 23%, 13%, 12% and 10% respectively; corresponding figures for the Whitehall II men are 5%, 11%, 19%, 34%). The differences in the percentage contributions could be the result of limitations or imprecision in either or both analyses, for example the limited two-point cholesterol data in the BRHS analysis may possibly have led to underestimation of the contribution of lipids in the BRHS. Other possible explanations could be the earlier start-date for the BRHS (seven years prior to Whitehall II) and the despite the overlap in age, the BRHS men are on average 10 years older in the same calendar year. That said, adjustment was made for age, and trends within each age-group were similar, and the time trends in the BRHS before and after the start-date for Whitehall II (1985) were consistent, thus the differences in age and start-date are unlikely to explain the variations in the relative roles of the risk factors. However, one could plausibly reason that the differences in the findings are reflections of differences in the population demographics of the cohorts other than age, in particular, the higher average socioeconomic status in the Whitehall II London-based cohort compared with the nationwide BRHS cohort, as described above. Tied to the higher socio-economic status of the cohort, the reduced impact of quitting smoking in Whitehall II men may be explained by an already lower prevalence of smokers at a later baseline (23% among men in Whitehall II compared with about 40% among men in the BRHS) and therefore less potential for a decline in prevalence over time (smoking prevalence declined by three-quarters among BRHS men over 20 years while among men in Whitehall II, there was only a non-significant decline of 9% over 12 years). The trend in and contribution of non-HDL cholesterol was smaller in the BRHS, (non-HDL cholesterol fell by 0.4mmol/L over 12 years in Whitehall II men, compared to 0.35mmol/L over 20 years in the BRHS). This

difference possibly reflects greater take-up of effective lipid lowering medication in Whitehall II[362] , which may again be associated with socio-economic status or possibly reflect better access to medical care in London as opposed to other UK regions. The contribution of SBP to the CHD decline was very similar in both cohorts, reflecting comparable declines over time in mean SBP levels (4.2mmHg over 12 years in Whitehall II men versus 7.2mmHg over 20 years in the BRHS). The contribution of HDL cholesterol was also broadly consistent in both cohorts, with a slightly faster rate of increase in HDL cholesterol occurring in the Whitehall II men (0.13mmol/L over 12 years compared with 0.15mmol/L over 20 years in the BRHS), leading to a slightly larger proportion of the CHD decline explained. Elements of diet associated with major CHD risk (frequency of consumption of fruit and vegetables, and type of bread predominantly consumed) were available for inclusion in the Whitehall II analysis, but not captured in the BRHS. While bread consumption did not influence the CHD trend, there was some suggestion that increasing fruit and vegetable consumption may have made a contribution when considered in isolation. However, when considered in conjunction with the other major risk factors, fruit and vegetable consumption had little added independent contribution; it is likely that the effect of fruit and vegetable consumption is largely mediated by factors such as HDL cholesterol. Note finally that the BRHS findings correspond more closely to findings from the IMPACT model[15] on the role of risk factors on the decline in CHD *mortality*, which also addresses trends among the whole British population, rather than in a single location.

6.5.5 Strengths and limitations

Multiple repeated measurements of risk factors, using consistent techniques on each occasion, are a key strength of this analysis. In particular, lipid and blood pressure measurements were available at three time-points, instead of the two measurements in the BRHS. Also, additional repeated data on elements of diet was available in Whitehall II. As for the corresponding analysis of BRHS data in chapter 5, risk factor trends to coronary events at an individual-level, thus avoiding the limitation of ecological analyses predominantly used to study time trends. A similar "lag" between the risk factor ascertainment and a major CHD event was allowed for as that in the BRHS analysis as risk factor levels were related to major CHD events up to five years ahead, based on the interval between clinic phases. Further, this is apparently the first such individual-level study of major CHD trends following both men and women, enabling extension of the analysis to women. That said, women in Whitehall II experienced few events leading to imprecision in the analysis (in particular some of the bootstrap CIs for the "percentage explained" estimates were unstable and very wide). Unstable bootstrap CIs tended to occur when the percentage explained estimate was large and/ or multiple risk factors were included in the models. Consequently the findings particularly for women need to be interpreted with some caution, although in the least the point estimates give an indication of how similar or dissimilar the results are to those for men. In the same vein, the analyses stratified by employment grade should be seen as exploratory and interpreted with caution – a consequence of the low power of each grade-specific analysis was lack of convergence of the interactions to estimate bootstrap CIs for the percentage contributions of the risk factors and so CIs could not be given.

As for the BRHS analysisin chapter 5, the analyses in this chapter were necessarily based on participants who re-attended after baseline, and provided complete risk factor data at one phase at least. The potential for survival or response biases needs consideration. Again, the most likely impact would be overestimation of the favourable trends observed in both the risk factors and major CHD incidence, due to the healthy participant effect. Unlike the BRHS, the estimate of the major CHD incidence decline in chapter 4 (whole Whitehall II cohort – see section 4.5.1.3) did differ from the estimate in this chapter (responders with risk factor data) – 58% versus 74%. This indicates some such bias, whereby the decline among responders is larger than that of non-responders. This is likely to reflect that a greater proportion of the Whitehall II cohort were missing risk factor information and so were excluded from this analysis than in the BRHS. We could arguably expect similar overestimation of the favourable risk factor trends, and so the percentage explained by each risk factor may still be reflective of the cohort as a whole. The comparability of the Whitehall II findings with that of the BRHS, particularly when broken down by employment grade, in terms of the relative contributions of the risk factors, supports this.

Any measurement imprecision of the risk factors, particularly likely for the dietary factors, physical activity and alcohol consumption, may have led to underestimation of the contribution to the CHD decline. Limited elements of diet were available (fruit and vegetables, milk, bread consumption). Had more aspects of diet been considered, diet as a whole may have had greater influence.

A limitation specific to this analysis of Whitehall II data is that HDL cholesterol values at baseline were derived from serum apolipoprotein-A1 for a subgroup of the

participants. The likely impact is underestimation of the variance associated with the baseline HDL measurements but without biasing the estimate of the contribution of HDL to the decline in major CHD. A further limitation specific to the Whitehall II analysis is the restricted London-based sampling frame and such that the Whitehall II cohort is not representative/ reflective of Britain as a whole in terms of socio-economic status. The lack of representativeness may help to explain the differences between the findings for Whitehall II and the BRHS in terms of the relative risk factor contributions.

6.5.6 Interpretation of findings

The results have shown that approximately half of the decline over 20 years in major CHD incidence among both men and women in the Whitehall II cohort may be attributed to concurrent time trends in the major coronary risk factors (specifically, non-HDL and HDL cholesterol, SBP and cigarette smoking), findings broadly consistent with the findings in the BRHS. Thus the results of the Whitehall II analysis in this chapter lend support to and help to validate the findings in the BRHS in chapter 5, including the novel finding of the role of HDL cholesterol (a risk factor not included in any previous time trends analyses of CHD, incidence or mortality). This strengthens the conclusions of the previous chapter; firstly that major coronary risk factors have made a substantial contribution to the decline in incidence of major CHD in men in Britain and secondly, that there remains a portion of the decline in major CHD not explained by the risk factors. The correspondence of the results for men from the two distinct cohorts suggests that the "unexplained portion" is not connected to limitations unique to each analysis, such as the limited two-point data on SBP and lipids in the BRHS analysis and the estimated baseline HDL cholesterol in the

Whitehall II analysis. The "unexplained portion" could reflect however methodological limitations common to both analyses, for example measurement imprecision, particularly for the factors assessed by questionnaire, which may have led to underestimation of the risk factor contributions. Otherwise some of the "unexplained portion" may reflect the influence of other factors as outlined in chapter 5, section 5.5.4, (psycho social factors, life course influences, and preventive treatments). Diet trends were also cited as a possible explanation for the unexplained portion of the decline in major CHD incidence in the BRHS. Elements of diet (fruit and vegetable consumption, bread consumption) were considered in the Whitehall II analysis. These dietary factors appeared to have little independent influence on the CHD incidence trends. However, other aspects of diet not considered may have made a contribution.

A further result common to both cohorts was the negative estimated impact of BMI on the CHD decline; both studies suggesting that rising BMI has reduced the scale of the decline in BMI. While the negative contribution of rising mean BMI over recent decades appears to have been outweighed by the favourable trends in other vascular risk factors, continued increases in BMI may further reduce or even reverse the decline in CHD incidence. The rising BMI in the UK and in other countries needs therefore urgent attention.

While there are evident similarities between the results for the two cohorts, certain differences were observed, in terms of the relative impact of each of the major risk factors. In particular a greater decline in non-HDL cholesterol was observed in Whitehall II corresponding to a greater role in the decline in major CHD, and a

greater decline in, and so greater role of, smoking prevalence in the BRHS. As discussed in section 6.5.4 these differences are plausible in the light of the differences in the demographics of the populations from which the two cohorts were derived. It suggests inequalities in healthcare access/health education according to socio-economic status, with certain less deprived groups (like the Whitehall II cohort) experiencing greater (non-HDL cholesterol) or earlier (smoking) health improvements than the general British population, which is of concern. However at the same time, the Whitehall II study is informative in showing health gain in the real world given favourable circumstances. The trends in this group may represent achievable goals for population-wide prevention of CHD, highlighting what can be achieved and emphasizing the value of measures to reduce exposure to these risk factors in the population.

Contrasting the results for men and women in Whitehall II, the risk factor reductions were of broadly comparable importance for men and women. The findings suggest that similar influences have operated to achieve declines in incidence of major CHD among both men and women, such that similar prevention strategies may be appropriate for both genders. However further research is needed to validate these findings, as the low power for the gender specific analyses warrants a need for caution in interpreting the results.

6.5.7 Chapter conclusions/ postscript

In chapter 5 and in this chapter 6, the factors that have influenced the decline in the incidence of major CHD have been explored. The key findings are that the major coronary risk factors appear to go at least half way towards explaining the decline in

incidence of major CHD in both men and women, with the findings for men evaluated in two separate cohorts. In particular, in addition to smoking, the favourable trends in SBP, and in non-HDL and HDL cholesterol, may explain a non trivial portion of the major CHD incidence decline. In the next chapter 7, the role of increased use of evidence-based medications (anti-hypertensive drugs and lipid-regulating drugs) in the favourable blood pressure and blood lipid changes is explored. Given that evidence-based medications are likely to influence major CHD risk primarily through changing blood pressure and blood lipid levels, the analyses by extension, may also indicate to what extent medication use may have contributed to the major CHD incidence decline.

Table 6.1 **Numbers of participants contributing data in each study phase by age group (participants with complete risk factor data and no prior MI)**

		Men							
		Age, years							
		34-39	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-68**	**All**
Study Phase	1 (1985-8)	1,333	1,354	928	1,048	129	0	0	4,792
	3 (1991-3)	100	1,537	1,401	1,015	1,029	143	0	5,225
	5 (1997-9)	0	9	783	964	614	653	180	3,203
		Women							
		Age, years							
		34-39	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-68**	**All**
Study Phase	1 (1985-8)	547	562	532	629	99	0	0	2,369
	3 (1991-3)	45	549	582	487	575	76	0	2,314
	5 (1997-9)	0	2	291	336	288	289	79	1,285
		All participants							
		Age, years							
		34-39	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-68**	**All**
Study Phase	1 (1985-8)	1,880	1,916	1460	1677	228	0	0	7,161
	3 (1991-3)	145	2,086	1983	1502	1604	219	0	7,539
	5 (1997-9)	0	11	1074	1300	902	942	259	4,488

Note: Overall number of participants contributing to analyses for at least one phase = **9,453**. The numbers of participants contributing data to each particular phase is lower because different participants may be missing risk factor data at (and so excluded from) different phases

Table 6.2 **Distribution of major coronary risk factors by age and study phase:**

men

	Age, years						
	34-39	40-44	45-49	50-54	55-59	60-64	65-68
Number of participants							
Phase 1 – 1985-8	1333	1354	928	1048	129		
Phase 3 – 1991-4	100	1537	1401	1015	1029	143	
Phase 5 – 1997-9		9	783	964	614	653	180
Number of current smokers (%)							
Phase 1 – 1985-8	235 (17.6)	226 (16.7)	145 (15.6)	139 (13.3)	21 (16.3)		
Phase 3 – 1991-4	11 (11.0)	224 (14.6)	192 (13.7)	117 (11.5)	92 (8.9)	13 (9.1)	
Phase 5 – 1997-9		NA*	77 (9.8)	92 (9.5)	60 (9.8)	39 (6.0)	12 (6.7)
Number at least moderately physically active (%)							
Phase 1 – 1985-8	1056 (79.2)	1068 (78.9)	719 (77.5)	794 (75.8)	86 (66.7)		
Phase 3 – 1991-4	73 (73.0)	1099 (71.5)	993 (70.9)	699 (68.9)	749 (72.8)	113 (79.0)	
Phase 5 – 1997-9		NA*	518 (66.2)	652 (67.6)	439 (71.5)	494 (75.7)	135 (75)
Number consuming over recommended limit of alcohol (%)							
Phase 1 – 1985-8	299 (22.4)	274 (20.2)	173 (18.6)	146 (13.9)	19 (14.7)		
Phase 3 – 1991-4	20 (20.0)	307 (20.0)	295 (21.1)	176 (17.3)	134 (13.0)	18 (12.6)	
Phase 5 – 1997-9		NA*	229 (29.2)	284 (29.5)	178 (29.0)	156 (23.9)	28 (15.6)
Number with white bread as usual bread type consumed (%)							
Phase 1 – 1985-8	1061 (79.6)	1038 (76.7)	712 (76.7)	796 (76.0)	96 (74.4)		
Phase 3 – 1991-4	77 (77.0)	1178 (76.6)	1058 (75.5)	770 (75.9)	800 (77.7)	123 (86.0)	
Phase 5 – 1997-9		NA*	582 (74.3)	723 (75.0)	462 (75.2)	513 (78.6)	136 (75.6)
Number consuming fruit or vegetables at least twice daily (%)							
Phase 1 – 1985-8	212 (15.9)	206 (15.2)	134 (14.4)	136 (13.0)	21 (16.3)		
Phase 3 – 1991-4	16 (16.0)	278 (18.1)	274 (19.6)	185 (18.2)	200 (19.4)	28 (19.6)	
Phase 5 – 1997-9		NA*	246 (31.4)	356 (36.9)	204 (33.2)	258 (39.5)	75 (41.7)
Mean BMI, kg/m2 (sd)							
Phase 1 – 1985-8	24.1 (3.2)	24.5 (3.0)	24.8 (2.9)	25.1 (2.8)	25.2 (3.2)		
Phase 3 – 1991-4	24.2 (3.2)	24.8 (3.3)	25.1 (3.3)	25.3 (3.0)	25.3 (2.9)	24.8 (2.9)	
Phase 5 – 1997-9		NA*	25.7 (3.7)	26.2 (3.5)	26.1 (3.4)	25.9 (3.2)	25.5 (3.0)
Mean SBP, mmHg (sd)							
Phase 1 – 1985-8	123.3 (12.9)	124.0 (13.5)	124.8 (13.8)	126.0 (15.0)	127.3 (16.5)		
Phase 3 – 1991-4	120.2 (13.1)	119.8 (12.2)	120.8 (12.3)	122.6 (13.4)	125.2 (14.2)	126.4 (16.4)	
Phase 5 – 1997-9		NA*	119.6 (14.2)	123.4 (15.4)	125.9 (16.5)	127.0 (16.8)	130.5 (18.6)
Mean non-HDL cholesterol, mmol/L (sd)							
Phase 1 – 1985-8	4.42 (1.1)	4.69 (1.1)	4.86 (1.1)	4.92 (1.1)	5.07 (1.1)		
Phase 3 – 1991-4	4.70 (1.2)	4.93 (1.2)	5.16 (1.2)	5.22 (1.1)	5.32 (1.1)	5.38 (1.1)	
Phase 5 – 1997-9		NA*	4.35 (1.1)	4.57 (1.1)	4.55 (1.1)	4.57 (1.0)	4.53 (1.0)
Mean HDL cholesterol, mmol/L (sd)							
Phase 1 – 1985-8	1.29 (0.3)	1.30 (0.3)	1.27 (0.3)	1.27 (0.3)	1.23 (0.3)		
Phase 3 – 1991-4	1.35 (0.3)	1.31 (0.3)	1.32 (0.4)	1.32 (0.4)	1.34 (0.4)	1.35 (0.4)	
Phase 5 – 1997-9		NA*	1.36 (0.3)	1.39 (0.3)	1.38 (0.4)	1.41 (0.3)	1.36 (0.3)

*Too few participants (n=9) to estimate risk factor levels for men aged 40-44 years in phase 5

Table 6.3 **Distribution of major coronary risk factors by age and study phase: women**

	Age, years						
	34-39	40-44	45-49	50-54	55-59	60-64	65-68
Number of participants							
Phase 1 – 1985-8	547	562	532	629	99		
Phase 3 – 1991-4	45	549	582	487	575	76	
Phase 5 – 1997-9		2	291	336	288	289	79
Number of current smokers (%)							
Phase 1 – 1985-8	106 (19.4)	138 (24.6)	128 (24.1)	158 (25.1)	26 (26.3)		
Phase 3 – 1991-4	12 (26.7)	65 (11.8)	100 (17.2)	87 (17.9)	104 (18.1)	9 (11.8)	
Phase 5 – 1997-9		NA*	31 (10.7)	50 (14.9)	40 (13.9)	37 (12.8)	8 (10.1)
Number at least moderately physically active (%)							
Phase 1 – 1985-8	363 (66.4)	338 (60.1)	297 (55.8)	332 (52.8)	52 (52.5)		
Phase 3 – 1991-4	30 (66.7)	322 (58.7)	310 (53.3)	221 (45.4)	257 (44.7)	34 (44.7)	
Phase 5 – 1997-9		NA*	137 (47.1)	174 (51.8)	134 (46.5)	145 (50.2)	40 (50.6)
Number consuming over recommended limit of alcohol (%)							
Phase 1 – 1985-8	72 (13.2)	59 (10.5)	41 (7.7)	45 (7.2)	7 (7.1)		
Phase 3 – 1991-4	6 (13.3)	67 (12.2)	60 (10.3)	36 (7.4)	38 (6.6)	4 (5.3)	
Phase 5 – 1997-9		NA*	51 (17.5)	56 (16.7)	47 (16.3)	29 (10.0)	13 (16.5)
Number with white bread as usual bread type consumed (%)							
Phase 1 – 1985-8	463 (84.6)	457 (81.3)	419 (78.8)	494 (78.5)	82 (82.8)		
Phase 3 – 1991-4	37 (82.2)	447 (81.4)	475 (81.6)	371 (76.2)	448 (77.9)	60 (78.9)	
Phase 5 – 1997-9		NA*	235 (80.8)	270 (80.4)	223 (77.4)	221 (76.5)	65 (82.3)
Number consuming fruit or vegetables at least twice daily (%)							
Phase 1 – 1985-8	120 (21.9)	127 (22.6)	89 (16.7)	131 (20.8)	25 (25.3)		
Phase 3 – 1991-4	14 (31.1)	164 (29.9)	171 (29.4)	108 (22.2)	139 (24.2)	18 (23.7)	
Phase 5 – 1997-9		NA*	134 (46.0)	171 (50.9)	136 (47.2)	140 (48.4)	32 (40.5)
Mean BMI, kg/m2 (sd)							
Phase 1 – 1985-8	23.7 (4.1)	24.1 (4.0)	25.0 (4.1)	25.7 (4.3)	26.4 (6.1)		
Phase 3 – 1991-4	24.9 (4.8)	24.8 (4.7)	25.6 (4.8)	25.8 (4.4)	26.4 (4.4)	26.4 (5.3)	
Phase 5 – 1997-9		NA*	25.9 (5.1)	26.3 (4.9)	27.0 (5.0)	26.7 (5.0)	26.0 (3.8)
Mean SBP, mmHg (sd)							
Phase 1 – 1985-8	114.7 (13.2)	117.5 (13.8)	122.1 (16.4)	124.5 (16.3)	128.5 (18.0)		
Phase 3 – 1991-4	114.1 (11.3)	113.5 (13.1)	115.6 (12.8)	119.5 (14.0)	122.2 (14.4)	124.4 (14.9)	
Phase 5 – 1997-9		NA*	115.3 (14.8)	120.5 (16.2)	123.4 (17.3)	127.2 (17.8)	129.2 (21.0)
Mean non-HDL cholesterol, mmol/L (sd)							
Phase 1 – 1985-8	3.80 (0.9)	3.93 (1.0)	4.33 (1.0)	4.91 (1.2)	5.18 (1.2)		
Phase 3 – 1991-4	4.36 (1.2)	4.33 (1.1)	4.56 (1.1)	4.99 (1.2)	5.38 (1.3)	5.88 (1.4)	
Phase 5 – 1997-9		NA*	4.00 (1.1)	4.29 (1.0)	4.48 (1.2)	4.66 (1.1)	4.88 (1.1)
Mean HDL cholesterol, mmol/L (sd)							
Phase 1 – 1985-8	1.59 (0.4)	1.59 (0.4)	1.59 (0.4)	1.64 (0.4)	1.70 (0.4)		
Phase 3 – 1991-4	1.59 (0.4)	1.66 (0.4)	1.70 (0.4)	1.71 (0.4)	1.68 (0.5)	1.62 (0.4)	
Phase 5 – 1997-9		NA*	1.69 (0.4)	1.69 (0.4)	1.67 (0.4)	1.66 (0.4)	1.63 (0.5)

*Too few participants (n=2) to estimate risk factor levels for women aged 40-44 years in phase 5

Table 6.4 **Age-adjusted population-averaged time trends in coronary risk factors among men and women over 12 years from 1985-8 (baseline) to 1997-9 (phase 5)**

	Men			Women		
Risk factor	**Change in mean levels per annum (95% CI)**	**p-value**	**Change over 12 years (95% CI)**	**Change in mean levels per annum (95% CI)**	**p-value**	**Change over 12 years (95% CI)**
BMI, kg/m^2	0.10 (0.08, 0.11)	<0.001	1.16 (0.99, 1.33)	0.07 (0.03, 0.10)	<0.001	0.78 (0.41, 1.15)
SBP, mmHg	-0.35 (-0.42, -0.28)	<0.001	-4.19 (-5.02, -3.35)	-0.52 (-0.63, -0.41)	<0.001	-6.21 (-7.52, -4.90)
Non-HDL cholesterol, mmol/L	-0.033 (-0.038, -0.028)	<0.001	-0.40 (-0.46, -0.33)	-0.047 (-0.054, -0.039)	<0.001	-0.56 (-0.65, -0.47)
HDL cholesterol, mmol/L	0.011 (0.009, 0.012)	<0.001	0.13 (0.11, 0.15)	0.006 (0.004, 0.009)	<0.001	0.08 (0.04, 0.11)
Risk factor	**% change in odds per annum (95% CI)**	**p-value**	**% change over 12 years (95% CI)**	**% change in odds per annum (95% CI)**	**p-value**	**% change over 12 years (95% CI)**
Current smoker	-0.80 (-1.89, 0.30)	0.2	-9.2 (-20.4, 3.6)	-3.78 (-4.94, -2.62)	<0.001	-37.1 (-45.5, -27.2)
At least moderate physical activity	-1.06 (-1.35, -0.76)	<0.001	-12.0 (-15.1, -8.8)	-0.48 (-1.16, 0.21)	0.2	-5.6 (-13.1, 2.5)
Consume alcohol over recommended limit	6.12 (5.15, 7.10)	<0.001	104 (82.8, 128)	7.96 (5.79, 10.17)	<0.001	151 (96.5, 220)
White bread as usual bread type	-0.26 (-0.53, 0.01)	0.06	-3.1 (-6.2, 0.1)	0.12 (-0.24, 0.47)	0.5	1.4 (-2.8, 5.8)
Consume fruit and vegetables ≥2 daily	7.99 (7.01, 8.98)	<0.001	151 (125, 180)	8.73 (7.56, 9.92)	<0.001	173 (140, 211)

Table 6.5 **Fall in hazard of a first major CHD event among all participants in Whitehall II between 1985 and 2004 and percentage of this fall explained by risk factor time trends**

Model	Risk factors adjusted for in addition to age and gender	β-coefficient for calendar time	Fall in hazard per annum, % (95% CI)	p-value	Corresponding fall in hazard over 20 years, %	% of the observed decline in hazard over 20 years explained by the risk factor(s), (95% CI)*
A	**No adjustment**	-0.0673	6.51 (3.22, 9.68)	<0.001	74.0	
	Effect of individual risk factors in isolation					
B	Smoking (current/ex/never)	-0.0633	6.13 (2.82, 9.33)	<0.001	71.8	**5.9 (2.3, 13.6)**
C	Physical activity (low/medium/high)	-0.0673	6.51 (3.20, 9.70)	<0.001	74.0	**0.1 (-4.5, 5.3)**
D	Alcohol units per week (none/within limit/over limit/heavy)	-0.0666	6.44 (3.13, 9.65)	<0.001	73.6	**1.0 (-6.1, 8.3)**
E	Usual bread consumption (white/wholemeal/granary or wheatmeal/other brown bread/combination)	-0.0677	6.55 (3.26, 9.72)	<0.001	74.2	**-0.6 (-3.3, 0.3)**
F	Usual fruit and vegetable consumption (<3 per week/3-4 per week/5-6 per week/daily/>1 per day)	-0.06266	6.07 (2.72, 9.31)	<0.001	71.4	**6.8 (-1.1, 19.9)**
G	BMI, kg/m2 (continuous)	-0.0745	7.18 (3.94, 10.32)	<0.001	77.5	**-10.8 (-23.2, -4.6)**
H	SBP, mmHg (continuous)	-0.0586	5.70 (2.41, 8.87)	0.001	69.1	**12.8 (7.4, 24.4)**
I	HDL cholesterol, mmol/L (continuous)	-0.0561	5.45 (2.13, 8.67)	0.001	67.4	**16.6 (9.9, 32.3)**
J	Non-HDL cholesterol, mmol/L (continuous)	-0.0441	4.32 (0.79, 7.72)	0.02	58.6	**34.4 (20.4, 75.7)**
	Effect of combinations of risk factors					
K	Smoking, non-HDL cholesterol, HDL cholesterol, SBP	-0.0309	3.05 (-0.47, 6.44)	0.09	46.2	**54.0 (34.4, 105)**
L	Smoking, non-HDL cholesterol, HDL cholesterol, SBP, usual fruit and vegetable consumption	-0.0297	2.92 (-0.64, 6.36)	0.1	44.8	**55.9 (34.3, 112)**
M	Smoking, non-HDL cholesterol, HDL cholesterol, SBP, usual fruit and vegetable consumption, BMI	-0.0350	3.44 (-0.15, 6.91)	0.06	50.4	**47.9 (26.6, 95.5)**

*% of the observed fall in hazard rate explained by risk factor = 100% × $(\beta_0 - \beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in the Cox regression model which only included calendar time (Model A), and β_1 is the coefficient of calendar time in the Cox regression model adjusting additionally for the risk factor(s)

Table 6.6 **Fall in hazard of a first major CHD event among men and women in Whitehall II between 1985 and 2004 and percentage of the fall explained by risk factor time trends, separate results for each gender**

		Men			Women		
Model	**Risk factors adjusted for in addition to age**	**Fall in hazard per annum, % (95% CI)**	**p-value**	**% of the observed decline in hazard explained by the risk factor(s), (95% CI)***	**Fall in hazard per annum, % (95% CI)**	**p-value**	**% of the observed decline in hazard explained by the risk factor(s), (95% CI)***
A	**No adjustment**	6.26 (2.66, 9.73)	0.001		8.12 (-0.25, 15.80)	0.06	
	Effect of adjustment for individual risk factors in isolation						
B	Smoking (current/ex/never)	5.96 (2.34, 9.45)	0.001	**4.8 (1.4, 13)**	7.51 (-0.96, 15.27)	0.08	**7.9 (-3.3, 43.9)**
C	Physical activity (low/medium/high)	6.31 (2.70, 9.79)	0.001	**-0.9 (-6.9, 4.7)**	7.78 (-0.75, 15.58)	0.07	**4.5 (-3.1, 60.7)**
D	Alcohol units per week (none/within limit/over limit/heavy)	6.25 (2.62, 9.75)	0.001	**0.1 (-9.2, 9.3)**	7.84 (-0.64, 15.60)	0.07	**3.7 (-10.2, 32.6)**
E	Usual bread consumption (white/wholemeal/granary or wheatmeal/other brown bread/combination)	6.29 (2.69, 9.75)	0.001	**-0.5 (-3.8, 0.6)**	8.16 (-0.26, 15.86)	0.06	**-0.4 (-9.1, 6.4)**
F	Usual fruit and vegetable consumption (<3 per week/3-4 per week/5-6 per week/daily/>1 per day)	5.87 (2.20, 9.40)	0.002	**6.3 (-2.2, 23.1)**	7.29 (-1.32, 15.18)	0.1	**10.6 (-23.1, 57.3)**
G	BMI, kg/m^2 (continuous)	7.32 (3.73, 10.77)	<0.001	**-17.6 (-41.1, -8.2)**	8.22 (-0.06, 15.81)	0.05	**-1.2 (-28.0, 14.2)**
H	SBP, mmHg (continuous)	5.58 (1.98, 9.05)	0.003	**11.1 (5.7, 25.5)**	6.67 (-1.73, 14.37)	0.1	**18.5 (6.8, 69.8)**
I	HDL cholesterol, mmol/L (continuous)	5.10 (1.43, 8.62)	0.007	**19.1 (10.2, 39.0)**	7.48 (-0.91, 15.17)	0.08	**8.3 (1.0, 44.4)**
J	Non-HDL cholesterol, mmol/L (continuous)	4.19 (0.32, 7.91)	0.03	**33.8 (18.2, 87.4)**	5.52 (-3.47, 13.73)	0.2	**33.0 (10.8, 214)**
	Effect of adjustment for combinations of risk factors						
K	Smoking, non-HDL cholesterol, HDL cholesterol, SBP	2.99 (-0.88, 6.71)	0.1	**53.0 (30.7, 123)**	3.66 (-5.35, 11.89)	0.4	**56.0 (21.5, 269)**
L	Smoking, non-HDL cholesterol, HDL cholesterol, SBP, usual fruit and vegetable consumption	2.90 (-1.02, 6.67)	0.1	**54.4 (29.8, 126)**	3.38 (-5.66, 11.65)	0.5	**59.4 (19.2, 221)**
M	Smoking, non-HDL cholesterol, HDL cholesterol, SBP, usual fruit and vegetable consumption, BMI	3.48 (-0.49, 7.30)	0.09	**45.1 (21.7, 119)**	3.76 (-5.27, 12.02)	0.4	**54.7 (11.2, 210)**

* % of the observed fall in hazard rate explained by risk factor = $100\% \times (\beta_0 - \beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in the Cox regression model which only included calendar time (Model A), and β_1 is the coefficient of calendar time in the Cox regression model adjusting additionally for the risk factor(s)

Table 6.7 **Fall in hazard of a first major CHD event among all participants in Whitehall II between 1985 and 2004 and percentage of this fall explained by risk factor time trends, separate results for each employment grade**

		Employment grade								
		High (civil service grades 1 to 7)			Medium (civil service executives, including senior)			Low (clerical)		
Model	**Risk factors adjusted for in addition to age and gender**	**Fall in hazard per annum, % (95% CI)**	**p-value**	**% of decline in hazard explained by risk factor(s), (95% CI)***	**Fall in hazard per annum, % (95% CI)**	**p-value**	**% of decline in hazard explained by risk factor(s), (95% CI)***	**Fall in hazard per annum, % (95% CI)**	**p-value**	**% of decline in hazard explained by risk factor(s), (95% CI)***
A	**No adjustment**	4.88 (-1.54, 10.89)	0.133		7.91 (3.49, 12.14)	0.001		4.53 (-3.85, 12.22)	0.28	
	Effect of individual risk factors in isolation									
B	Smoking (current/ex/never)	4.71 (-1.73, 10.75)	0.148	**3.4**	7.61 (3.16, 11.86)	0.001	**4.0**	3.97 (-4.54, 11.78)	0.35	**12.6**
C	Physical activity (low/medium/high)	4.73 (-1.69, 10.76)	0.145	**3.0**	8.08 (3.63, 12.33)	<0.001	**-2.2**	4.14 (-4.31, 11.9)	0.326	**8.7**
D	Alcohol units per week (none/within limit/over limit/heavy)	5.07 (-1.38, 11.11)	0.121	**-4.0**	7.83 (3.35, 12.09)	0.001	**1.1**	4.46 (-3.96, 12.2)	0.29	**1.4**
E	Usual bread consumption (white/wholemeal/granary or wheatmeal/other brown bread/combination)	4.85 (-1.57, 10.87)	0.136	**0.6**	7.93 (3.51, 12.15)	0.001	**-0.2**	4.6 (-3.78, 12.3)	0.273	**-1.6**
F	Usual fruit and vegetable consumption (<3 per week/3-4 per week/5-6 per week/daily/>1 per day)	5.06 (-1.44, 11.14)	0.124	**-3.8**	7.45 (2.93, 11.76)	0.001	**6.1**	3.72 (-4.83, 11.56)	0.383	**18.2**
G	BMI, kg/m2 (continuous)	5.78 (-0.64, 11.79)	0.077	**-19.1**	8.34 (3.96, 12.52)	<0.001	**-5.7**	5.66 (-2.56, 13.22)	0.172	**-25.7**
H	Systolic blood pressure, mmHg (continuous)	4.56 (-1.86, 10.57)	0.16	**6.7**	6.96 (2.54, 11.18)	0.002	**12.5**	3.11 (-5.27, 10.82)	0.455	**31.7**
I	HDL cholesterol, mmol/L (continuous)	3.8 (-2.66, 9.85)	0.243	**22.6**	6.75 (2.24, 11.05)	0.004	**15.2**	3.86 (-4.54, 11.59)	0.357	**14.9**
J	Non-HDL cholesterol, mmol/L (continuous)	2.32 (-4.54, 8.74)	0.497	**53.0**	5.83 (1.01, 10.41)	0.018	**27.2**	2.59 (-6.31, 10.75)	0.556	**43.3**
	Effect of combinations of risk factors									
K	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure	1.76 (-5.04, 8.12)	0.602	**64.4**	4.36 (-0.47, 8.95)	0.076	**46.0**	0.24 (-8.77, 8.51)	0.956	**94.7**
L	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure, usual fruit and vegetable consumption	2.19 (-4.67, 8.6)	0.523	**55.8**	4.14 (-0.74, 8.79)	0.095	**48.7**	-0.5 (-9.59, 7.83)	0.91	**110.7**
M	Smoking, non-HDL cholesterol, HDL cholesterol, systolic blood pressure, usual fruit and vegetable consumption, BMI	2.26 (-4.75, 8.8)	0.518	**54.3**	4.33 (-0.62, 9.03)	0.085	**46.3**	1.05 (-7.98, 9.32)	0.813	**77.2**

* % of the observed fall in hazard rate explained by risk factor = 100% × (β_0- β_1)/ β_0, where β_0 is the coefficient of calendar time in the Cox regression model which only included calendar time (Model A), and β_1 is the coefficient of calendar time in the Cox regression model adjusting additionally for the risk factor(s)

Chapter 7: Assessing the role of medication in the time trends in the major coronary aetiological exposures in the British Regional Heart Study

7.1 Introduction

In chapters 5 and 6 it was shown that a substantial portion of the decline in major CHD incidence in Britain in recent decades may be attributed to concurrent favourable trends in the major aetiological exposures. Among other factors, favourable trends in blood pressure (BP), HDL cholesterol and non-HDL cholesterol have made appreciable contributions. The reasons for the favourable changes in BP and blood lipids however have not been examined. The trends may reflect favourable changes in the underlying determinants of BP or blood lipids in the population; for BP, adiposity, alcohol intake, physical activity, and dietary factors (particularly salt intake) are known modifiable determinants[363] while for total and LDL cholesterol dietary saturated fat intake, adiposity and physical activity are important[364]. Alternatively, the trends in these risk factors may reflect the increasingly widespread use[365] of specific medications to lower BP (including particularly ACE inhibitors, beta blockers, calcium channel blockers, diuretics)[156-160] and to lower total and LDL-cholesterol (particularly statins)[152-155].

The evidence suggest that blood pressure lowering medications influence major CHD risk primarily through changing blood pressure[160], and lipid-regulating medications prevent major CHD events primarily through changing blood lipid levels (principally LDL levels)[153]. Therefore understanding the contributions of medication-related and non-medication-related factors to the changes in BP and blood lipids which have occurred during recent decades could help to inform efforts to bring about further reductions in the risk of CHD.

The aim of this chapter is therefore to assess the role of medication in changes in systolic BP (SBP), diastolic BP (DBP), non-HDL cholesterol and HDL cholesterol which have occurred. This corresponds to objective iii) b) of the overall thesis objectives.

In particular, the analyses will explore the extent to which increased uptake of blood pressure lowering medications[365] (including particularly angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers and diuretics) may have contributed to blood pressure changes, and the extent to which increased uptake of lipid-regulating medications[365] (particularly statins) may have contributed to the changes in lipid levels. The British Regional Heart Study is used for this analysis, to explore the BP and lipid trends in older British men between 1978 and 2000.

Objective

To estimate the contribution of increased uptake of medication to the trends in blood pressure and cholesterol in the BRHS

The structure of this chapter is as follows: Section 7.2 details methods specific to this chapter, including statistical methods. Results are given in section 7.3. Finally, section 7.4 provides a discussion and interpretation of the findings of the chapter.

7.2 Methods

7.2.1 Data source

Analyses in this chapter are carried out using the BRHS. Marked favourable trends in blood pressure and blood lipids were demonstrated in chapter 5 to be associated with the decline in major CHD incidence in this cohort. Medication use was ascertained repeatedly, at each of the questionnaires.

7.2.2 Coronary risk factors as the principal outcomes

The main outcomes were systolic blood pressure (SBP), diastolic blood pressure (DBP), HDL cholesterol and non-HDL cholesterol, measured at physical examinations at baseline (1978 to 1980) and after 20 years (1998 to 2000).

7.2.3 Medication use

From questions about medication use in every questionnaire between baseline and 20 years (that is, in 1978-80, in 1983-5, in 1992 and in 1996), current use of drugs to lower blood pressure and current use of drugs to regulate lipid levels at each time-point was determined. The information at each time-point was then combined to produce an indicator for blood pressure-lowering drug use at any time between baseline and 20 years, and a similar indicator for lipid-regulating drug use at any time between baseline and 20 years.

7.2.4 Potential confounding variables: factors associated with dyslipidemia and hypertension

Potential factors that may increase risk of high SBP and DBP considered in this analysis were BMI, physical inactivity and alcohol intake as these factors have been found to be

associated with blood pressure levels[363]. For high non-HDL cholesterol factors considered were BMI and physical inactivity, again factors previously shown to be associated with non-HDL or LDL cholesterol levels[364]. For low HDL cholesterol, BMI, physical inactivity, alcohol use and smoking status were considered as all four factors have been shown to be associated with HDL cholesterol levels[364]. Differences between medication users and non-medication users in the overall levels of these lifestyle factors, as well as in temporal changes in these factors could potentially confound estimates of the modifying effect of medication use on trends in blood pressure and cholesterol. Therefore, recorded levels of each factor at both baseline and the 20-year follow-up, categorised as outlined in chapter 3, section 3.2.5, were used in analyses.

7.2.5 Statistical methods

Again the dataset was split such that measurements at baseline and 20 years formed two separate rows of data for each man. Age-adjusted changes in each of the four outcomes were estimated from linear regression of the outcome on a time variable (taking the value 0 at baseline, and value 20 at 20 years), adjusting for age. Generalised estimating equations with robust standard errors were used in the regressions to take account of the repeated measures of each outcome (one at baseline and a second at 20 years) for each man. An interaction term of time with an indicator for medication use at any time between baseline and 20 years was added to the model to estimate the trend in the outcome according to whether a man had received medication or not. Predicted BP and cholesterol levels for a 60 year old man at baseline and at 20 years were estimated from the regression models. Multivariable models, adjusting additionally for the current levels at both time points of the risk factors for each outcome (BMI as a continuous variable and physical activity, smoking status and alcohol intake categorised as described above) ,

were used to take account of possible differences in these factors between the men receiving and not receiving medication.

7.2.6 Participants included in analysis

In this analysis, only those men who were alive at the 20 year follow-up and attended the 20-year physical examination were included. In contrast to the analyses in chapter 5, men were included regardless of previous MI. However analyses were also repeated separately among men who did and did not experience an MI before or during the 20 year follow-up to correspond to the study sample in chapter 5. Further, as sensitivity analyses, the analyses were repeated among men who did not have any previous cardiovascular disease (MI, other CHD or stroke) as all forms of cardiovascular disease are known to affect blood pressure and cholesterol levels (in particular, blood pressure and lipid levels may fall as a result of an MI or stroke[103]).

7.3 Results – Examining the role of medication in the risk factor changes

Of 7735 men who entered the study, 4252 surviving men were re-examined at 20 years. Of these men, 21 (0.5%) were missing a valid blood pressure measurement at baseline and/or 20 years, leaving 4231 men for inclusion in analyses of trends in SBP and DBP. 386 men (9%) were missing a valid lipid measurement at baseline and/or 20 years and a further 4 men (0.09%) were missing records of lipid-regulating medication use, leaving 3862 men for inclusion in analyses of trends in non-HDL and HDL cholesterol. 1561 (37%) out of 4231 men reported use of blood pressure-lowering drugs at some point over the 20 years; the proportion increased from 3.0% at baseline (1978-1980) to 33% at 20 years follow-up (1998-2000). 302 (7.8%) out of 3862 men reported use of lipid-regulating

drugs at some point over the 20 years; none reported use at baseline, compared with 7.4% at 20 years.

Adjusting for age, mean SBP changed by -7.6mmHg; 95% confidence interval (CI) -9.7 to -5.4, $p<0.001$, while mean DBP changed by +3.3mmHg (95% CI +2.2 to +4.5, $p<0.001$) over 20 years (table 7.1). The trends in SBP and DBP varied according to blood pressure-lowering drug use: Mean changes in SBP were -12.3mmHg (95% CI -14.7 to -9.9) among medication users and -1.6mmHg (95% CI -3.7 to +0.5) among men not on medication ($p<0.001$ for medication-time interaction). Mean changes in DBP were -1.2mmHg (95% CI -2.5 to +0.07) among medication users and +7.7mmHg (95% CI +6.6 to +8.8) among men not on medication ($p<0.001$ for medication-time interaction).

Adjusting for age, mean non-HDL cholesterol changed by -0.35mmol/L (95% CI -0.46 to -0.24, $p<0.001$). The change among medication users was -1.78mmol/L (95% CI -1.96 to -1.60), compared with a change of -0.24mmol/L (95% CI -0.35 to -0.13) among men not on medication ($p<0.001$ for medication-time interaction). Mean HDL cholesterol changed by +0.16mmol/L (95% CI +0.13 to +0.19, $p<0.001$). There was no evidence that the trend in HDL cholesterol varied according to lipid-regulating drug use. HDL cholesterol changed by +0.18 (95% CI +0.14 to +0.23) among medication users and by +0.16 (95% CI +0.13 to +0.19) among men not on medication ($p=0.15$ for medication-time interaction).

The results suggest that had none of the men using blood pressure-lowering medication been present, we would have expected an overall average decline in SBP among all men of 1.61mmHg (the change among men not on medication). Given that the actual average

decline observed was 7.56mmHg, this suggests that (7.56-1.61)/7.56 = 79% of the overall cohort-wide decline in SBP may be attributed to the greater changes occurring among that select (high-risk) group of medication users, over and above the changes occurring among men not on medication. Similarly, 29% of the decline in non-HDL cholesterol and none of the increase HDL cholesterol may be attributed to greater changes occurring only among lipid-regulating drug users, over and above the background changes occurring in men not on medication.

With additional adjustment for measured confounders (BMI, alcohol use and physical activity for SBP and DBP; BMI and physical activity for non-HDL cholesterol; BMI, physical activity, smoking and alcohol use for HDL cholesterol) the favourable trends in SBP, non-HDL cholesterol and HDL cholesterol became slightly stronger and the unfavourable trend in DBP became weaker, but the interactions between medication use and time were essentially unchanged (table 7.2), reflecting the little variation in the absolute levels and temporal changes in these behavioural factors according to BP-lowering medication use (table 7.3) and lipid-regulating medication use (table 7.4). In sensitivity analyses adjusted for the (non-significant) systematic differences in lipid measurements between the baseline and 20-year assay techniques described in the chapter 3, section 3.2.6, the trends in non-HDL cholesterol were unchanged and, while the increase in HDL became slightly weaker, it remained significant and there remained no difference according to medication use (table 7.5).

Analogous results among that subgroup of men with no prior MI before the 20-year follow-up (to correspond with the sample of men included in the previous analysis to explain the decline in MI) are shown in table 7.6. The 20-year trends and predicted levels

for a 60-year old for each risk factor, overall and according to medication use, were all very similar to the results for the whole cohort, and therefore in particular, the differences and similarities between those who did and did not report medication use, persisted. Indeed, combining the trends estimates as above, among this sub-cohort, 75% of the overall cohort-wide decline in SBP may be attributed to the greater changes occurring among that select (high-risk) group of medication users, over and above the changes occurring among men not on medication. 30% of the decline in non-HDL cholesterol and none of the increase HDL cholesterol may be attributed to greater changes occurring only among lipid-regulating drug users, over and above the background changes occurring in men not on medication. Excluding further men who did not have any previous CHD (that is, angina or MI) or stroke before the 20-years, the results did not alter appreciably (data not shown).

7.4 Discussion

7.4.1 Summary of main findings

Over a 20-year period between 1978-1980 and 1998-2000, a significant favourable increase of 14% in average HDL cholesterol, and significant but more modest favourable falls of 5% and 7% in SBP and non-HDL cholesterol respectively, were observed in this survivor cohort of British men. Most (80%) of the fall in SBP and a smaller proportion (33%) of the fall in non-HDL cholesterol could be attributed to larger decreases in medication users over and above the decreases among men not on medication. The favourable increase in HDL cholesterol however was independent of medication use. DBP did not change favourably over the 20 years.

The results were similar for men with and without a major CHD event or CVD event before or during the 20-year follow-up.

7.4.2 Comparison with other studies

In terms of the risk factor trends seen, as discussed in chapter 5, section 5.5.2, the overall decline in SBP is consistent with cross-sectional routine data for England reported in the Health Survey for England 1998[351] and with SBP trends observed in Glasgow, Scotland (WHO MONICA, (mean fall of 4.5mmHg over an overlapping 10-year period between 1986 and 1995 compared with our figure of 7.6mmHg over 20 years)[245]. However modest declines in DBP were also reported in these two studies, in contrast to our observed increase. The limited data on national trends in cholesterol in the UK[352] is consistent with the trends seen here (see chapter 5, section 5.5.2).

There is little data on blood pressure and cholesterol temporal trends according to medication use and few studies have formally investigated the impact of medication use on secular trends in blood pressure and cholesterol. A report from the Minnesota Heart Survey compared the trend in total cholesterol from 1980 to 2002 among the entire population with the trend among that subgroup not using lipid-regulating medication[366]. The trends were fairly similar until the last few study years, when the general population showed a steeper decline in total cholesterol compared with the subgroup not using medication, suggesting that lipid-regulating drug use may be partially responsible for the overall population-wide trend in total cholesterol at least in later years. A separate recent study in the US population found that one-quarter of an observed 0.34mmol/L mean fall in total cholesterol between 1980 and 2000 could be attributed to statin use[367], broadly consistent with the present findings of one third of the (smaller) decline in non-HDL

cholesterol the UK over the same period associated with users of medication. A study in Finland observed declines in total cholesterol of 0.86mmol/L in men and 0.97mmol/L in women between 1982 and 2007[368]. Expected declines given dietary and medication trends over the same period were estimated, and compared with the observed declines to estimate the contribution of diet and medication use to the total cholesterol declines. The results were that the majority of the total cholesterol decline (65% in men and 60% in women) could be attributed to changes in dietary fat quality and cholesterol intake, while lipid-regulating medication explained 16% in men and 7% in women. The conclusions are consistent with the present study in that other factors (diet) may have been more important than use of lipid-regulating medications in the favourable lipid trends. However, the contribution of lipid-regulating medications is even smaller than that estimated in the present analysis. Since uptake of lipid-regulating drugs was greater in the Finnish population (up to 30% among older adults), reflecting the more recent time-period, differences in uptake cannot explain this. The difference could instead reflect the limitations of the ecological analysis in the Finnish study, or that total cholesterol instead of non-HDL was considered or that concerted efforts have been made to reduce dietary intake of cholesterol in Finland[369, 370] which was initially very high, more so than in the UK, leading to overall greater lipid changes and a greater impact of diet in the Finnish population. As discussed in chapter 2, section 2.6.1.1, the WHO MONICA project investigated the role of medication on time trends in blood pressure by comparing the shape of the distribution of blood pressure in the mid-1980s with that in the mid-1990s in different world-wide populations[245]. The hypothesis was that the effect of blood pressure-lowering medication would be realised in a selective depression of the top end of the population bell curve over time (reflecting the impact of blood pressure-lowering medication as a high risk as opposed to mass population intervention). The study found

no significant evidence for such a medication effect for the overall analysis of all populations combined (mean blood pressure changes, pooled across all the populations, were similar in the different blood pressure centiles) but may have been limited by this indirect ecological approach. Considering the UK populations in isolation however gives a different picture. In Glasgow, use of anti-hypertensive medications increased from 7% to 10% of the study population, between 1985 and 1994. Over the same period, average systolic blood pressure declined by -4.5mmHg and diastolic blood pressure declined by -3.6mmHg in men. The declines were greatest among participants above the 80th blood pressure centiles, that is, with the highest blood pressure: declines of -6.0mmHg and -4.0mmHg for systolic and diastolic blood pressure respectively. A similar pattern was seen among women: systolic blood pressure declined by -6.9mmHg on average and by -7.0mmHg among women above the 80th centile; diastolic blood pressure declined by -5.9mmHg on average and by -7.0mmHg above the 80th centile. This suggests a selective depression of the top end of the bell curve over time which in turn suggests an influence of medication on the blood pressure trends, in line with the present BRHS findings for Great Britain as a whole. In Belfast, use of anti-hypertensive medication did not increase; at the same time blood pressure levels changed little, which neither supports nor refutes an influence of medication in blood pressure time trends in general.

7.4.3 Strengths and Limitations

This study provided data on long-term changes in BP and cholesterol in a socially and geographically representative sample of older British men. Cross-calibration of BP and lipid measurement techniques used at 20 years with those at baseline ensured comparability between the two time-points (as outlined in chapter 3, section 3.2.6). Further, in subsidiary analyses adjusting for the non-significant systematic differences

between the baseline and 20-year lipid measurement techniques, the conclusions did not change.

The ascertainment of medication use needs consideration. Questions on medication use in repeated questionnaires over the 20-year follow-up helped to ensure all users of relevant medications over this period were identified, particularly by asking in the questionnaires not only about specific medications but to list all prescriptions. Comparison data on population-wide prevalence of medication use is limited, particularly in earlier years. Findings from routine prescription records showed that in 1998, among men aged 65-to-74 years, the prevalence of prescribing of lipid-regulating medication was 7.8%[315], a figure which agrees closely with our data (7.7% in 1998-2000), which helps to validate our self-reported medication measure. Corresponding figures for blood pressure medication from this report could not be compared as patients may be prescribed more than one type of blood pressure medication, leading to larger prescription numbers. However a population-based study found self-report of antihypertensive medication use to agree reasonably closely with prescription data[371]. Moreover, self-report may arguably be a better reflection of medication compliance than prescription records.

The analyses were necessarily based on those surviving men who attended the 20-year follow-up re-examination. This potential for survival and response biases needs consideration. The most likely impact would be overestimation of the favourable trends observed (healthy participant effect). Importantly, the healthy participant effect is unlikely to explain the *differential* trends according to medication use and thus the role of medication, which is the key finding (since both groups may be similarly influenced by the healthy participant effect, such that the *difference* between the groups is unlikely to be

affected). Also, as discussed in chapter 5, section 5.5.3, baseline levels of blood pressure and cholesterol among those who survived to attend the 20-year examination have been shown to be similar to levels among non-attendees[355], especially when compared with the overall changes over time, suggesting that a healthy participant effect was unlikely to have had a dramatic influence on the observed trends.

As might be expected, baseline levels of SBP, DBP, and non-HDL cholesterol were much higher in those men who reported subsequent medication use (table 7.1), thus there was arguably greater potential for a decline in these groups. Nevertheless, in separate analyses, including baseline levels of the outcome as a covariate to adjust for regression to the mean[372], the changes in SBP, DBP and non-HDL cholesterol in the medication users remained significantly greater than the changes in men not using medication while there remained no significant difference in the HDL cholesterol trends.

A limitation is that only 8% of men were on lipid-regulating medications, raising issues of low statistical power (wide CIs). The cohort comprises older British men, for whom prevalence of medication use is higher than for younger men and women and therefore generalisability of these results to other populations is uncertain. In particular, if prevalence of medication use is lower in another population, the percentage of the BP and cholesterol trends attributable to added changes among medication users will be lower.

7.4.4 Interpretation of findings

The marked increase in levels of the protective factor HDL-cholesterol, which rose by about 14% between 1980 and 2000, was independent of medication use. The trend is likely to reflect secular changes in the determinants of HDL-cholesterol, in particular the

decline in cigarette smoking prevalence among the study population, since cigarette smoking is associated with markedly reduced HDL-cholesterol levels[373] and smoking cessation has been shown to raise HDL-cholesterol levels[374]. Other possible factors include diet and vitamin C supplementation[364, 375]. Of the more modest overall 7% decline in non-HDL cholesterol, approximately one-third of the decline could be accounted for by the decline occurring in users of lipid-regulating medications. The remaining population wide decline in non-HDL cholesterol may reflect the contemporaneous fall in the dietary consumption of saturated fat; household purchase data suggest that daily total and saturated fat intake fell in the UK from 47g to 29g between 1980 and 2000[376]. However dietary data was not available to directly examine the role of dietary factors in the BRHS. The overall 5% decline in population SBP in this survivor cohort was largely accounted for by changes among users of blood pressure-lowering medication, reflecting the high prevalence of blood pressure- lowering medication use in this cohort of older British men. No material decline in SBP occurred among men not receiving blood pressure-lowering medication, while DBP increased which was unexpected and merits further study. The much stronger favourable declines in non-HDL cholesterol and SBP among medication users, compared with men not using medication, could be attributed entirely to the medication itself or could also partly reflect more favourable life-style changes or a differing risk-profile among medication users compared with men not using medication. The persistence of differential trends according to medication use even after adjustment for concurrent changes in major potential confounders (smoking status, alcohol use, BMI and physical inactivity), and in sensitivity analyses excluding men with previous MI, suggests that it is most likely the treatment itself that is bringing about the changes in medication users. Indeed in further sensitivity analyses, excluding men with *any* previous cardiovascular morbidity (MI or other CHD

or stroke), the differential trends remained (data not shown). However a limitation is that diet was not measured in this analysis. Medication users may also have made more favourable changes to their diet than those not using medication which may explain some part of the differential trends. That said, while it is recognised that lipid-regulating medications act principally on non-HDL cholesterol rather than HDL, we might expect diet to have more similar influences on both lipid types. Thus if diet did differ substantially between the two medication groups we might have expected differences in the trends in HDL between the two groups as well, which we did not see.

The results of the present study confirm that the use of medication to lower BP was widespread before 2000, and suggest that use of anti-hypertensive drugs may explain much of the fall in SBP. Since in chapter 5 (section 5.4) it was estimated that falling SBP levels could explain 13% of the decline in major CHD incidence in the BRHS, it might be inferred that the contribution of increased use of anti-hypertensive drugs to the CHD decline is close to this figure. This assumes however that the effect of anti-hypertensive drugs on CHD risk is only through lowering BP; the contribution of these drugs to the CHD decline may be greater if anti-hypertensive drugs have a broader effect on CHD risk. That said, studies suggest that the effect of anti-hypertensive drugs is predominantly through moderating BP levels[160].

Around one third of the decline in non-HDL cholesterol could be attributed to use of lipid-regulating drugs. Since in chapter 5 (section 5.4), it was estimated that falling non-HDL cholesterol levels could explain 10% of the decline in major CHD incidence, it might be inferred that the contribution of increased use of lipid-regulating drugs to the CHD decline is modest, at around 3%. This again assumes that the effect of lipid-

regulating drugs on CHD risk is only through lowering non-HDL cholesterol; the contribution of these drugs to the CHD decline may be greater if the drugs have a broader effect on CHD risk. Again, studies suggest however that the effect of lipid-regulating drugs is predominantly through moderating cholesterol levels.[153]

The modest impact of lipid-regulating drugs reflects in part the low uptake of these drugs during the period of study. Since 2000, further population-wide declines in blood cholesterol and BP have occurred[352]. At least part of these changes are likely to reflect further increases in the prevalence of lipid lowering and BP-lowering drugs since 2000[377].

7.4.5 Chapter conclusions/ postscript

The key finding of this chapter is that the changes in SBP in this cohort appear to be largely confined to medication users, while the change in non-HDL cholesterol probably reflects a combination of medication and lifestyle and the change in HDL cholesterol likely reflects predominantly lifestyle factors. The implication is that use of anti-hypertensive drugs may have made an appreciable contribution to the decline in major CHD incidence. The contribution of lipid-regulating drugs is much more modest but the effects of lipid-regulating drugs may be yet to be realised due to low uptake during the period of study.

Together, chapters 5, 6 and 7 have explored the reasons for the favourable decline in major CHD incidence in Britain in recent decades. In the next chapter 8, the factors influencing the unfavourable parallel rise in T2DM incidence are investigated.

Table 7.1 **Mean age-adjusted changes over 20 years from 1978-80 to 1998-2000 in SBP, DBP, HDL cholesterol and non-HDL cholesterol and predicted levels for a 60-year old in 1978-80 and in 1998-2000, overall and according to medication use between the two time-points**

	N	Predicted level for 60 year old in 1978-80 (95% CI)	Mean age-adjusted change over 20 years (95%CI)	P	Predicted level for 60 year old in 1998-2000 (95% CI)
SBP, mmHg					
All men	4231	150.4 (149.1, 151.7)	-7.56 (-9.69, -5.43)	<0.001	142.9 (141.8, 143.9)
Men using BP-lowering medication	1561	158.3 (156.8, 159.7)	-12.30 (-14.69, -9.92)	<0.001	146.0 (144.4, 147.5)
Men not using BP-lowering medication	2670	144.1 (142.7, 145.4)	-1.61 (-3.71, 0.49)	0.13	142.4 (141.3, 143.6)
			p-value for interaction	**<0.001**	
DBP, mmHg					
All men	4231	81.6 (80.9, 82.3)	3.31 (2.18, 4.45)	<0.001	84.9 (84.4, 85.5)
Men using BP-lowering medication	1561	86.9 (86.0, 87.8)	-1.22 (-2.51, 0.07)	0.06	85.7 (84.9, 86.4)
Men not using BP-lowering medication	2670	77.6 (76.9, 78.3)	7.68 (6.57, 8.79)	<0.001	85.3 (84.7, 85.9)
			p-value for interaction	**<0.001**	
HDL cholesterol, mmol/L					
All men	3862	1.16 (1.14, 1.18)	0.16 (0.13, 0.19)	<0.001	1.32 (1.30, 1.34)
Men using lipid-regulating medication	302	1.12 (1.09, 1.16)	0.18 (0.14, 0.23)	<0.001	1.30 (1.27, 1.34)
Men not using lipid-regulating medication	3560	1.16 (1.14, 1.18)	0.16 (0.13, 0.19)	<0.001	1.32 (1.30, 1.34)
			p-value for interaction	**0.15**	
Non-HDL cholesterol, mmol/L					
All men	3862	5.08 (5.01, 5.14)	-0.35 (-0.46, -0.24)	<0.001	4.73 (4.67, 4.78)
Men using lipid-regulating medication	302	6.01 (5.87, 6.15)	-1.78 (-1.96, -1.60)	<0.001	4.23 (4.10, 4.35)
Men not using lipid-regulating medication	3560	5.00 (4.94, 5.07)	-0.24 (-0.35, -0.13)	<0.001	4.76 (4.70, 4.82)
			p-value for interaction	**<0.001**	

Note: Mean changes, associated p-values and predicted levels from linear regression models with generalised estimating equations and robust standard errors

Table 7.2 **Mean changes over 20 years from 1978-80 to 1998-2000 in SBP, DBP, HDL cholesterol and non-HDL cholesterol, overall and according to medication use between the two time-points, adjusting for age and risk factors for hypertension or hypercholesterolemia**

	N	Mean age- and risk-factor adjusted* change over 20 years (95%CI)	p
SBP, mmHg			
All men	4229	-9.00 (-11.14, -6.86)	<0.001
Men using BP-lowering medication	1561	-13.39 (-15.81, -10.98)	<0.001
Men not using BP-lowering medication	2668	-3.21 (-5.33, -1.09)	0.003
		p-value for interaction	**<0.001**
DBP, mmHg			
All men	4229	1.98 (0.84, 3.11)	0.001
Men using BP-lowering medication	1561	-2.43 (-3.73, -1.13)	<0.001
Men not using BP-lowering medication	2668	6.20 (5.08, 7.32)	<0.001
		p-value for interaction	**<0.001**
HDL cholesterol, mmol/L			
All men	3858	0.18 (0.15, 0.21)	<0.001
Men using lipid-regulating medication	302	0.21 (0.17, 0.25)	<0.001
Men not using lipid-regulating medication	3556	0.18 (0.15, 0.21)	<0.001
		p-value for interaction	**0.11**
non-HDL cholesterol, mmol/L			
All men	3860	-0.40 (-0.51, -0.29)	<0.001
Men using lipid-regulating medication	302	-1.84 (-2.02, -1.66)	<0.001
Men not using lipid-regulating medication	3558	-0.29 (-0.40, -0.18)	<0.001
		p-value for interaction	**<0.001**

*Confounders adjusted for:
SBP, DBP: BMI, alcohol use, physical activity; **non-HDL cholesterol**: BMI, physical activity; **HDL cholesterol**: BMI, smoking, alcohol use, physical activity

Table 7.3 **Baseline level, 20-year level, and change in risk factors for high SBP or DBP according to blood pressure lowering medication use between baseline and 20-years**

	Blood pressure lowering medication use			
	No (n=2670)		Yes (n=1561)	
	Total non-missing	*Mean (sd)*	*Total non-missing*	*Mean (sd)*
Age, years				
Baseline	2670	48.3 (5.51)	1561	49.8 (5.39)
20 year follow-up	2670	68.3 (5.51)	1561	69.8 (5.39)
Body mass index, kg/m2				
Baseline	2670	25.1 (2.89)	1561	26.1 (3.07)
20 year follow-up	2660	26.5 (3.57)	1552	27.7 (3.88)
Change	2660	+1.44 (2.34)	1552	+1.65 (2.61)
	Total non-missing	*N (%)*	*Total non-missing*	*N (%)*
Alcohol use				
Baseline	2669		1560	
none		123 (4.6)		89 (5.7)
occasional		665 (24.8)		376 (24.1)
light		981 (36.8)		550 (35.3)
moderate		678 (25.4)		383 (24.6)
heavy		225 (8.4)		162 (10.4)
20 year follow-up	2613		1525	
none		263 (10.1)		166 (10.9)
occasional		670 (25.6)		446 (29.3)
light		1170 (44.8)		648 (42.5)
moderate		430 (16.5)		220 (14.4)
heavy		80 (3.1)		45 (2.9)
Change	2612		1524	
reduced alcohol use		985 (37.7)		644 (42.3)
no change		1205 (46.1)		651 (42.7)
increased alcohol use		422 (16.2)		229 (15.0)

Table 7.3 *continued* **Baseline level, 20-year level, and change in risk factors for high SBP or DBP according to blood pressure lowering medication use between baseline and 20-years**

	Blood pressure lowering medication use			
	No (n=2670)		Yes (n=1561)	
	Total non-missing	*N (%)*	*Total non-missing*	*N (%)*
Physical activity				
Baseline	2640		1543	
vigorous		242 (9.2)		109 (7.1)
moderately vigorous		502 (19.0)		231 (15.0)
moderate		474 (18.0)		238 (15.4)
light		568 (21.5)		339 (22.0)
occasional		703 (26.6)		505 (32.7)
inactive		151 (5.7)		121 (7.8)
20 year follow-up	2579		1497	
vigorous		420 (16.3)		199 (13.3)
moderately vigorous		493 (19.1)		192 (12.8)
moderate		399 (15.5)		189 (12.6)
light		481 (18.7)		279 (18.6)
occasional		561 (21.8)		394 (26.3)
inactive		225 (8.7)		244 (16.3)
Change	2551		1479	
more active		1014 (39.8)		526 (35.6)
no change		688 (27.0)		399 (27.0)
less active		849 (33.3)		554 (37.4)

Table 7.4 **Baseline level, 20-year level and change in risk factors for low HDL cholesterol, or high non-HDL cholesterol according to lipid-regulating medication use between baseline and 20-years**

	Lipid-regulating medication use			
	No (n=3560)		Yes (n=302)	
	Total non-missing	*Mean (sd)*	*Total non-missing*	*Mean (sd)*
Age, years				
Baseline	3560	49.0 (5.52)	302	48.0 (5.25)
20 year follow-up	3560	69.0 (5.52)	302	68.0 (5.25)
Body mass index, kg/m2				
Baseline	3560	25.3 (2.93)	302	25.9 (3.10)
20 year follow-up	3544	26.8 (3.62)	299	27.6 (3.76)
Change	3544	+1.47 (2.37)	299	+1.68 (2.38)
	Total non-missing	*N (%)*	*Total non-missing*	*N (%)*
Smoking status				
Baseline	3555		302	
smoker		1133 (31.9)		118 (39.1)
non-smoker		2422 (68.1)		184 (60.9)
20 year follow-up	3551		302	
smoker		455 (12.8)		29 (9.6)
non-smoker		3096 (87.2)		273 (90.4)
Change	3548		302	
gave up smoking		718 (20.2)		91 (30.1)
no change		2786 (78.5)		209 (69.2)
took up smoking		44 (1.3)		2 (0.7)
Alcohol use				
Baseline	3558		302	
none		168 (4.7)		16 (5.3)
occasional		883 (24.8)		65 (21.5)
light		1305 (36.7)		105 (34.8)
moderate		883 (24.8)		79 (26.2)
heavy		319 (9.0)		37 (12.2)
20 year follow-up	3484		297	
none		351 (10.1)		22 (7.4)
occasional		949 (27.2)		79 (26.6)
light		1532 (44.0)		129 (43.4)
moderate		549 (15.8)		57 (19.2)
heavy		103 (3.0)		10 (3.4)
Change	3482		297	
reduced alcohol use		1363 (39.1)		128 (43.1)
no change		1563 (44.9)		117 (39.4)
increased alcohol use		556 (16.0)		52 (17.5)

Table 7.4 *continued* **Baseline level, 20-year level and change in risk factors for low HDL cholesterol, or high non-HDL cholesterol according to lipid-regulating medication use between baseline and 20-years**

	Lipid-regulating medication use			
	No (n=3560)		Yes (n=302)	
	Total non-missing	*N (%)*	*Total non-missing*	*N (%)*
Physical activity				
Baseline	3522		300	
vigorous		299 (8.5)		20 (6.7)
moderately vigorous		625 (17.8)		52 (17.3)
moderate		622 (17.7)		43 (14.3)
light		760 (21.6)		63 (21.0)
occasional		998 (28.3)		93 (31.0)
inactive		218 (6.2)		29 (9.7)
20 year follow-up	3429		294	
vigorous		521 (15.2)		53 (18.0)
moderately vigorous		585 (17.1)		45 (15.3)
moderate		506 (14.8)		39 (13.3)
light		642 (18.7)		49 (16.7)
occasional		812 (23.7)		62 (21.1)
inactive		363 (10.6)		46 (15.7)
Change	3393		292	
more active		1280 (37.7)		125 (42.8)
no change		933 (27.5)		69 (23.6)
less active		1180 (34.8)		98 (33.6)

Table 7.5 **Mean changes over 20 years from 1978-80 to 1998-2000 in HDL cholesterol and non-HDL cholesterol and predicted levels for a 60-year old in 1978-80 and in 1998-2000, overall and according to medication use between the two time-points, adjusting for the non-significant systematic differences between the baseline and 20-year assay techniques**

	Adjusting for age only					Adjusting additionally for risk factors*		
	N	**Predicted level for 60 year old in 1978-80 (95% CI)**	**Mean change over 20 years (95%CI)**	**p**	**Predicted level for 60 year old in 1998-2000 (95% CI)**	**N**	**Mean change over 20 years (95%CI)**	**p**
HDL cholesterol, mmol/L								
All men	3862	1.22 (1.20, 1.24)	0.09 (0.06, 0.13)	<0.001	1.32 (1.30, 1.33)	3858	0.12 (0.09, 0.15)	<0.001
Men using lipid-regulating medication	302	1.19 (1.16, 1.22)	0.12 (0.07, 0.16)	<0.001	1.30 (1.27, 1.34)	302	0.14 (0.10, 0.18)	<0.001
Men not using lipid-regulating medication	3560	1.23 (1.21, 1.25)	0.09 (0.06, 0.12)	<0.001	1.32 (1.30, 1.34)	3556	0.12 (0.09, 0.15)	<0.001
			p-value for interaction	**0.15**			**p-value for interaction**	**0.11**
non-HDL cholesterol, mmol/L								
All men	3862	5.08 (5.02, 5.15)	-0.36 (-0.47, -0.25)	<0.001	4.73 (4.67, 4.78)	3860	-0.41 (-0.52, -0.29)	<0.001
Men using lipid-regulating medication	302	6.01 (5.87, 6.15)	-1.79 (-1.97, -1.61)	<0.001	4.23 (4.10, 4.35)	302	-1.85 (-2.03, -1.66)	<0.001
Men not using lipid-regulating medication	3560	5.01 (4.94, 5.08)	-0.25 (-0.36, -0.14)	<0.001	4.76 (4.70, 4.82)	3558	-0.30 (-0.41, -0.19)	<0.001
			p-value for interaction	**<0.001**			**p-value for interaction**	**<0.001**

*Confounders adjusted for: **non-HDL cholesterol**: BMI, physical activity; **HDL cholesterol**: BMI, smoking, alcohol use, physical activity

Table 7.6 **Mean age-adjusted changes over 20 years from 1978-80 to 1998-2000 in SBP, DBP, HDL cholesterol and non-HDL cholesterol and predicted levels for a 60-year old in 1978-80 and in 1998-2000, overall and according to medication use between the two time-points, among men who did not experience an MI before the 1998-2000 examination.**

	Adjusting for age only					Adjusting additionally for confounders*		
	N	**Predicted level for 60 year old in 1978-80 (95% CI)**	**Mean change over 20 years (95%CI)**	**p**	**Predicted level for 60 year old in 1998-2000 (95% CI)**	**N**	**Mean change over 20 years (95%CI)**	**p**
SBP, mmHg								
All men	3722	150.3 (148.9, 151.8)	-7.18 (-9.45, -4.90)	<0.001	143.2 (142.0, 144.3)	3720	-8.86 (-11.16, -6.57)	<0.001
Men using BP-lowering medication	1279	158.8 (157.2, 160.4)	-11.12 (-13.68, -8.55)	<0.001	147.7 (146.0, 149.3)	1279	-12.39 (-14.99, -9.79)	<0.001
Men not using BP-lowering medication	2443	144.0 (142.6, 145.5)	-1.77 (-4.00, 0.46)	0.1	142.3 (141.1, 143.5)	2441	-3.47 (-5.73, -1.22)	0.003
			p-value for interaction	**<0.001**			**p-value for interaction**	**<0.001**
DBP, mmHg								
All men	3722	81.3 (80.5, 82.1)	3.90 (2.69, 5.11)	<0.001	85.2 (84.6, 85.8)	3720	2.47 (1.26, 3.68)	<0.001
Men using BP-lowering medication	1279	86.9 (85.9, 87.8)	-0.46 (-1.84, 0.92)	0.5	86.4 (85.6, 87.2)	1279	-1.77 (-3.16, -0.38)	0.012
Men not using BP-lowering medication	2443	77.4 (76.6, 78.2)	7.94 (6.77, 9.11)	<0.001	85.3 (84.7, 85.9)	2441	6.44 (5.25, 7.62)	<0.001
			p-value for interaction	**<0.001**			**p-value for interaction**	**<0.001**
HDL cholesterol, mmol/L								
All men	3404	1.16 (1.14, 1.18)	0.15 (0.12, 0.19)	<0.001	1.32 (1.30, 1.34)	3400	0.18 (0.15, 0.21)	<0.001
Men using lipid-regulating medication	228	1.14 (1.11, 1.18)	0.17 (0.12, 0.22)	<0.001	1.31 (1.27, 1.35)	228	0.19 (0.14, 0.24)	<0.001
Men not using lipid medication	3176	1.16 (1.14, 1.19)	0.15 (0.12, 0.19)	<0.001	1.32 (1.30, 1.34)	3172	0.18 (0.15, 0.21)	<0.001
			p-value for interaction	**0.5**			**p-value for interaction**	**0.6**
non-HDL cholesterol, mmol/L								
All men	3404	5.04 (4.97, 5.11)	-0.30 (-0.41, -0.18)	<0.001	4.75 (4.69, 4.81)	3402	-0.36 (-0.48, -0.24)	<0.001
Men using lipid-regulating medication	228	6.00 (5.84, 6.16)	-1.69 (-1.90, -1.48)	<0.001	4.31 (4.16, 4.46)	228	-1.76 (-1.97, -1.54)	<0.001
Men not using lipid medication	3176	4.98 (4.91, 5.05)	-0.21 (-0.32, -0.09)	<0.001	4.77 (4.71, 4.83)	3174	-0.27 (-0.39, -0.15)	<0.001
			p-value for interaction	**<0.001**			**p-value for interaction**	**<0.001**

*Confounders: **SBP, DBP**: BMI, alcohol use, physical activity; **Non-HDL**: BMI, physical activity; **HDL**: BMI, smoking status, alcohol use, physical activity

Chapter 8: Analysing the trend in type 2 diabetes incidence in the British Regional Heart Study

8.1 Introduction

In chapter 4 it was shown that incidence of T2DM has risen, at least as far as the early 2000s, in the UK. In particular, according to data from the British Regional Heart Study (BRHS), an average annual increase of roughly 5-7% occurred between 1985 and 2007, in line with estimates from THIN and from other data sources.

Understanding the reasons for this unfavourable trend may help to inform efforts to curb future T2DM increases, both in the UK and in other locations. The rise in T2DM is thought to result from the marked rises in population adiposity which have also occurred, given the established strong association between adiposity and T2DM[43, 175-181, 185, 186, 378, 379] identified in numerous studies, including in the BRHS[185, 378, 379]. Analysis of BRHS data in chapter 5 suggested that body mass index (BMI) among British men increased on average by 1.9kg/m2 over 20 years from 1979 to 1999, and a separate report from the Health Survey for England showed that the prevalence of overweight and obesity in England had increased from 58% of men and 51% of women in 1994 to 68% and 71% in 2006 respectively[352]. However, few attempts have been made to quantify the contribution of trends in adiposity to the observed time trend in T2DM, partly reflecting the paucity of studies that have simultaneously monitored both T2DM and adiposity levels in the same population over an extended period. Can the rise in T2DM in the UK be fully accounted for by rising adiposity levels, as speculated, or are other factors also playing a role? The aim of this chapter is to address this question by quantifying the contribution of increasing population adiposity levels to the time trend in incidence the incidence of doctor-

diagnosed T2DM in British men over 24 years between 1984 and 2007, using data from the BRHS. Similar modelling methods will be applied to those used in chapters 5 and 6, when explaining the trend in incidence of major CHD. This corresponds to objective iv) of the overall thesis objectives.

Objective

Estimate the contribution of the time trend in BMI to the rise in incidence of T2DM in the BRHS

The structure of this chapter is as follows: Section 8.2 details the methods employed to address the objective. Results of the analyses are presented in section 8.3 and finally a discussion and interpretation of the findings are given in section 8.4.

8.2 Methods

8.2.1 Data Source

Follow-up data from five years into the study in 1983-5 until 2007 for men in the BRHS was used for this analysis, as incident T2DM data with validated diagnosis dates were available from the 5-year follow-up onwards (see chapter 3, section 3.2.4 for details). The end-date of end of 2007 reflects the date the analyses were carried out. Questionnaire/ examination data up to and including the examination at 20 years follow-up in 1998-2000 were used. As for the major CHD trends analysis, the BRHS is particularly suitable for this analysis as T2DM incidence and risk factors levels have been concurrently monitored over an extended period. Moreover a marked rise in incidence of T2DM was demonstrated in chapter 4 (section 4.5.2), and the men

recruited to the BRHS cohort are socially and geographically representative of men of the same age across Britain.

8.2.2 Principal outcome as a first diagnosis of T2DM

The principal outcome was a first diagnosis of T2DM. Details of methods to ascertain new T2DM cases in the BRHS are given in chapter 3, section 3.2.4. T2DM incidence was compared in three consecutive follow-up periods of approximately 8 years each in length, separated by intermittent questionnaires/examination sessions: period 1 from 1983-1985 to 1992; period 2 from 1992 to 1998-2000; and period 3 from 1998-2000 to 2007 (figure 8.1). For ease of presentation, where questionnaires or examinations were completed over a 2.5-year period, in 1983-5, and 1998-2000, the central year (1984, 1999) will be used hereon to refer to these. Thus the three periods are: period 1 from 1984 to 1992; period 2 from 1992 to 1999 and period 3 from 1999 to 2007.

8.2.3 BMI as the key explanatory factor

The principal exposure was BMI recorded in the questionnaire/examination at the start of each period, that is in 1984, in 1992 and in 1999 (measurement techniques detailed in chapter 3, section 3.2.5). The influence of prior BMI levels recorded at recruitment in 1978-80 was also considered.

8.2.4 Confounding factors

Factors which could potentially confound the relationship between BMI and T2DM, and/or the relationship between calendar time and T2DM, could as a result also influence the estimated contribution of the BMI trend to the rise in T2DM. Analyses

adjusting for such factors (where data was available) were therefore carried out. Specifically, factors considered were: cigarette smoking,[199] physical activity[188, 378] and alcohol consumption[200]. Diet is likely to be an important confounding factor[189-198], however as it was not measured at repeated intervals in the BRHS, the influence of diet could not be directly assessed. Blood pressure[201, 202] may play a role but was only measured once between 1984 and 2007 (the follow-up period for T2DM) and therefore could not be accounted for in the analysis.

8.2.5 Participants included in analysis

All men who had a diagnosis of diabetes prior to the start of the follow-up in 1984 (identified from self-report in the questionnaires at baseline and in 1984) were excluded. Since diabetes diagnoses before 1990 were identified using the 1992 questionnaire data (see chapter 3, section 3.2.4), diabetes diagnoses were only available between 1984 and 1990 for men who had survived to 1992. To ensure a fair comparison between the time periods, the analyses were therefore restricted to estimate incidence of T2DM in each period among men who were still alive at the end of the particular period. Men who had a diagnosis of diabetes during the study follow-up, from 1984 onwards, contributed to all analyses only up to the time of the diagnosis, and were excluded from analyses thereafter. Men who had a diagnosis within one year of the start of each period of follow-up were also excluded to limit reverse causality[380] whereby the BMI level at the start of the period is the result of development of diabetes before the BMI measurement (since a diagnosis of diabetes may occur some time after the patient first develops the disease). At the same time, follow-up for T2DM in each time period among the retained men was started from one year after the start of the period. Thus note that when incidence of T2DM in the

three periods is discussed, period 1 from 1984 to 1992 actually corresponds to incidence between 1985 and 1992; period 2 from 1992 to 1999 corresponds to 1993 to 1999 and period 3 from 1999 to 2007 corresponds to 2000 to 2007.

8.2.6 Statistical methods

As in chapters 5 and 6, analysis entailed splitting the follow-up time for each man into separate periods, in this case the three periods defined above: period 1 from 1984 to 1992; period 2 from 1992 to 1999 and period 3 from 1999 to 2007. Using the repeated measurements of BMI at the start of each of the three time-periods as well as at baseline, estimates of the population-averaged annual age-adjusted changes in BMI, over the whole length of the follow-up and between each consecutive time-period, were obtained from linear regression on this split dataset of BMI on calendar time, including age as a covariate. Generalised estimating equations with robust standard errors were used to account for the dependency between repeated measures of BMI from the same individual. The contribution of increasing BMI to the trend in incidence of T2DM was estimated by comparing Cox models regressing incident T2DM on indicators for each time period, with and without additional adjustment for the BMI measures at the start of each period (as a continuous variable with all significant powers). The proportion of the trend in T2DM hazard from period 1 (start of follow-up) to period 3 (end of follow-up) that could be statistically explained by increasing BMI was estimated by the expression: $(\beta 0 - \beta 1)/\beta 0$, where $\beta 0$ is the coefficient of the indicator for the period 3 in the Cox regression model which only included time period, and $\beta 1$ is the coefficient of the indicator for the period 3 in the Cox regression model adjusting additionally for BMI[348]. A 95% confidence interval (CI) for this estimate was obtained using bias-corrected bootstrap resampling[349].

Similarly, period 3 was compared with period 2, and period 2 was compared with period 1, to determine whether the percentage explained was constant over time. In each model, age was used as the underlying time scale, with date of birth as a time-origin and age at time of questionnaire (plus one year to limit reverse causality) as the delayed entry time to take account of left truncation, thereby automatically adjusting for age and permitting time period to be entered into the model. Survival times were censored at the end of each period. Schoenfeld residuals were used to test the proportional hazards assumption of the Cox regression. To explore the possible impact of not just current BMI but earlier BMI as well, additional analysis models were constructed, incorporating an earlier "lagged" measurement, approximately 5-8 years prior to the current measurement. In particular, BMI measured at the physical examination at baseline (1978-80) was used to predict diabetes in period 1 (1984 to 1992); BMI in 1984 was used for period 2 (1992 to 1999); and BMI in 1992 was used for period 3 (1999 to 2007). Models were also considered with BMI categorised as underweight (<18.5kg/m^2), normal weight (18.5-25kg/m^2), overweight (25-30kg/m^2) and obese (>30kg/m^2), and excluding those aged over 65 years (as BMI may predict T2DM risk less well in older men[381]). Additional analyses were carried out adjusting the Cox models for the repeated measures of the potential confounding factors at the start of each period, listed in section 8.2.4.

8.3 Results

6451 of the 7735 men initially recruited in 1978-1980 were included in the present analyses. The remainder had died before the end of the first follow-up period in 1992 (1152, 14.9%), or had a diagnosis of diabetes (123, 1.6%) before the start of follow-

up for diabetes in 1984, or had a diagnosis of diabetes within one year of the BMI measurement for a particular time period (9, 0.1%).

8.3.1 Comparison of incidence of T2DM in the three separate time-periods

The incidence rate of T2DM increased substantially from each time-period to the next, both within 5-year age groups and overall (table 8.1 and figure 8.1). The hazard of T2DM was more than two fold greater in the most recent period 1999-2007 than in the earliest period 1984-1992 (age-adjusted hazard ratio 2.33, 95% CI 1.75 to 3.10). Between the periods 1984-1992 and 1992-1999 the risk of T2DM increased by about a half (age-adjusted hazard ratio 1.59, 95% CI 1.23 to 2.05). A similar increase was observed between the periods 1992-1999 and 1999-2007 (age-adjusted hazard ratio 1.47, 95% CI 1.17 to 1.84). There was no evidence of departure from the proportional hazards assumption of the Cox regression.

8.3.2 Time trend in mean BMI

The average annual age-adjusted increase in mean population BMI between 1984 and 1999 (that is, during the follow-up for T2DM) was 0.074kg/m^2, (95% CI 0.058 to 0.09), corresponding to a total increase over the 15 years of 1.42kg/m^2 (95% CI 1.10 to 1.74) (figure 8.1). The average annual increase in age-adjusted BMI was 0.13kg/m^2 (95% CI 0.11 to 0.14) between 1979 and 1984, 0.058kg/m^2 (95% CI 0.041 to 0.074) between 1984 and 1992, and 0.087kg/m^2 (95% CI 0.063 to 0.112) between 1992 and 1999. The average annual age-adjusted increase in mean population BMI from 1979 to 1999, that is before and during the period of follow-up for T2DM, was 0.087kg/m^2 per annum (95% CI 0.073 to 0.101, $p<0.001$), corresponding to an increase of 1.74kg/m^2 (95% CI 1.46 to 2.02) over the 20 year period.

8.3.3 Contribution of time trend in BMI to time trend in T2DM incidence

From Cox modelling, using "current" BMI measurements (that is, BMI immediately prior to each 8-year follow-up period) to predict T2DM hazard, 26% (95% bootstrap CI 17.5 to 41.1) of the doubling in T2DM hazard from the period 1984-1992 to 1999-2007 could be statistically explained by the increase in BMI from 1984 to 1999 (table 8.2). A smaller percentage, 20.5% (95% bootstrap CI 12.5 to 33.2) could be explained by "lagged" BMI changes (that is, BMI approximately 5-8 years prior to each follow-up period, corresponding to looking at BMI changes over an earlier period from 1979 to 1992). The combination of current and lagged BMI measurements, equivalent to adjusting for the change in BMI from lagged to current measurements of an individual, did not appreciably increase the contribution of BMI (percentage explained: 25.8%, 95% CI 17.3 to 41.4).

The contribution of increasing BMI to the trend in T2DM incidence was examined separately in earlier and later portions of the follow-up. Of the increase in T2DM risk between 1984-1992 to 1992-1999, 21.7% (95% CI 11.9 to 47.9) could be statistically explained by an age-adjusted increase in BMI from 1984 to 1992 of 0.40kg/m^2 (95% CI 0.29 to 0.52). During the later periods (1992-1999 to 1999-2007), 31.1% (95% CI 16.8 to 80.6) of the increase in T2DM could be statistically explained by an age-adjusted increase in BMI from 1992 to 1999 of 0.61kg/m^2 (95% CI 0.44 to 0.78).

The results changed little when including the follow-up for men only until the age of 65; the trends in T2DM hazard and mean BMI were very similar leading to a percentage contribution of BMI to the trend in T2DM of 25.3%, very close to the percentage contribution for the full dataset. The above analyses include BMI in the

analysis models as a continuous variable with all significant powers (squared). In sensitivity analyses including BMI as a categorical variable the proportions of the T2DM time trends explained by BMI changed little.

Adjustment for potential confounding factors (cigarette smoking, physical activity, alcohol consumption), both individually and together, made little difference to the estimated hazard ratios of T2DM comparing the time-periods nor to the proportion of the increase in hazard of T2DM explained by BMI (table 8.3).

8.4 Discussion

8.4.1 Summary of main findings

In this survivor cohort of British men, the hazard rate of T2DM more than doubled between the periods 1984-1992 and 1999-2007. An estimated 26% (95% bootstrap CI 17 to 41) of this increase in T2DM could be attributed to a rise in BMI levels between 1984 and 1999. The results suggest that an appreciable portion of the substantial rise in T2DM incidence is associated with the unfavourable population wide increase in BMI. Nevertheless, a substantial portion of the observed increase in diagnoses of T2DM was not accounted for by the changes in BMI.

8.4.2 Comparison with other studies

In chapter 4, section 4.6.4.2, it was shown that the trends in T2DM incidence observed in this cohort are consistent with other available (albeit limited) data on UK T2DM trends. Information on trends in BMI levels before the 1990s are scarce. Based on data from the Health Survey for England, mean BMI levels in men aged 55 years and over increased between 1993 and 2000 by an average of 0.11 kg/m^2 per

annum, a figure close to but slightly greater than the per annum increase of 0.09 kg/m2 between 1992 and 1998-2000 estimated in our study[73]. No other studies to our knowledge have directly estimated the contribution of increasing BMI, or trends in other risk factors, to the rise in diabetes, either in the UK or in other settings. Previous studies on US populations[382], in line with a separate study of this cohort in the UK[3] have investigated the trend in diabetes according to adiposity level and found that the increase in diabetes prevalence was greater among overweight and obese groups: The per-decade increase in diabetes prevalence in the US in those with BMI≥35kg/m^2 was double that in the general population[382]. Among men in the BRHS, the rate of increase in prevalence odds of T2DM over 25 years rose steadily with increasing BMI, such that the rate of increase in T2DM prevalence among those with a BMI of over 27.5kg/m^2 was roughly four-fold greater than among those with a BMI of 22.5kg/m^2 or less[3].

Studies assessing population attributable risks of adiposity in T2DM have reported similar estimates to those in the present analysis[178, 181]. However as discussed in chapter 5 (section 5.5.2) in relation to CHD, in such studies, which examine overall T2DM incidence in the population, the contribution of modifiable risk factors, such as adiposity, are necessarily affected by contributions of population static variables including genetic factors. In contrast our analysis examines time trends in T2DM, attributable only to modifiable factors which have changed over time in the population. The information provided by this analysis therefore complements rather than duplicates studies of attributable risk, and addresses a different question. Note that although the paper by Atlantis *et al*[178] discusses time trends, the analyses carried

out to assess the role of BMI in T2DM risk are still classic attributable risk calculations, distinct from the analysis in this chapter.

8.4.3 Strengths and limitations

A key strength of this analysis is the linkage of diabetes events to corresponding BMI measurements for each individual, thus avoiding the potential hazards of ecological approaches often used to examine time trends[258]. The study was based on a socially and geographically representative sample of British men. As shown in chapter 4, the increase in diabetes incidence observed in this cohort was close to that observed in other studies, while as shown above, the increase in mean BMI was close to estimates from the relevant national health surveys[73]. The strength of association between BMI and T2DM risk in our study was found to be similar to (though slightly stronger than) the association observed in men of a similar age and during a similar follow-up period in the large US Health Professionals Follow-Up Study[180], once BMI was re-categorized in the same way. Our model allowed inherently for a time delay from the BMI measurement to a T2DM diagnosis of between one and about eight years (the approximate length of the follow-up periods, excluding the first year), and earlier BMI measurements were incorporated to allow for even longer time-lags, up to 16 years (although these early measurements were found to have limited independent influence on T2DM risk). The first year of follow-up following each BMI measurement was excluded to limit the potential impact of reverse causality; weight loss occurring following the development of T2DM could otherwise have led to underestimation of the contribution of BMI due to weight tending to fall after T2DM develops[380].

A potentially important limitation of the analysis is the use of BMI, which was the only marker of adiposity consistently available over the period of the investigation. While BMI is the traditional means of assessing adiposity, other measurements exist including waist circumference and wait-to-hip ratio. These two measurements capture in particular central, or abdominal, adiposity levels, which is reasoned to be more strongly associated with risk of T2DM, than BMI, because it is more strongly associated with visceral adipose tissue compartments[383], (that is, the fat that accumulates around the internal organs), than BMI. Visceral adipose tissue has been shown to be the component of adiposity particularly implicated in the development of T2DM as opposed to subcutaneous adipose tissue (fat stored under the skin) or intramuscular adipose tissue (fat stored in skeletal muscle)[43]. However, as outlined in chapter 2, section 2.5.3.1, recent studies indicate that BMI is at least as strong predictor of T2DM risk as other markers of adiposity such as waist circumference[180, 185, 186]. This has also been shown to the case among the BRHS men[379].

The role of BMI may have been further complicated in the present study population of middle-aged and older men by the influence of lean mass on BMI; loss of lean mass in men in their 60s and 70s may have led to underestimation of the true increases in adiposity over time. However, repeating the analyses including the follow-up for men only as far as the age of 65, the trends in BMI and T2DM and the consequent proportion of the T2DM trend explained, changed very little, reflecting that in older men in this cohort, BMI continues to predict T2DM strongly[379].

A second limitation is that diabetes data was available between 1984 and 1990 only for those men who were alive in 1992. Given this restriction, including all BRHS

participants in the analysis would have led to underestimation of T2DM incidence in the first period as we would miss T2DM incidence among men who died before 1992 (but who were alive for some length of time from 1984 so included in the incidence rate denominators). The resulting bias would be overestimation of the trend in diabetes incidence over time. Instead, to overcome this bias, in each period, the population sample was limited to those men who survived to the end of the particular period. This constraint ensured a fair comparison between time periods (since population samples in each period are equivalent). The limitation of this approach is that the analysis is on a restricted cohort of survivors; thus the generalisability of the trend estimate to the whole population is put into question. However, in chapter 4, section 4.5.2.3, it was observed that the estimates of the average annual increases in T2DM among the "survivor" cohort and full cohort (over the period when both could be estimated) were very consistent, suggesting that the results in this chapter may be applicable to the whole cohort. To explore this issue further, the analysis comparing the latter two periods (1992-1999 and 1999-2007) was repeated, this time using the whole study population in these periods, including individuals who died during the follow-up, censoring at date of death. The hazard ratio in the full sample comparing the period 1999-2007 with the period 1992-1999 was 1.55 (95% CI 1.26 to 1.91). This was similar to the increase reported for the survivor sub-sample (hazard ratio 1.47, 95% CI 1.17 to 1.84). The proportion of the rise in T2DM explained by BMI was 23% in the full sample, compared to 31% reported for the survivor sub-sample. The broad similarity of these results for the two samples further supports extension of the findings to the wider population.

Model mis-specification (in particular the modelling of BMI) could lead to under or overestimation of the proportion of the rise in T2DM explained by BMI. However BMI was modelled both as a continuous variable and categorised; in both forms the estimate of the proportion of the time trend in T2DM was similar at around one-quarter. Adjustment was made for potential confounders where data was available (cigarette smoking, alcohol consumption and physical activity). Dietary factors and blood pressure and lipid levels could not be considered. However evidence for the role of lipid levels in T2DM risk in general is weak. Blood pressure may be more likely to mediate the effect of BMI (since BMI raises blood pressure), rather than be a confounder.

8.4.4 Interpretation of findings

The results of the present analysis suggest that increasing adiposity (as assessed by BMI) has made an important contribution to the increase in T2DM incidence observed. Control and reversal of the recent rise in adiposity levels is therefore an important priority in controlling the diabetes epidemic. However, the estimated contribution of BMI was lower than had been expected. Although this may partly reflect the methodological limitations of the study, particularly the use of BMI as the measure of adiposity, it suggests that other factors may have played important roles.

The potential influence of changes in the ascertainment of T2DM and in diagnostic criteria needs consideration, since (as discussed in chapter 4, section 4.6.5.2) these changes may have influenced the T2DM trends (more so than for the CHD trends). It was discussed in chapter 4, section 4.6.5.2, that recommendations on cardiovascular prevention from the late 1990s[97], potentially leading to increased ascertainment, may

have contributed to the observed rise in T2DM incidence from this time onwards. In terms of the findings of this chapter, a possible resulting bias would therefore be towards a lower portion of the rise in T2DM explained by BMI after this time, the rise in T2DM instead partially due to more cases being identified. However, the proportion of the T2DM increase explained by BMI was actually higher during the later follow-up periods (1992-1999 to 1999-2007) than during the earlier follow-up periods (1984-1992 to 1992-1999) (31% versus 22%). Thus changes in case ascertainment methods are unlikely to have had a large influence on the findings. The change in diagnostic criteria in 1999[93, 94] appears to have led to different patients being diagnosed as having T2DM, but not necessarily an increased number of patients (see chapter 4, section 4.6.5.2). However, the change in diagnostic criteria might plausibly influence the extent to which BMI trends explain the T2DM rise if the association between T2DM and BMI is stronger or weaker among the new patients than among the patients identified under the former criteria. Nevertheless, in subsidiary analyses, an interaction between BMI and calendar period in the Cox models of T2DM hazard was not significant, implying a consistent relationship between T2DM and BMI over time. Regular reviews of GP records were used to identify T2DM cases after 1990 (the date that regular reviews of GP records began). Before 1990, diabetes cases were initially identified from self-report in the 1992 questionnaire. Any self-reported T2DM diagnosis in the questionnaire prompted the researchers to go back to the GP records to confirm the diagnosis and date of diagnosis. Thus any self-reported diagnosis may be taken as a true doctor-diagnosis, consistent with diagnoses after 1990; that is, the false-positive rate will be negligible. However it is possible that some diabetes cases may have been missed where a patient with a GP record of diabetes has not reported a diagnosis in the 1992 questionnaire

(false-negatives). The likely impact of the use of self-report before 1990 would therefore be to underestimate the incidence of T2DM in the earliest period (1984 to 1992). The result of this bias would be overestimation of the increase in incidence of T2DM over time and underestimation of the percentage of the T2DM increase explained by BMI. This limitation thus may help to resolve some of the "unexplained" portion of the increase in T2DM. However, impact of changing methods of case identification is unlikely to be marked as all self-reported cases were verified, and previous studies have shown questionnaire self-report of diabetes to agree closely with medical records[328-331]. Indeed, the consistency between self-report and GP diagnosis was found to be as high as 98% in the BRHS[384].

If study limitations or changes in diagnostic criteria or the methods of case identification do not help to fully resolve the "unexplained" portion of the rise in T2DM, it may be that time trends in other risk factors for T2DM are playing a role independently of BMI. In particular, changes in dietary determinants of T2DM, which could not be assessed in this analysis, could also have been important. For example, dietary factors associated with reducing T2DM risk include a high fibre diet[192, 195], and daily consumption of fibre declined between 1987 and 2000[376]. Most other potential risk factors (physical activity, cigarette smoking, alcohol consumption, SBP, total and HDL cholesterol) are unlikely to explain the rise in T2DM as the time trends in these factors have been generally favourable or negligible in the cohort (see chapter 5, section 5.3), thus in the "opposite" direction to the rise in T2DM. The possible exception is the apparent rise in diastolic blood pressure (DBP) in this cohort (see chapter 7, section 7.3). That said, although physical activity data was available, the data in 1984 was imputed (see chapter 3, section 3.2.7) and the data collected at

the other time points was not consistent (different questions were used each time). Thus the robustness of the physical activity time trend estimated from the BRHS (and consequence influence on T2DM trends) is uncertain. If physical activity has instead fallen over time, given the strong protective effect on T2DM risk, which operates at least partly independent of BMI[188], physical activity may also help to explain the trend in T2DM. Secular changes in early life determinants of T2DM[212, 213] may have had an influence, although the major documented changes (such as a secular increase in maternal gestational diabetes) have occurred too recently to affect the adult generations studied in this report, suggesting cohort effects (and therefore effects of trends in early-life determinants) may be limited[217]. Another possible contributory factor is the increased use of certain drugs indicated for other conditions, which have been shown to adversely be associated with an increased risk of developing T2DM. In particular, recent studies have documented an increased risk of T2DM with use of statins[174]. Since statins conversely reduce risk of CHD, the rise in the use of these drugs over the period is consistent with the divergent trends in these two conditions. Other drugs such as anti-psychotics have also been shown to have adverse metabolic effects and increased risk of T2DM[385].

The present study is based on older British men of white European origin; generalisability of these results to other sections of the population (women, younger men and different ethnic groups) is less clear, particularly since the relationships between BMI and T2DM are stronger in younger age-groups and differ between ethnic groups[386]. Extrapolation of the results to trends in other populations also needs to be cautious; in the US the secular increase in T2DM incidence has been less

marked[387] and the increase in BMI more marked[388], suggesting that a larger portion of the increase in T2DM in the US is likely to be attributable to increased BMI.

Further time trend studies in other populations are needed to verify the findings and establish the roles of other risk factors. The presence of other contributing factors would suggest the need for a more multi-factorial approach to combat rising T2DM in the population.

8.4.5 Chapter conclusions/ Postscript

In this chapter the reasons for the rise in T2DM have been explored. The key finding is that while approximately one-quarter of the rise in T2DM in older British men over the last 23 years or so may be associated with a concurrent rise in mean BMI levels, a large proportion is not accounted for by BMI trends.

Chapters 5, 6 and 7 sought to identify possible explanations for the favourable decline in major CHD incidence. In this chapter 8, the potential drivers (in particular rising adiposity) behind the overlapping unfavourable rise in T2DM were considered. The aim of the next and final results chapter 9 is to bring the two opposing time trends in major CHD and T2DM together and investigate the relationship between the trends in these two associated conditions. Of interest is whether the trends in CHD among patients with T2DM have been as favourable as the trends in the general population, and, given that T2DM is a risk factor for CHD, to what extent the rise in T2DM has curtailed the decline in CHD.

Table 8.1 **Incidence rates of T2DM, per 1000 person-years by age and calendar period**

	Age group, years							
	45-49	*50-54*	*55-59*	*60-64*	*65-69*	*70-74*	*75-79*	*All*
Number of men								
1984 to 1992*	1,729	1,678	1,623	1,430	0	0	0	6,460
*1992 to 1999**	0	453	1,597	1,458	1,228	708	0	5,444
1999 to 2007*	0	0	0	1,350	1,107	813	478	3,748
Person-years								
1984 to 1992*	14,921	14,370	13,850	12,162				55,303
*1992 to 1999**		2,950	10,296	9,381	5,963	5,569		34,159
1999 to 2007*				11,852	10,721	11,552	7,320	41,445
Incident diabetes cases								
1984 to 1992*	36	52	39	42				169
*1992 to 1999**		12	67	51	47	25		202
1999 to 2007*				109	103	81	30	323
Incident rate (95% CI)								
1984 to 1992*	2.41 (1.74, 3.34)	3.62 (2.76, 4.75)	2.82 (2.06, 3.85)	3.45 (2.55, 4.67)				3.06 (2.63, 3.55)
*1992 to 1999**		4.07 (2.31, 7.16)	6.51 (5.12, 8.27)	5.44 (4.13, 7.15)	5.96 (4.48, 7.94)	5.57 (3.76, 8.24)		5.77 (5.03, 6.63)
1999 to 2007*				9.20 (7.62, 11.1)	10.7 (8.84, 13.0)	11.6 (9.29, 14.4)	7.32 (5.12, 10.5)	9.92 (8.89, 11.1)

*Year shown is central year of a 2.5-year period.

Table 8.2 **Hazard ratios for T2DM comparing the periods 1984-1992, 1992-1999 and 1999-2007, and percentage of the hazard ratios explained by the higher BMI levels in the later periods**

		Comparing the period 1999-2007 with the period 1984 to 1992			
Model		**β-coefficient for indicator for period 1999-2007**	**Corresponding hazard ratio, (95% CI)**	**p-value**	**% of the hazard increase explained by BMI*, (95% bootstrap CI)**
A	**Indicator for time-period; 1984-1992= reference period**	0.8468	2.33 (1.75, 3.11)	<0.001	
B	+Adjustment for "current" BMI, kg/m^2†	0.6271	1.87 (1.41, 2.49)	<0.001	**25.9 (17.5, 41.1)**
C	+Adjustment for "lagged" BMI, kg/m^2†	0.6732	1.96 (1.47, 2.61)	<0.001	**20.5 (12.5, 33.2)**
D	+Adjustment for current+lagged BMI	0.6281	1.87 (1.41, 2.49)	<0.001	**25.8 (17.3, 41.4)**
		Comparing the period 1992 to 1999 with the period 1984 to 1992			
Model		**β-coefficient for indicator for period 1992-1999**	**Corresponding hazard ratio, (95% CI)**	**p-value**	**% of the hazard increase explained by BMI*, (95% bootstrap CI)**
A	**Indicator for time-period; 1984-1992= reference period**	0.4635	1.59 (1.23, 2.05)	<0.001	
B	+Adjustment for "current" BMI, kg/m^2†	0.3628	1.44 (1.12, 1.85)	0.005	**21.7 (11.9, 47.9)**
C	+Adjustment for "lagged" BMI, kg/m^2†	0.3536	1.42 (1.10, 1.84)	0.007	**23.7 (13.6, 52.6)**
D	+Adjustment for current + lagged BMI	0.3615	1.44 (1.12, 1.85)	0.005	**22.0 (12.0, 47.4)**
		Comparing the period 1999-2007 with the period 1992 to 1999			
Model		**β-coefficient for indicator for period 1999-2007**	**Corresponding hazard ratio, (95% CI)**	**p-value**	**% of the hazard increase explained by BMI*, (95% bootstrap CI)**
A	**Indicator for time-period; 1992-1999= reference period**	0.3833	1.47 (1.17, 1.84)	0.001	
B	+Adjustment for "current" BMI, kg/m^2†	0.2642	1.30 (1.04, 1.63)	0.02	**31.1 (16.8, 80.6)**
C	+Adjustment for "lagged" BMI, kg/m^2†	0.3197	1.38 (1.10, 1.72)	0.005	**16.6 (6.8, 47.1)**
D	+Adjustment for current + lagged BMI	0.2666	1.31 (1.04, 1.64)	0.02	**30.4 (16.4, 81.2)**

"Current" BMI is BMI at start of the relevant period; "lagged" BMI is BMI 5-8 years prior to start of period

β-coefficients, hazard ratios and corresponding p-values from Cox regression, using age as the underlying time-scale, thereby automatically adjusting for age

* % of the observed rise in hazard rate explained by BMI = 100% × $(\beta_0 - \beta_1)/\beta_0$, where β_0 is the coefficient of the indicator for the period in the Cox regression model which only included time period (Model A), and β_1 is the coefficient of the indicator for the period in the Cox regression model adjusting additionally for the particular BMI measure

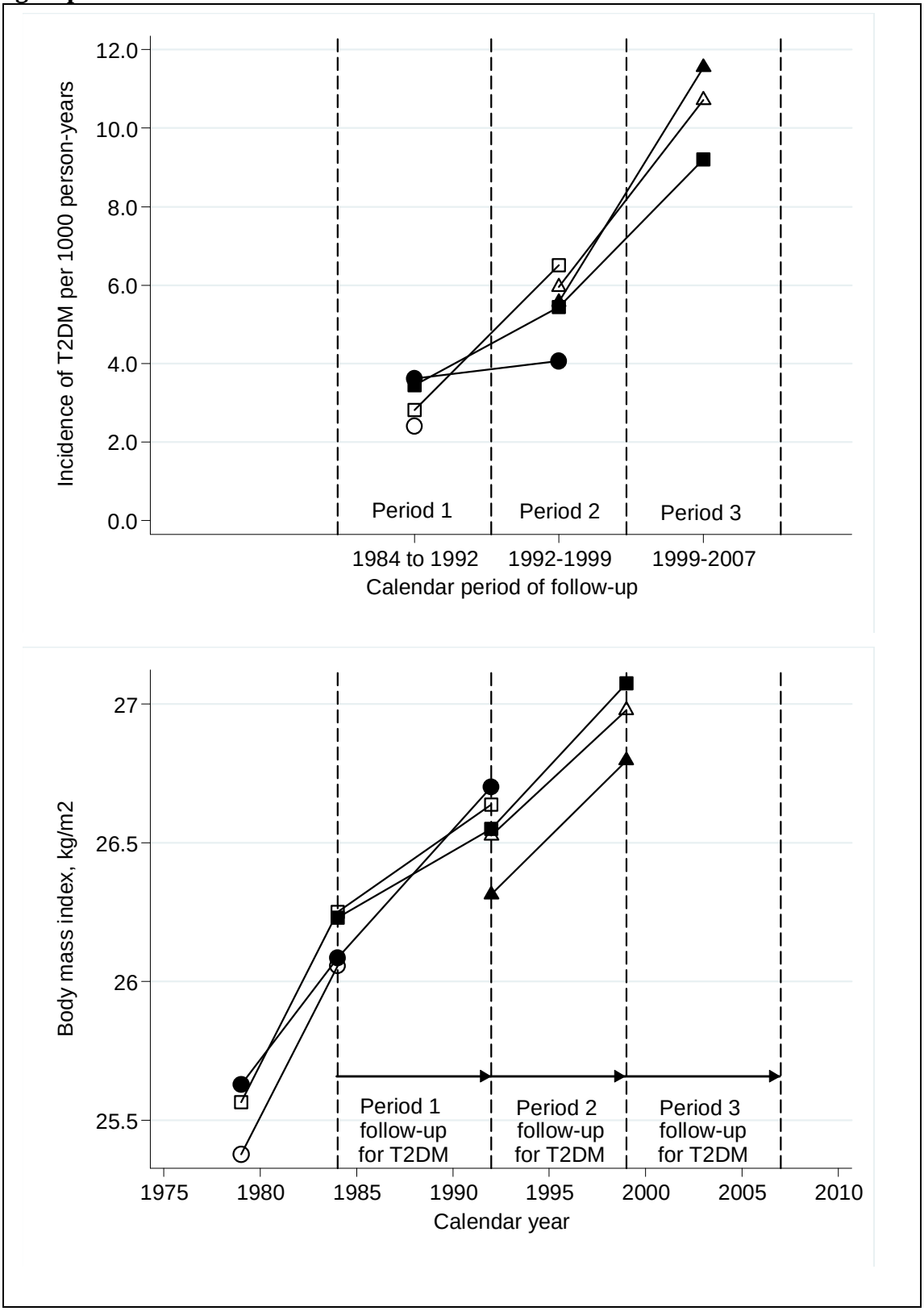
† includes a squared term (cubed term is non-significant)

Table 8.3 **Hazard ratios for T2DM comparing the periods 1984-1992 and 1999-2007, and percentage of the hazard ratio explained by BMI, adjusting for potential confounding factors**

Model	Potential confounding factors adjusted for*	Hazard ratio comparing period 1999-2007 with period 1984-1992 *before* adjustment for BMI†, (95% CI)	Hazard ratio comparing period 1999-2007 with period 1984-1992 *after* adjustment for BMI†, (95% CI)	% of the observed rise in hazard from period 1984-1999 to period 1999-2007 explained by BMI‡, (95% bootstrap CI)
A	Smoking (current/ex/never)	2.37 (1.77, 3.17)	1.90 (1.43, 2.53)	20.6 (10.3, 45.5)
B	Physical activity (inactive/occasional/light/moderate/moderately vigorous/vigorous)	2.39 (1.78, 3.21)	1.90 (1.42, 2.55)	24.3 (14.4, 56.4)
C	Alcohol consumption (never/occasional/light/moderate/heavy)	2.32 (1.73, 3.10)	1.85 (1.39, 2.47)	20.2 (10.6, 48.9)
D	Smoking + physical activity + alcohol consumption	2.34 (1.74, 3.16)	1.87 (1.38, 2.52)	22.3 (10.9, 53.5)

*****Levels of confounding factors at the start of each period
†BMI at start of each period, continuous variable with squared term
‡ % of the observed rise in hazard rate explained by BMI = $100\% \times (\beta_0 - \beta_1)/\beta_0$, where β_0 is the coefficient corresponding to the hazard ratio comparing period 1999-2007 with period 1984-1992 *before* adjustment for BMI (=log(hazard ratio)), and β_1 is the coefficient corresponding to the same hazard ratio *after* adjustment for BMI.

Figure 8.1 **Trend over time in incidence of T2DM and in mean BMI, by age group**



Legend: White circles = age 45-49 years; black circles = age 50-54 years; white squares = age 55-59 years; black squares = 60-64 years; white triangles = 65-69 years; black triangles = 70-74 years.

Chapter 9: Analysing the relationship between the time trends in incidence of major coronary heart disease and type 2 diabetes using data from The Health Improvement Network and the British Regional Heart Study

9.1 Introduction

In chapter 4 time trends in incidence of both major coronary heart disease (CHD) and type 2 diabetes (T2DM) in the UK, over overlapping periods from the 1980s to the present, were examined. The available evidence suggested a favourable decline in incidence of major CHD over much of the period, while conversely the incidence of T2DM appears to have increased. In the subsequent results chapters 5 to 8, the reasons for the time trends in incidence of these two conditions were separately investigated.

Diabetes is associated with an elevated risk of a major CHD event, with the risk among patients with diabetes generally shown to be around two-fold greater than that of patients without diabetes[27-33]. Thus a natural progression in this study of CHD and diabetes time trends is to examine the influence of diabetes on the decline in major CHD incidence and the relationship between the opposing time trends in incidence of major CHD and T2DM. Questions to consider include whether patients with diabetes have experienced the same rates of decline in major CHD incidence as patients without diabetes and, if not, whether the relationship between diabetes and major CHD incidence has changed over time. A further central issue still to be addressed is whether the decline in major CHD incidence has been curtailed by the increase in

T2DM. This would imply that, had the increase in T2DM not occurred, a larger decline in major CHD incidence than that actually observed would have been feasible.

Assessing whether or not similar declines in major CHD incidence have benefited both the population of diabetic patients and the population without diabetes will help to ascertain whether the elevated risk of risk of major CHD among patients with diabetes has persisted over time. This is turn is important in helping to evaluate whether the management and treatment of diabetes has improved, for example following the publication of recommendations on cardiovascular prevention from the late 1990s[97] and the introduction of the Quality and Outcomes Framework (QOF) for managing patients in General Practice in 2004. Or alternatively, if the elevated risk remains, whether more concerted efforts are needed to manage diabetes. Understanding the influence of T2DM on the trend in major CHD incidence could help to define the likely future CHD disease burden, by helping to gain insight into whether current or future increases in T2DM could lead to a future attenuation, or even reversal, of the favourable declines over time in CHD incidence.

Several studies in the US and Scandinavia (but apparently none based in the UK) have investigated time trends in CHD and/or cardiovascular disease (CVD) *mortality* in patients with and without diabetes, with mixed findings[32, 389-394]. Some studies have reported faster rates of decline in CHD/CVD mortality among male and/or female diabetic patients compared with those without diabetes[32, 389, 391] (leading to an attenuation of the elevated risk of CHD/CVD mortality among diabetic patients). Others have reported slower rates of decline in CHD/CVD mortality[392, 394] or even increasing CHD/CVD mortality rates[393] among diabetic patients, while some report

no difference in the rates of decline in CHD/CVD mortality among patients with and without diabetes[390]. Few studies however have investigated time trends in *incidence* of CHD/CVD by diabetes status[389, 395, 396]. These studies (none in the UK) have again reported mixed findings on the relative improvement in incidence among patients with and without diabetes. The IMPACT group assessed the role of rising diabetes prevalence on in the time trend in CHD *mortality* in England and Wales[15]. However, there is a lack of data, from any country, on the extent to which rising diabetes has curbed the decline in major CHD *incidence*.

The overall purpose of this chapter is therefore to bring together the two opposing disease trends and explore the relationship between them. This corresponds to objective v) of the overall thesis objectives.

Objectives

1. Evaluate whether the hazard of a subsequent major CHD event among patients with a new diagnosis of T2DM has changed over calendar time. That is, are T2DM patients now surviving longer after their diagnosis free of a major CHD event?
2. a) Estimate and compare the time trends in incidence of major CHD in patients with and without T2DM diabetes

   and equivalently:

   b) Assess whether the relationship between T2DM and risk of a major CHD event is changing over time. That is, compare the relative survival from major CHD of patients with and without diabetes in different time periods
3. Evaluate the extent to which the population-wide decline in major CHD may have been curtailed by rising T2DM prevalence, and estimate the decline in major CHD incidence that might have occurred in the absence of the rise in T2DM.

The structure of this chapter is as follows: Section 9.2 details the methods employed to address the objectives. Results of the analyses in relation to the objectives are presented in section 9.3. A discussion and an interpretation of the findings are given in section 9.4.

9.2 Methods

9.2.1 Data sources

The Health Improvement Network (THIN) database is primarily used to address the objectives of this chapter as the analyses mostly involve estimation of time trends in the risk of major CHD among the subset of patients with diabetes. The British Regional Heart Study (BRHS) and Whitehall II cohorts, once restricted to those patients with diabetes, are too small for precise estimates of the time trends. In addition, the THIN database comprises the most generally representative population, including both men and women, from all regions in the UK, making the findings more widely applicable to the UK population as a whole, than the cohort studies. The analyses to address the final objective, assessment of the role of diabetes in the time trend in major CHD, were also feasible in the BRHS cohort (in which the overall excess risk of major CHD among diabetic men has already been reported[33]) and so results are presented from both THIN and the BRHS for comparison. The THIN data available cover a 14 year period from 1995 to 2008. As for chapter 5, which assessed the role of other risk factors in the time trend in major CHD, event data in the BRHS from baseline (1978-80) up to 31 December 2004 was used, providing 25 years of follow-up.

9.2.2 Methods to address chapter objective 1 - Temporal trend in survival time from T2DM diagnosis to a major CHD event

For objective 1, the population sample comprised solely those patients in THIN aged 30 years and over who developed T2DM between 1995 and 2008. That is, the study sample corresponded to those patients forming the numerators of the T2DM incidence estimates in chapter 4 (therefore see figure 4.2 for inclusion and exclusion criteria and

derivation of this study sample). Incident T2DM cases were identified as patients with a first ever record relating to diabetes (a Read code for T2DM or for non-specific diabetes, as outlined in chapter 4, section 4.2.5, and listed in Appendix A.3) between 1995 and 2008. As in chapter 4, since patients were aged 30 or over at time of diagnosis, any non-specific diabetes record was assumed to indicate T2DM, rather than T1DM. Patients were then followed from the date of the incident T2DM record for a subsequent major CHD event up to end of 2008 (again identified by relevant Read codes, as used to estimate major CHD incidence in chapter 4 – see Appendix A.2).

Statistical methods 1-, 3- and 5-year incident rates of major CHD following a T2DM diagnosis, according to calendar year of T2DM diagnosis, were computed. Patient follow-up time was defined as the time from the T2DM diagnosis to the earliest of: the date of a major CHD event, date of death, date of (patient or practice) exit from THIN, or 1-/3-/5- years follow-up. 1-year incidence rates of major CHD were computed for patients diagnosed with T2DM between 1995 and 2008. To ensure an equal potential follow-up for all patients, 3-year incidence rates were computed for patients diagnosed with T2DM only up to 2006, while 5-year incidence rates were computed for patients diagnosed with T2DM up to 2004. Cox regression models were constructed, regressing each of the three outcomes (1-, 3- and 5- year major CHD incidence) on year of T2DM diagnosis, adjusting for age at T2DM diagnosis and gender, to estimate the average annual relative change in the hazard of major CHD. Robust standard errors were used to account for clustering of patients in practices.

9.2.3 Methods to address chapter objective 2 – Temporal trend in incidence of major CHD among patients with and without T2DM and changing relationship between T2DM and major CHD incidence over time

To address the second objective, the whole THIN population, both with and without T2DM, was used. Major CHD incidence rates were compared among patients with and without T2DM, in three separate equal 4-year length periods: 1995-1998, 2000-2003 and 2005-2008 (periods chosen to be maximum length possible while still all equal in length to ensure a fair comparison). To do this, three sub-cohorts of patients were formed comprising all patients in present in THIN aged 30 years or over on each of 1 January 1995, 1 January 2000 and 1 January 2005 (the first day of each period). Inclusion and exclusion criteria correspond to those used to define the population sample for computation of major CHD incidence rates in chapter 4, as detailed in figure 4.1, with the additional condition of being present with no prior major CHD diagnosis on the first day of the relevant period. Patients identified were followed to the end of each 4-year period for incident major CHD. Patients in each of these cohorts were categorised according to whether they had prevalent T2DM at the start of the period or developed incident T2DM during the 4-year follow-up. A patient was taken to have prevalent T2DM if s/he had a Read code in their patient records relating to T2DM in the year prior to the start of the period. Patients with no prior diagnosis were taken to be free from T2DM, unless a new record of T2DM was found during the follow-up, in which case the patient was considered an incident case and excluded from the analyses for this second objective. ***Statistical methods*** The time trend in incidence of major CHD according to T2DM status was estimated using grouped Poisson regression of incidence of major CHD on date of start of period, with 10-year age group and gender as covariates, and stratified by diabetes status (prevalent T2DM

at start of follow-up or not). The analysis necessitated grouped Poisson regression, as opposed to the Cox regression used for the previous objective, as the whole THIN population is used here, which is too large to analyse ungrouped (see chapter 4, section 4.2.7). An interaction between T2DM status and period was added to the models to assess whether the time trends in incidence of major CHD differed significantly between patients with and without prevalent T2DM, and equivalently, whether the excess risk of major CHD associated with T2DM varied between calendar periods. Person-years for each patient were calculated as the time from 1 January of the first year of the relevant period to the first of the date of a subsequent major CHD event, date of death, date of exit from THIN or end of 4-year period. Multilevel random intercept models with patients nested in practices were used to adjust for clustering of patients in practices. Crude absolute incidence rates of major CHD according to calendar period and T2DM status were estimated, along with incidence rates standardised to the overall age and gender distribution in THIN (to account for variations in age and gender between those with and without T2DM).

9.2.4 Methods to address chapter objective 3 – Role of rising T2DM in decline in major CHD incidence

The same data sample used for objective 2 was used to address objective 3, that is three sub-cohorts comprising all patients in THIN present and with no history of major CHD on 1 January of 1995, 2000 and 2005 respectively, categorised according to T2DM status, and followed for major CHD for 4 years. Incident T2DM cases occurring during each four-year period were this time included in the analysis.

Statistical methods The contribution of the time trend in T2DM to the decline in major CHD incidence was assessed by comparing grouped multilevel Poisson

regression models regressing incidence of major CHD on date of start of period, adjusted for age and gender, with and without additional adjustment for the indicator for T2DM status (prevalent at start of period or incident during period or T2DM-free). Person-years for each patient were defined as for objective 2. As in previous chapters, the proportion of the decline in major CHD incidence statistically explained, or attributable to, the T2DM trend is then given by the expression $(\beta_0-\beta_1)/\beta_0$, where β_0 is the coefficient of time period in the Poisson model without adjustment for T2DM diagnosis, and β_1 is the coefficient of time period in the Poisson model with adjustment for diabetes diagnosis. A 95% confidence interval (CI) for the estimate was obtained from bias-corrected bootstrap resampling.

A quirk of the above analysis is that the separate category of incident cases may include patients who develop a major CHD event before the T2DM diagnosis (if both occur during the follow-up). The justification for this is that patients will most likely have T2DM for some time before being diagnosed as such, or at least have some degree of glucose intolerance, and would therefore be at increased risk of CHD beforehand. Sensitivity analyses to better account for the date of incident T2DM diagnosis were carried out. The population sample in chapter 4 to estimate major CHD incidence trends was used (see section 4.2.2). As well as grouping by age, gender and calendar year, the follow-up time for each patient was split at the date of incident T2DM diagnosis, as time before and after diagnosis. An indicator variable took the value 0 if the patient did not develop T2DM or for patient-time before a T2DM diagnosis and value 1 for patients with prevalent T2DM at the start of the follow-up or for patient-time after a T2DM diagnosis. The Poisson model in chapter 4 (see section 4.2.7) used to estimate the relative decline in major CHD incidence was

then applied to this split dataset and compared with a Poisson model adjusting additionally for T2DM using the indicator variable. The percentage contribution of increasing incidence of T2DM to the decline in major CHD incidence was then estimated in the usual way as $(\beta_0-\beta_1)/\beta_0$, where β_0 is the coefficient of time period in the Poisson model without adjustment for T2DM diagnosis, and β_1 is the coefficient of time period in the Poisson model with adjustment for T2DM diagnosis.

9.2.5 Validation of findings for objective 3 using the BRHS

To address objective 3 using BRHS data, similar methods were employed to those in chapter 5 to consider the role of risk factors in the decline in major CHD (see section 5.2.4). That is, the principal outcome was a first major CHD event, defined as a fatal or non-fatal myocardial infarction (MI), over the 25 year period between baseline (1978-80) and 31 December 2004. T2DM prevalence was ascertained in each of the questionnaires during this period (in 1978-80, 1983-5, 1992, 1996 and 1998-2000), as a self-reported diagnosis of diabetes and/or self-reported use of medication to control diabetes (it should be noted that this is distinct from the direct ascertainment of (date of) T2DM *incidence* from GP records in chapter 8). Medication used for the control of diabetes was defined as any drug with a British National Formulary code of 6.1.1 (insulin) or 6.1.2 (oral glucose-lowering drugs). All men were included in the analysis except those who had had a major CHD event before entry to the study in 1978-80 (n=952), or who reported having diabetes before the age of 30 (so presumed to have T1DM, n=8), or who had missing baseline data on diabetes (n=3). This left 6772 men available for inclusion in the analyses.

Statistical methods The follow-up for each man was split into separate consecutive periods, divided by the questionnaire time-points (1978-80, 1983-5, 1992, 1996 and

2000), resulting in an expanded dataset of pseudo-individuals (one in each period) with a pseudo-baseline as the date of the questionnaire at the start of the period, as in chapter 5. The contribution of the time trend in T2DM to the decline in major CHD hazard was assessed by comparing Cox proportional hazards regression models of incident MI on "calendar time", with and without adjustment for an indicator for T2DM prevalence at the pseudo-baseline for each pseudo-individual (see chapter 5, section 5.2.4, for details). Age was used as the underlying time scale in these time-dependent regressions, with date of birth as a time origin, and age at the date of the "baseline" for each pseudo-individual as a delayed entry time to take account of left truncation. Follow-up time was defined as the time from the questionnaire at the start of the period to the earliest of date of major CHD event, death, or the next questionnaire date or 31 December 2004. Robust standard errors were used to account for the dependency between the different pseudo-individuals corresponding to the same man. The proportion of the decline in major CHD hazard statistically explained, or attributable to, the trend in T2DM is given as before by the expression $(\beta_0-\beta_1)/\beta_0$, where β_0 is the coefficient of calendar time in a Cox regression model with just calendar time as a covariate, and β_1 is the coefficient of calendar time in a Cox regression model adjusting additionally for an indicator for T2DM prevalence. Bias-corrected bootstrap re-sampling was used to give an approximate 95% CI for this estimate. For a closer comparison with the THIN analyses, the BRHS analyses were repeated over the restricted period from 1992 to 2004.

9.3 Results

9.3.1 Objective 1 – Temporal trend in survival time from T2DM diagnosis to a major CHD event

Figure 9.1 presents trends over calendar time in 1-, 3- and 5- year incidence of major CHD following a T2DM diagnosis, by year of T2DM diagnosis. The 1-, 3- and 5-year incidence rates according to year of T2DM diagnosis are also given in table 9.1, along with the numbers of incident T2DM cases in each year. Steady declines may be seen in the 3- and 5-year incidence of major CHD following a T2DM diagnosis over calendar time. This implies an improved prognosis such that in more recent years patients with T2DM are surviving longer following diagnosis before experiencing a major CHD event. The trend may be similar for 1-year survival but the pattern is less clear, reflecting a lack of power due to smaller numbers of CHD events within 1 year of the T2DM diagnosis. From regression modelling, average annual percentage relative falls in the rate of 1, 3 and 5 year incidence of major CHD following T2DM diagnosis were 6.32% (95% CI 3.48 to 9.08), 8.37% (95% CI 5.72 to 10.94) and 8.22% (95% CI 5.1 to 11.24) respectively, adjusting for age at time of T2DM diagnosis, gender and general practice. The estimated declines were all statistically significant ($p<0.001$).

9.3.2 Objective 2 – Temporal trend in incidence of major CHD among patients with and without T2DM and changing relationship between T2DM and major CHD incidence over time

Overall time trends in incidence of major CHD events among the whole population, regardless of diabetes status, were presented in chapter 4, section 4.3. In this section, the time trend in incidence of major CHD is estimated separately for patients with and

without prevalent T2DM. Rate ratios comparing incidence in three consecutive 4-year periods 1995-1998, 2000-2003 and 2005-2008 are presented in table 9.2, according to T2DM status. The results indicate that incidence of major CHD was approximately two-thirds lower in the most recent period 2005-2008 compared with the earliest period 1995-1998 among patients with prevalent T2DM (rate ratio of 0.31, 95% CI 0.28 to 0.35). Among patients without T2DM, a smaller reduction in incidence occurred (rate ratio of 0.46, 95% CI 0.44 to 0.48). The greater decline in incidence of major CHD among patients with T2DM occurred consistently across the whole time-frame. That is, a greater decline occurred among the T2DM population compared with the rest of the population, between the earlier two periods 1995-1998 and 2000-2003 (rate ratios of 0.39 versus 0.52 for patients with and without T2DM respectively), and between the later two periods 2000-2003 and 2005-2008 (rate ratios of 0.79 versus 0.88). An interaction between time-period and T2DM status, reflecting the difference in the decline in major CHD incidence over time between patients with and without T2DM, was statistically significant ($p<0.001$). In analyses stratified by gender (table 9.2), the declines in major CHD incidence among men and women with and without T2DM were broadly similar to that for the whole population of men and women combined. The difference in the major CHD incidence trends among those with and without T2DM was slightly more marked for women than for men.

Table 9.3 presents crude and age-sex-standardised incidence rates of major CHD according to calendar period and T2DM status (no T2DM before or during period versus prevalent T2DM at start of period). Age-sex-adjusted rate ratios of major CHD comparing patients with and without T2DM, for each calendar period, are also given. In all periods, incidence of major CHD was higher among those with T2DM at

the start of the period, than among those without T2DM. However, as well as the overall incidence rates falling over time, the absolute and relative differences between the rates among those with and without T2DM have also fallen. Among men and women combined, the age-sex-adjusted rate ratio comparing those with and without T2DM was attenuated from 2.70 (95% CI 2.42 to 3.02) in 1995-1998 to 2.23 (95% CI 2.04 to 2.45) in 2000-2003 to 1.90 (95% CI 1.80 to 2.00) in 2005-2008. Table 9.4 presents corresponding results by gender. Among men, the age-adjusted rate ratio comparing those with and without T2DM was attenuated from 2.16 (95% CI 1.87 to 2.50) in 1995-1998 to 1.88 (95% CI 1.67 to 2.11) in 2000-2003 to 1.68 (95% CI 1.57 to 1.79) in 2005-2008. Among women, the age-adjusted rate ratio comparing those with and without T2DM was attenuated from 3.30 (95% CI 2.79 to 3.90) in 1995-1998 to 2.57 (95% CI 2.21 to 3.00) in 2000-2003 to 2.06 (95% CI 1.90 to 2.24) in 2005-2008. This narrowing in the relative difference in major CHD risk among patients with and without T2DM reflects the observed greater decline in major CHD incidence among patients with T2DM described above.

9.3.3 Objective 3 – Role of rising T2DM in decline in major CHD incidence

Table 9.5 presents the rate ratios and associated beta-coefficients comparing incidence of major CHD in the periods 1995-1998, 2000-2003 and 2005-2008, with and without adjustment for prevalent T2DM at the start of each period. Also shown is the relative difference between the beta-coefficients with and without adjustment for T2DM, representing the extent to which the rising prevalence of T2DM may "explain" the lower major CHD risk in the more recent periods. The results show that rising T2DM prevalence may "explain" -6.46% (95% bootstrap CI -7.89 to -5.13) of the 53% reduction in major CHD risk between the earliest period 1995-1998 and the most

recent period 2005-2008. The negative sign indicates that the increase in diabetes has been counter-productive and has reduced the potential scale of the decline in major CHD by roughly 6%. The findings are similar for men and women, although among women the negative impact of diabetes was slightly greater: Among men only, the proportion of the 54% rate reduction from 1995-1998 to 2005-2008 "explained" by rising diabetes was -5.69% (95% bootstrap CI -7.47 to -4.23). Among women only, the corresponding figure was -8.08% (95% bootstrap CI -10.9 to -5.57).

In an alternative analysis, taking into account the date of incidence of T2DM, and including patient-time before a T2DM diagnosis with patient-time of patients who do not develop T2DM, and comparing the average annual relative declines in major CHD incidence with and without adjustment for T2DM, the percentage of the decline in major CHD incidence explained by rising T2DM was -8.38 (95% bootstrap CI -9.22 to -7.53), similar in magnitude to the estimate from the first analysis.

The results of corresponding analyses carried out using BRHS data examining the "contribution" of rising T2DM prevalence to the decline in major CHD between 1979 and 2004 are presented in table 9.6. The results suggest that -10.1% (95% bootstrap CI -17.2 to -6.04) of the average annual age-adjusted 3.65% relative decline in major CHD hazard over the whole period can be explained by rising T2DM prevalence, that is, the fall in major CHD incidence was approximately 10% lower than it might have been in the absence of rising T2DM prevalence. Restricting to the period 1992 to 2004 to reflect more closely the period covered by THIN, the point estimates of the average annual decline in major CHD hazard and percentage of the decline explained by rising T2DM prevalence were similar to the overall estimates at 3.74% and -

11.3%. However, because of the reduced numbers of men contributing data in this later period, the bootstrap CI for the percentage explained is very wide and largely uninformative. Similarly, considering the hazard ratio of major CHD comparing the period 2000-2004 with the period 1992-1996, to reflect more closely the analysis of the THIN data, the percentage of this hazard reduction explained by rising T2DM prevalence was -10.4% (95% bootstrap CI -52.1 to -3.78).

9.4 Discussion

9.4.1 Summary of main findings

This chapter has explored the relationship between the time trends in major CHD and T2DM. It was found firstly that between 1995 and 2008, the prognosis, in terms of major CHD risk, of patients newly diagnosed with T2DM has improved: patients are surviving longer after a new T2DM diagnosis before experiencing a major CHD event. Secondly, while significant declines in incidence of major CHD occurred among both patients with and without prevalent T2DM over this period, the decline was slightly larger among those with prevalent T2DM, leading to an attenuation over time of the excess risk of major CHD among T2DM patients from a relative risk of 2.7 to a relative risk of 1.9. The attenuation was more marked in women than men. Finally, analysis of THIN data suggests that rising prevalence of T2DM has limited the decline in major CHD between 1995 and 2008 by approximately 6-8%; that is, in the absence of a rise in prevalence of T2DM a 6-8% larger decline in major CHD incidence than that observed might have occurred. Analysis of BRHS data showed similarly that rising prevalence of T2DM limited the scale of the decline in major CHD incidence in men between 1979 and 2004 by approximately 10%.

9.4.2 Strengths and limitations

As in previous chapters, strengths of this study include the large sample size and nationwide scope of the THIN database, enabling precise estimates of trends across the UK and in the relative risk of major CHD according to diabetes status. Consistent methods were used to identify diagnoses of both T2DM and major CHD in THIN throughout the follow-up period, such that the time trends cannot be biased by changes in the identification methods. Moreover, in each analysis, consistent length follow-up times for incident major CHD were used in each calendar period. That is, for the first objective, the outcome was 1, 3 and 5 year incidence of major CHD from date of first T2DM diagnosis; for the other objectives, an equal 4 year's follow-up was used. Again this limits bias in the time trend estimates which could occur if the hazard of major CHD varies with time from start of follow-up and patients in different calendar periods are followed for different lengths of time. Regarding specifically the third objective to assess the role of the rising T2DM prevalence in the decline in major CHD, a key strength over and above the one previous comparable analysis[15] is the use of individual-level data, linking individual diabetes status to CHD events. The previous analysis (IMPACT model), which estimated the role of diabetes in the decline in CHD *mortality*, combined different aggregate data sources and is thus potentially subject to limitations inherent in ecological analyses[258]. Repetition of the analysis for this third objective using the BRHS cohort, with broadly consistent findings, further adds weight to the validity of the results.

The analyses are not without limitations. First, as outlined in chapter 4, section 4.6.2, it is likely that some fatal major CHD events will not be captured in the analysis due to the nature of recording of death records in THIN, thus the results may reflect

mainly non-fatal MI events. However, as discussed in section 4.6.2, this appears to have had limited impact on the CHD time-trend estimates, and also, since one might expect similar CHD recording patterns for those with and without diabetes, this exclusion of fatal events is unlikely to bias estimates of the *differences* in the CHD trends between patients with and without diabetes (relevant for objectives 2 and 3). Second, in the analyses relating to the first objective, which involved identification of incident T2DM cases, it is possible that some of the incident T2DM events are not truly incident, if T2DM records before the patient registered or patient data was captured on computer are not captured in THIN, as discussed in chapter 4, section 4.6.2. However, as detailed in chapter 4, section 4.6.2, allowing a year after registration before following up patients for incident events (and excluding patients with an event during that year as prevalent cases), should ensure most new records are incident cases (as this allows for recording of patient history at or soon after registration[324] and because 99.7% of T2DM records occur less than one year before the next record, a consistent finding across all calendar years). Third, in the analyses relating to the second and third objectives, which involved comparing patients with and without prevalent T2DM on certain dates, patients were considered prevalent cases if they had a T2DM record in the previous year, and were taken to be T2DM-free if they did not. If T2DM records for a patient are more than a year apart, it is possible that some patients with diabetes will be mis-classified as diabetes-free. The impact would be a dilution of the association between T2DM and CHD risk, and so also a dilution of the percentage contribution of diabetes to the decline in major CHD. However again, given that the vast majority of diabetes records occur less than a year apart, the mis-classification is likely to be small. Moreover, the estimates of the overall relative risks of incidence of major CHD by T2DM status correspond closely

to those reported in other studies, particularly substantiating the higher relative risk among women: reported relative risks for major CHD of 2.13 and 2.95 in men and women in the UK between 1992 and 1999[28]; and reported relative risks for *fatal* CHD of 1.85 and 2.06 in men and 2.58 and 3.50 in women from two recent meta-analyses[27, 31]. A final limitation is the possible inclusion of T1DM cases among the T2DM cases, where the diabetes diagnosis was non-specific. However again, as this was the case throughout the time period covered, importantly this will not bias the estimates of the time trends. Moreover, previous studies have shown that much of the rise in prevalence of diabetes reflects a rise in T2DM, rather than T1DM[6]. Thus in relation to objective 3, the percentage contribution of rising diabetes to the decline in major CHD, is likely to primarily reflect a contribution of T2DM. The correspondence between the results for THIN and the BRHS findings (which do relate specifically to T2DM) supports this further.

9.4.3 Comparison with other studies

To my knowledge, there have been no previous studies of CVD trends (incidence or mortality) according to diabetes status in the UK population. Three previous studies were found which assess in particular time trends in *incidence* of CHD or CVD by diabetes status, in North America and Scandinavia. A study in Ontario, Canada[395], found that between 1992 and 2000 the rate of patients aged 20 years or over admitted for MI fell more sharply in the diabetic than the non diabetic population (declines of 15% versus 9%), consistent with the findings in this chapter. Results by gender were not presented. A study in Finland[389] compared the relative risk of major CHD for diabetic patients in two separate cohorts in the 1970s and 1990s. Among men, the relative risk was attenuated from 1.67 in the 1970s to 1.37 in the 1990s but in women

the relative risk *increased* from 2.33 to 3.42. This contrasts with the present study findings, where the attenuation in relative risk over time appeared greater in women. This could reflect the earlier time-period in a different country. The US Framingham Heart Study compared 12-year incidence of CVD among 45-64 year olds in two cohorts: the original cohort in 1950-66 and the "offspring" cohort in 1977-1995[396]. Again, a larger decline in incidence was observed comparing participants in the two cohorts with diabetes than comparing those without (49.3% versus 35.4%), leading to an attenuation of the excess risk of CVD among diabetic patients (from 2.98 in the original cohort to 2.48 in the offspring cohort). Results did not differ by gender. A similar pattern emerged for the outcome of CVD *mortality* in the Framingham cohorts[32]. Despite the attenuation in the relative risks, patients with diabetes still remained at a much elevated risk of CVD outcomes in the second Framingham cohort (as in the results of this chapter). A separate, more recent, analysis was based only on the second cohort, studied between 1970 and 2005[222]. In that report it was observed that, among cardiovascular risk factors, blood pressure declined to a similar degree among participants with and without diabetes, while blood cholesterol fell more among diabetic patients, who also experienced a larger increase in BMI[222]. The authors concluded that because of the larger increase in BMI, despite the favourable trend in cholesterol, the increased CVD risk among diabetic patients was persisting.

The role of rising diabetes prevalence in the decline in major CHD *incidence* has not been previously addressed in the UK population or elsewhere. The IMPACT model considered the contribution of diabetes to the decline in CHD *mortality* in England and Wales between 1981 and 2000, finding that an extra 2900 deaths in 2000 compared with 1981 could be attributable to the rise in diabetes, corresponding to a

"contribution" to the decline in CHD mortality of -4.7%[15]. That is, rising diabetes had an adverse effect, limiting the decline in CHD mortality by 4.7%, in line with the present study findings.

9.4.4 Interpretation of findings

The positive conclusion to be drawn from the results is that over the 14 year calendar period from 1995 to 2008, the prognosis for patients with diabetes, in terms of major CHD risk, appears to have improved. Patients who are given a new diagnosis of T2DM are surviving longer following the diagnosis before developing major CHD and the excess risk of major CHD among patients with prevalent T2DM has attenuated slightly (more noticeably for women). What might be the reasons for these favourable time trends? First, as in earlier chapters, the potential influences of changes in diagnostic criteria for major CHD and/or diabetes need to be considered. As detailed in chapter 4, section 4.6.5.1, the change in 1999 in diagnostic criteria for MI (to use of troponins) is likely to have led to more patients being diagnosed with MI and so possibly to underestimation of extent of the decline in major CHD. Thus this change would not help to explain the improvement in survival seen among incident T2DM cases. Also, because the increased diagnosis of MI would have affected both the diabetic and diabetes-free population similarly, the change in diagnosis does not explain the attenuation of the relative risk of major CHD for diabetes either. In chapter 4, section 4.6.5.1, it was discussed that while evidence was inconclusive as regards the extent to which the change in diagnostic criteria for T2DM in 1999 may have increased or decreased the numbers of people diagnosed, one consistent finding is that the change in diagnostic criteria has resulted in different people being diagnosed[96]. Studies have also shown that one difference is that for

elderly people the new criteria, focussing on fasting glucose levels, result in elderly T2DM patients with a lower overall lower excess risk of CVD relative to elderly people with normal glucose levels, when compared to elderly T2DM patients identified using the original criteria[397, 398]. Thus in more recent calendar years, T2DM cases may include patients with a lower risk of major CHD. The attenuation of the relative risk for major CHD among diabetics may therefore to some extent be plausibly explained by the change in diagnostic criteria. However, the difference in CVD risk among T2DM patients using the different criteria has not been shown consistently among all populations[399] and may therefore be limited to elderly patients. The policy recommendations for CHD prevention in 1999 and the introduction of the Quality and Outcomes Framework (QOF) for diabetes in 2003 may also help to explain the favourable time trends. Both policy interventions may have led on the one hand to increased testing for diabetes and so improved case-ascertainment, possibly again with an increase particularly in less advanced/severe diabetes which might otherwise go undiagnosed. This again would tend to lead to patients with lower CHD risk among the prevalent diabetes cases and so is consistent with a greater decline in major CHD risk relative to the diabetes-free population. Perhaps in earlier years, the presence of CVD prompted testing for a T2DM diagnosis (a type of reverse causal situation), whereas in more recent years, patients have been tested for T2DM more widely and regardless of CVD risk. On the other hand, the policy interventions have been shown to result in better management and treatment of T2DM patients[342], particularly as regards hypercholesterolemia control (a major CVD risk factor) and so these policies may have alternatively led to an improvement in survival from major CHD due to improved management and care. Further research is needed to identify the reasons for the attenuation of the excess risk of major CHD among T2DM patients

and establish whether the favourable change reflects the better management and treatment of T2DM or changed diagnosis and improved case ascertainment.

Despite the attenuation of the relative risk, patients with T2DM remain at approximately double the risk of major CHD than those without T2DM. Thus there is still considerable scope for improvement and a need for continued concerted efforts to better the management of T2DM. The need to better manage T2DM is further emphasized given the increase in incidence of T2DM over time. Thus although the relative risk comparing those with and without T2DM has attenuated, as more patients develop T2DM, the proportion of all patients experiencing a major CHD event who have T2DM is likely to increase – that is, the absolute contribution of T2DM to the major CHD burden is set to rise, as already demonstrated in the US population[395, 400].

The results show that rising T2DM prevalence may have limited the decline in major CHD incidence by roughly 6 to 10%. That is, had T2DM prevalence remained constant over time, the decline in major CHD could have been 6 to 10% larger than that observed. Since in the analysis of BRHS data, rising T2DM prevalence had an adverse impact on the extent of the decline in CHD incidence both before and after the changes in diagnostic criteria and various policy interventions, these factors are unlikely to explain the findings. The negative contribution of T2DM appeared larger for women than men in THIN (8% versus 6%), which fits with the observed greater relative risk of CHD among women with diabetes relative to women without diabetes, compared with the relative risk among men. The similarity in the size of the negative contribution of T2DM to that of BMI (7-10% in chapters 5 and 6) raises the possibility that much of the adverse effect of BMI on the major CHD incidence trend

may operate through rising T2DM. This possibility is supported by the results of chapter 8 showing the role of BMI on rising T2DM incidence. Although the adverse impact of rising T2DM appears so far to have been outweighed by the favourable trends in other cardiovascular risk factors, the concern is that continued increases in T2DM prevalence may further reduce or even reverse the decline in major CHD incidence. This emphasizes the need to address the rising incidence of T2DM in the population.

Table 9.1 **1-, 3-, and 5-year incidence of a major CHD event, following a new T2DM diagnosis, according to calendar year of T2DM diagnosis**

Calendar period of T2DM diagnosis	No. of incident T2DM patients	Major CHD events within 1 year of diagnosis	Person-years of follow-up	1-year major CHD incidence rate (95% CI)	Major CHD events within 3 years of diagnosis	Person-years of follow-up	3-year major CHD incidence rate (95% CI)	Major CHD events within 5 years of diagnosis	Person-years of follow-up	5-year major CHD incidence rate (95% CI)
1995-1996	2,054	18	1,967	9.15 (5.77 to 14.5)	48	5,464	8.78 (6.62 to 11.7)	75	8,504	8.82 (7.03 to 11.1)
1997-1998	3,567	20	3,416	5.85 (3.78 to 9.07)	73	9,507	7.68 (6.10 to 9.66)	116	14,793	7.84 (6.54 to 9.41)
1999-2000	6,856	47	6,585	7.14 (5.36 to 9.50)	126	18,515	6.81 (5.72 to 8.10)	192	28,937	6.64 (5.76 to 7.64)
2001-2002	12,499	107	12,057	8.87 (7.34 to 10.7)	228	33,854	6.73 (5.92 to 7.67)	304	53,275	5.71 (5.10 to 6.39)
2003-2004	15,867	92	15,363	5.99 (4.88 to 7.35)	203	43,534	4.66 (4.06 to 5.35)	282	65,534	4.30 (3.83 to 4.84)
2005-2006	17,075	67	16,548	4.05 (3.19 to 5.14)	159	43,310	3.67 (3.14 to 4.29)			
2007-2008	17,344	60	12,714	4.72 (3.66 to 6.08)						

Table 9.2 **Decline in major CHD incidence over time, comparing populations with and without T2DM**

		All participants	Men	Women
Rate ratio of major CHD incidence, 2005-2008 versus 1995-1998 (95% CI)	**T2DM at start of period**	0.31 (0.28 to 0.35)	0.33 (0.28 to 0.38)	0.29 (0.24 to 0.34)
	No T2DM at start of period	0.46 (0.44 to 0.48)	0.45 (0.43 to 0.48)	0.47 (0.44 to 0.51)
Rate ratio of major CHD incidence, 2000-2003 versus 1995-1998 (95% CI)	**T2DM at start of period**	0.39 (0.34 to 0.45)	0.43 (0.36 to 0.51)	0.35 (0.28 to 0.43)
	No T2DM at start of period	0.52 (0.50 to 0.55)	0.54 (0.51 to 0.57)	0.49 (0.45 to 0.53)
Rate ratio of major CHD incidence, 2005-2008 versus 2000-2003 (95% CI)	**T2DM at start of period**	0.79 (0.71 to 0.87)	0.76 (0.67 to 0.87)	0.83 (0.70 to 0.97)
	No T2DM at start of period	0.88 (0.85 to 0.92)	0.85 (0.81 to 0.89)	0.96 (0.91 to 1.03)
p-value for interaction between time period and diabetes status		<0.001	<0.001	<0.001

Estimates from multilevel Poisson regression, adjusting for age and gender, and general practice as a random intercept

Table 9.3 **Crude and age-sex-standardised major CHD incidence rates according to calendar period and T2DM status. Age-sex-adjusted rate ratios of major CHD incidence, comparing populations with and without T2DM, in each calendar period.**

	1995-1998		2000-2003		2005-2008	
	No T2DM before or during period	**T2DM at start of period**	**No T2DM before or during period**	**T2DM at start of period**	**No T2DM before or during period**	**T2DM at start of period**
All participants						
Number of major CHD events	2848	366	4202	510	9375	1736
Total person-years	929989	25650	2733892	95558	6373026	391634
Crude incidence rate of major CHD, per 1000 person years (95% CI)	3.06 (2.95 to 3.18)	14.3 (12.9 to 15.8)	1.54 (1.49 to 1.58)	5.34 (4.89 to 5.82)	1.47 (1.44 to 1.50)	4.43 (4.23 to 4.65)
Age-sex-standardised incidence rate of major CHD, per 1000 person years (95% CI)*	3.26 (3.14 to 3.38)	9.30 (8.20 to 10.4)	1.66 (1.61 to 1.71)	4.23 (3.79 to 4.67)	1.50 (1.47 to 1.53)	3.14 (2.96 to 3.32)
Age-sex-adjusted rate ratio of major CHD incidence, T2DM versus no T2DM (95% CI)†	**1**	**2.70 (2.42 to 3.02)**	**1**	**2.23 (2.04 to 2.45)**	**1**	**1.90 (1.80 to 2.00)**

*Standardised to the age-sex-distribution of the whole THIN population. †From multilevel Poisson regression, adjusting for age and gender, and general practice. Note: Because of the adjustment for general practice as a random effect in the multilevel modelling, the rate ratios presented in the bottom row do not equate exactly to the ratios of the age-sex-standardised incidence rates in the third row (which are not adjusted for practice).

Table 9.4 **Crude and age-standardised major CHD incidence rates according to calendar period and T2DM status, by gender. Age-adjusted rate ratios of major CHD incidence, comparing populations with and without T2DM, in each calendar period.**

	1995-1998		2000-2003		2005-2008	
	No T2DM before or during period	**T2DM at start of period**	**No T2DM before or during period**	**T2DM at start of period**	**No T2DM before or during period**	**T2DM at start of period**
Men						
Number of major CHD events	1781	207	2781	321	5876	1045
Total person-years	435784	13182	1285331	49481	3026111	199616
Crude incidence rate of major CHD, per 1000 person years (95% CI)	4.09 (3.90 to 4.28)	15.7 (13.7 to 18.0)	2.16 (2.08 to 2.25)	6.49 (5.82 to 7.24)	1.94 (1.89 to 1.99)	5.24 (4.93 to 5.56)
Age-standardised incidence rate, per 1000 person years (95% CI)*	4.77 (4.54 to 4.99)	11.1 (9.41 to 12.9)	2.45 (2.35 to 2.55)	5.30 (4.62 to 5.99)	2.14 (2.08 to 2.19)	4.06 (3.76 to 4.37)
Age-adjusted rate ratio of major CHD incidence, T2DM versus no T2DM (95% CI) †	**1**	**2.16 (1.87 to 2.50)**	**1**	**1.88 (1.67 to 2.11)**	**1**	**1.68 (1.57 to 1.79)**
Women						
Number of major CHD events	1067	159	1421	189	3499	691
Total person-years	494205	12467	1448560	46076	3346915	192018
Crude incidence rate of major CHD, per 1000 person years (95% CI)	2.16 (2.03 to 2.29)	12.8 (10.9 to 14.9)	0.98 (0.93 to 1.03)	4.10 (3.56 to 4.73)	1.05 (1.01 to 1.08)	3.60 (3.34 to 3.88)
Age-standardised incidence rate, per 1000 person years (95% CI)*	2.03 (1.90 to 2.15)	7.66 (6.24 to 9.08)	0.98 (0.93 to 1.04)	3.33 (2.75 to 3.90)	0.95 (0.92 to 0.98)	2.33 (2.12 to 2.54)
Age-adjusted rate ratio of major CHD incidence, T2DM versus no T2DM (95% CI) †	**1**	**3.30 (2.79 to 3.90)**	**1**	**2.57 (2.21 to 3.00)**	**1**	**2.06 (1.90 to 2.24)**

*Standardised to the age-distribution of the whole THIN population. †From multilevel Poisson regression, adjusting for age and gender, and general practice. Note: Because of the adjustment for general practice as a random effect in the multilevel modelling, the rate ratios presented in the bottom row do not equate exactly to the ratios of the age standardised incidence rates in the third row (which are not adjusted for practice).

Table 9.5 **Fall in rate of major CHD between 1995-1998 and 2005-2008 among men and women in the THIN population, and % of the fall "explained" by rising T2DM prevalence**

Measure of time trend	Point estimate, (95% CI), age-adjustment only	Corresponding β-coefficient, age-adjustment only	Corresponding p-value	Point estimate, (95% CI), adjusted for age + T2DM status at start of each period	Corresponding β-coefficient, adjusted for age + T2DM status	Corresponding p-value	% of the time trend in major CHD incidence "explained" by rising T2DM prevalence, (95% bootstrap CI)*
All participants							
Rate ratio of major CHD comparing the periods 2005-2008 with 1995-1998	0.47 (0.45 to 0.49)	-0.7610	<0.001	0.44 (0.43 to 0.46)	-0.8102	<0.001	**-6.46 (-7.89 to -5.13)**
Men							
Rate ratio of major CHD comparing the periods 2005-2008 with 1995-1998	0.46 (0.44 to 0.49)	-0.7691	<0.001	0.44 (0.42 to 0.47)	-0.8128	<0.001	**-5.69 (-7.47 to -4.23)**
Women							
Rate ratio of major CHD comparing the periods 2005-2008 with 1995-1998	0.48 (0.45 to 0.51)	-0.7369	<0.001	0.45 (0.42 to 0.48)	-0.7965	<0.001	**-8.08 (-10.9 to -5.57)**

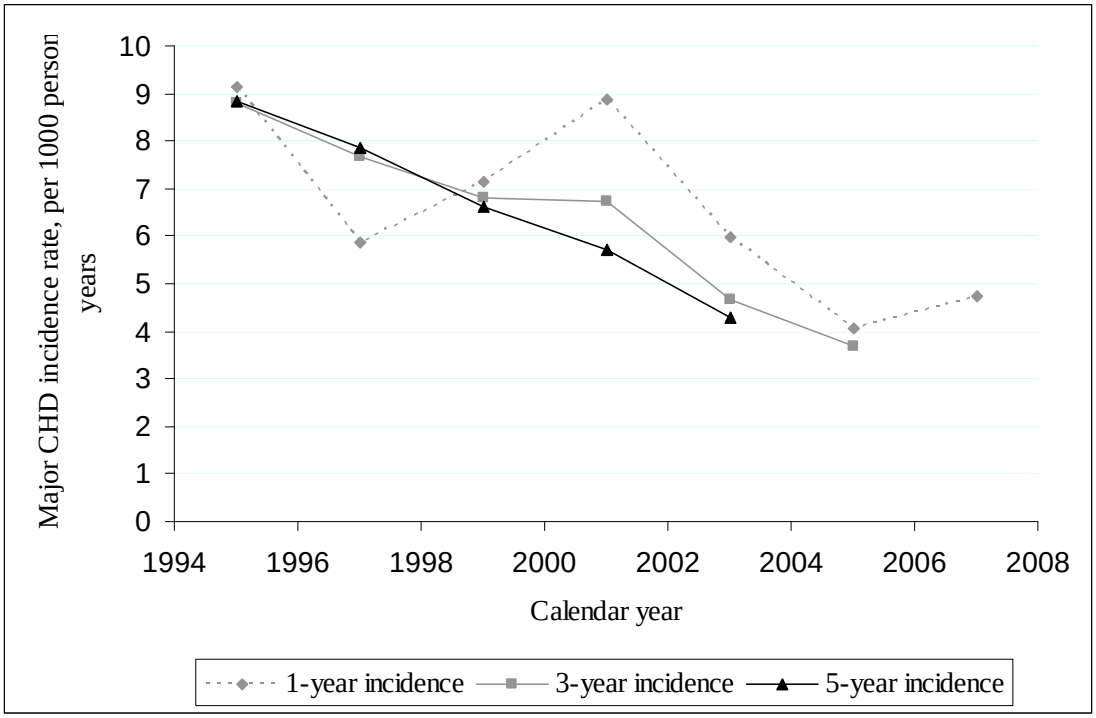
*% of the time trend in major CHD incidence explained by rising T2DM prevalence = $100\% \times (\beta_0 - \beta_1)/ \beta_0$ where β_0 is the coefficient for calendar period in the model only adjusting for age and β_1 is the coefficient for calendar period in the model adjusting additionally for T2DM status.

Table 9.6 **Fall in hazard of major CHD between 1979 and 2004 among men in the BRHS cohort, and % of the fall "explained" by rising T2DM prevalence**

Measure of time trend	Point estimate, (95% CI), age-adjustment only	Corresponding β-coefficient, age-adjustment only	Corresponding p-value	Point estimate, (95% CI), adjusted for age + T2DM status at start of each period	Corresponding β-coefficient, adjusted for age + T2DM status	Corresponding p-value	% of the time trend in major CHD incidence "explained" by rising T2DM prevalence, (95% bootstrap CI)*
Average annual percentage decline in hazard of major CHD between 1979 and 2004*	3.65 (2.50 to 4.78)	-0.0371	<0.001	4.01 (2.85 to 5.15)	-0.0409	<0.001	**-10.1 (-17.2 to -6.04)**
Average annual percentage decline in hazard of major CHD between 1992 and 2004*	3.74 (0.19 to 7.17)	-0.0381	0.04	4.15 (0.61 to 7.58)	-0.0424	0.02	**-11.3 (-56.7 to 38.4)**
Rate ratio of major CHD comparing the periods 2000-2004 with 1992-1996	0.75 (0.59 to 0.94)	-0.2939	0.01	0.72 (0.57 to 0.91)	-0.3246	0.006	**-10.4 (-52.1 to -3.78)**

*% of the time trend in major CHD incidence explained by rising T2DM prevalence = $100\% \times (\beta_0 - \beta_1)/ \beta_0$ where β_0 is the coefficient for calendar period in the model only adjusting for age and β_1 is the coefficient for calendar period in the model adjusting additionally for T2DM status.

Figure 9.1 **1-, 3-, and 5-year incidence of a major CHD event, following a new T2DM diagnosis, according to calendar year of T2DM diagnosis**



Chapter 10: Implications

10.1 Introduction – summary of all main findings

10.1.1 Recap of thesis aim

The motivation for the research in this thesis stemmed from observations of the striking and divergent time trends in coronary heart disease (CHD) and type 2 diabetes (T2DM) which have occurred in the UK in recent decades. In particular, the "headline" statistics are a fall in mortality from CHD of almost three quarters from 1961 to the present, compared with a rise in prevalence of T2DM of around 5% per annum since the 1990s. Understanding the reasons for these contrasting disease time trends may have potentially important public health implications. In particular, gaining insight into which associated factors have most influenced the observed trends may help to inform future efforts to reduce CHD mortality and T2DM prevalence. However few studies have sought to carry out formal analyses of the reasons for the time trends.

A key step towards understanding the major CHD mortality and T2DM prevalence trends is to examine time trends in the incidence of these two conditions. This notion led to formation of the overall thesis aim to describe and explain time trends in incidence of major CHD and T2DM.

Recall from chapter 1, section 1.2, the five thesis objectives:

i) Estimate recent time trends in incidence of major CHD in the UK

ii) Estimate recent time trends in incidence of T2DM in the UK

iii) Examine the potential contribution of secular time trends in major aetiological factors and preventative medications to the time trend in incidence of major CHD:

iii)a) Examine the possible contribution of secular time trends in major aetiological factors to the time trend in incidence of major CHD

iii)b) Examine the contribution of increased preventative medication use to the time trends in the major aetiological factors

iv) Examine the possible contribution of secular time trends in major aetiological factors (particularly rising adiposity levels) to the time trend in incidence of T2DM

v) Examine the paradox that CHD has declined while T2DM has increased.

v)a) Estimate whether the time trend in incidence of major CHD among individuals with T2DM differs from the time trend in incidence of major CHD among those without T2DM, and if so, how the excess risk of major CHD among those with T2DM has changed over time.

v)b) Estimate the potential decline in major CHD incidence had no increase in T2DM occurred and the extent to which rising T2DM prevalence has curtailed the decline in major CHD incidence.

10.1.2 Findings in relation to thesis objectives

In relation to the first two thesis objectives, to describe trends in major CHD incidence and T2DM incidence, analysis of data from nationwide The Health

Improvement Network (THIN) primary care database in chapter 4, showed a 50% relative decline in major CHD incidence in the UK over the 14 year period from 1995 to 2008. Over the same period, incidence of T2DM rose by 64%, although the influence of changes in diagnostic criteria and case ascertainment may account for some of the T2DM rise in later years. Analysis of data from the British Regional Heart Study (BRHS) and Whitehall II cohorts in chapter 4 revealed consistent trend estimates, and also showed that the decline in major CHD incidence occurred from at least the 1980s, while T2DM incidence appears to have been rising at least since the mid-1980s.

The analyses presented in chapters 5, 6 and 7 addressed the third objective, to explore reasons for the decline in major CHD incidence. In chapter 5, it was shown that, of the decline in the hazard of major CHD in the BRHS over 25 years from 1978-80 to 2004, 46% could be explained by a combination of time trends in the major coronary risk factors over this time: a fall in the number of cigarette smokers (most powerful of all), a decrease in the mean SBP among the cohort, an increase in mean HDL cholesterol and a decrease in mean non-HDL cholesterol. Chapter 6 revealed comparable findings for the decline in major CHD hazard among men and women in Whitehall II, supporting the findings from the BRHS, and extending the results to women. Further analyses of the BRHS men in chapter 7 showed that most (80%) of the fall in SBP and a smaller proportion (33%) of the fall in non-HDL cholesterol could be attributed to larger decreases among users of relevant medications over and above the decreases among men not on medication. The favourable increase in HDL cholesterol however was independent of medication use. Changes in diet, physical activity and alcohol consumption appeared to have limited influence on the decline in major CHD

incidence, but the effects may have been underestimated due to measurement imprecision. While the overall changes in CHD were generally favourable, it was not all good news as in both cohorts rising adiposity had an adverse impact, such that had other favourable risk factor trends not occurred, the unfavourable trend in body mass index (BMI) may have led to an increase in major CHD incidence.

Chapter 8 addressed the fourth thesis objective, to explore the reasons for the rise in T2DM incidence, using data from the BRHS. In particular, the possibility that much of the rise in T2DM (that which is independent of changes in population demographics) may be connected to rising adiposity levels was investigated. Approximately one quarter of the rise in T2DM incidence among men in the BRHS between 1984 and 2007 could be attributed to a rising BMI levels. The results suggest that an appreciable portion of the substantial rise in T2DM incidence is associated with the unfavourable population wide increase in BMI but a substantial portion of the observed increase in T2DM incidence remained unaccounted for.

T2DM is associated with an estimated two-fold increased risk of CHD. The final results chapter 9 thus investigated the relationship between the opposing trends in these related conditions (the fifth thesis objective). It was found firstly that between 1995 and 2008, the prognosis, in terms of major CHD risk, of patients newly diagnosed with T2DM has improved: patients are surviving longer after a new T2DM diagnosis before experiencing a major CHD event. Secondly, while significant declines in incidence of major CHD occurred among both patients with and without prevalent T2DM over this period, the decline was slightly larger among those with prevalent T2DM, leading to an attenuation over time of the excess risk of major CHD

among T2DM patients from a relative risk of 2.7 to a relative risk of 1.9. The attenuation was more marked in women than men. Finally, analysis of THIN data suggests that the rising prevalence of T2DM has limited the decline in major CHD between 1995 and 2008 by approximately 6-8%. That is, in the absence of a rise in prevalence of T2DM a 6-8% larger decline in major CHD incidence than that observed might have occurred. Analysis of BRHS data showed similarly that rising prevalence of T2DM limited the scale of the decline in major CHD incidence in men between 1979 and 2004 by approximately 10%.

10.1.3 Novelty of the present findings (What this study adds)

The research in this thesis provides further evidence on time trends in incidence of major CHD and T2DM in the UK, using representative populations studied over extended periods. While there was already some data on time trends in incidence of major CHD or T2DM, as discussed in chapter 2, sections 2.2.2 and 2.3.2, this data was limited (for example restricted to a particular region or with gaps in the time periods covered). This reflects in part a paucity of suitable data sources and the difficulties in capturing incidence (as opposed to CHD mortality or T2DM prevalence). Through the consistency of the estimates of the time trends from the three different data sources studied, this thesis provides strong evidence in support of declining major CHD incidence and rising T2DM incidence, confirming the findings from previous studies. The thesis also presents little-reported time trends in incidence by socio-demographic group, highlighting a possible widening socio-economic inequality in incidence of both CHD and T2DM.

The investigations reported in chapters 5 to 8 are also apparently the first studies of this kind to formally analyse the reasons for the time trends in CHD and T2DM in the UK, using individual-level data. The results highlight the contribution of favourable risk factor trends to the decline in major CHD incidence, and also quantify the adverse role of adiposity on the rise in incidence of T2DM. While several studies have reported on concurrent trends in CHD and CHD risk factors, and hypothesised a relationship between the two, just two previous studies have sought to formally relate risk factor trends to CHD trends in the UK - the IMPACT study[12, 15] and the WHO MONICA study[13]. However both studies involved a synthesis of different aggregate data sources, and are thus subject to ecological limitations. Also, the IMPACT study considered trends in CHD mortality rather than in CHD incidence, while the WHO MONICA study was limited to two specific UK cities (Glasgow and Belfast) and so the findings may not be reflective of the UK as a whole. Even worldwide, there are few studies of time trends of this kind, formally relating individual risk factor levels to CHD events[17]. Meanwhile, literature examining the reasons for the rise in T2DM is even sparser. While rising adiposity levels are thought to contribute to the rising T2DM prevalence, this is apparently the first study to attempt to quantify the role of adiposity. The results confirm an appreciable contribution to the increasing T2DM burden of rising levels of this key risk factor, whilst also suggesting that rising adiposity levels may not be the whole story, and other factors may be playing a role too. The excess risk of a CHD event among patients with T2DM, relative to those without, is well established[27-33]. On a positive note, the results of the final chapter of the thesis show further (and apparently for the first time) some evidence of an improvement and that this excess risk has attenuated over time in the UK population; this finding is in line with those in other countries.

The validity of each of these findings, and coherence of the findings with existing research, were demonstrated in each of the results chapters. In subsequent sections of this final chapter, the potential implications of the findings, both in terms of public health and in terms of future epidemiological research, are discussed.

10.2 Public health implications

10.2.1 Implications for the UK

Time trend in incidence of major CHD

The findings of chapter 4 indicate that at least from the 1980s onwards the decline in mortality from CHD may be partially explained by a fall in incidence of major CHD events, that is fewer people experiencing a major CHD event in the first place. This good news story indicates that it has been possible for major CHD incidence to decline over time, to, in turn, contribute to reduced CHD mortality rates in the UK population. However, as outlined in chapter 2, section 2.4.1, despite the decline in CHD mortality, CHD remains the leading single cause of death. Therefore, efforts are needed to reduce CHD mortality rates further. The present study results suggest that a major contribution to achieving this can come through reductions in incidence, that is preventing men and women from developing major CHD in the first place.

Time trend in incidence of T2DM

The rise in prevalence of T2DM, at least from the mid 1980s until the late 1990s, may be seen to reflect at least in part a rise in incidence of T2DM, that is an increase in the rate at which people develop T2DM. The observed rise in T2DM incidence, at least during the 1990s, is apparently independent of population demographic changes and

changes in diagnostic criteria and case ascertainment. In chapter 2, section 2.3.2, it was noted that the extent to which rising T2DM prevalence is an unfavourable occurrence and an "epidemic" depends on the drivers behind the rising prevalence[19, 74, 75]. If the rise is seen to reflect mainly improved survival, or a change in the population structure, these are changes that do not necessarily indicate a public health problem requiring resolution, and (in the case of improved survival) could be conceived to be a public health "success story". The findings from chapter 4 indicate that, at least in part, the rising prevalence over this period is resulting from rising incidence, and thus emphasizes the need for urgent action to prevent men and women from developing T2DM. In the last decade, the extent of the rise in T2DM incidence, given the possible influence of changing diagnostic criteria and case ascertainment, was less certain. However, it could be argued that it is more likely for the pattern of rising incidence in the 1990s to have continued than not, especially since, as was shown subsequent chapters, adiposity has continued to increase. Indeed, in the BRHS analyses of chapter 8, the continuing increase in adiposity made a similar contribution to rising T2DM incidence in the latest period as in earlier years.

Socio-demographic variations in incidence time trends

Chapter 4 also presented previously little reported trends in incidence of major CHD and T2DM according to different socio-demographic characteristics. The general pattern was that more favourable trends occurred in higher socioeconomic groups: the rate of decline in major CHD appeared faster while the rate of increase of T2DM was slower among those in more professional/ senior employment grades compared with more junior grades or unskilled occupations and among those living in less deprived areas compared with more deprived areas. Incidence of both major CHD and T2DM

was initially greater among more deprived groups. Therefore the results highlight a concerning widening socio-economic inequality in T2DM and CHD incidence rates, suggesting that public health measures to reduce incidence of these conditions, while aiming to reduce both overall rates across the country, should also focus particularly on reducing rates within more deprived communities.

The least favourable relative changes in incidence of T2DM and major CHD were shown to have occurred in the youngest age groups. This is concerning as it is these age groups which will influence the future prevalence and burden of disease. For major CHD, this finding is corroborated by the observed flattening of the decline in CHD mortality in younger groups[52-54]. This highlights that the CHD trends are not entirely favourable and despite the striking decline in CHD mortality to date, public health focus should not shift away from CHD, as there may be the possibility of a resurgence of a CHD epidemic among younger generations.

Contributions of aetiological exposures to the decline in major CHD incidence

The results from chapters 5 and 6 showed that approximately half of the decline in major CHD incidence may be attributed to favourable trends in major modifiable exposures in the population. As discussed in chapter 5, section 5.5.2, the analyses are distinct from studies assessing the more familiar "population attributable risk fraction" (PARF) of major CHD for given risk factors[143]. In studies of PARF, the objective is to assess the degree to which overall risk of major CHD in a population is attributable to risk factors. In this study the objective is instead to assess the degree to which the *trend over time* in major CHD risk in the population is attributable to risk factor trends; in particular how much of the favourable decline in major CHD may be

attributable to risk factor improvements. As well as a difference in the interpretation of the findings, the key difference in the modelling is that overall risk of major CHD in a PARF calculation may be attributed to a combination of modifiable risk factors, such as adiposity, and static risk factors, such as genetics, while in contrast, trends over time in major CHD may be attributed to only modifiable risk factors, which have changed over time in the cohort. Thus the estimated relative contributions of risk factors may differ between the present analyses and PARF-based analyses. Since the trends in major CHD may be attributed only to modifiable risk factors, the analyses reported here may arguably be considered to have more immediate public health implications in terms of identifying ways to reduce underlying risk of major CHD in a population. The results show what can be achieved in terms of reducing smoking, lipid levels, and blood pressure, and the considerable resultant reductions in CHD incidence in the population. This highlights the value of population-wide measures to reduce exposure to the major coronary risk factors. The potential for further reductions in CHD in the UK population through cigarette smoking may be constrained by the already low remaining cigarette smoking prevalence. However, the changes in blood pressure and particularly in blood lipids that have so far occurred are relatively modest and appreciable further opportunities for the reduction in blood pressure and lipid levels remain. CHD mortality risk continues to decline to 115/75mmHg for BP, and 3.5mmol/L for non-HDL cholesterol[100, 103], lower than the levels among the participants in both the Whitehall II and BRHS cohorts at the end of the follow-up periods, despite the favourable declines. A recent analysis of 2006 data from the Health Survey for England suggested that, even now, BP is controlled in only about 28% of hypertensive individuals[401]. This echoes similar findings from the US population[402]. The results of chapter 7 highlight that while much of the decline in

SBP to date may be attributed to use of anti-hypertensive medications, the favourable trends in non-HDL cholesterol, and especially HDL cholesterol, were more likely to reflect changes in health behaviours. Both medication-based strategies and non-medical population-wide strategies still have considerable potential to reduce levels of these coronary risk factors in the UK. Non-medical strategies include in particular reduction of saturated fat and salt intakes, given that in 2010, average sodium intake was estimated to be 2.83 grams per person per day, corresponding to a salt intake above 7 grams per person per day[403], considerably greater than the 5.8 grams per day advocated by DASH (Dietary Approaches to Stop Hypertension)[404]. Likewise, the percentage of energy derived from saturated fat was 14.5%[405], roughly twice the desirable levels seen in Japan[406], a country with exceptionally low CHD rates. It has not been possible to assess the role of hospital interventions (for example bypass procedures or angioplasties) in the decline in major CHD incidence in these analyses due to a lack of secondary care data. However arguably it is of greater public health importance to establish the roles of factors or exposures which are readily modifiable, as this shows what can be achieved through primary prevention approaches which could obviate the need for major surgical procedures.

Considering the Whitehall II gender-specific analyses in chapter 6, the risk factor reductions were of broadly comparable importance for the CHD risk reductions in men and women, with any differences in the estimated contributions of the risk factors explained by differences in the time trends in these factors (HDL and SBP). The findings suggest that similar influences have operated to achieve similar overall declines in incidence of major CHD among both men and women, such that similar prevention strategies may be appropriate for both genders.

Adverse role of rising adiposity levels on the CHD and T2DM time trends

A further implication of the results of chapters 5 and 6 is the apparent counter-productive role of rising adiposity levels on the time trend in major CHD incidence. While the negative contribution of rising adiposity over recent decades appears to have been outweighed by the favourable trends in other coronary risk factors, the concern is that continued increases in adiposity may further reduce or even reverse the decline in major CHD incidence. Indeed there may already be some evidence of this phenomenon within the younger age groups, predominantly affected by rising obesity levels in early adult life and younger[9, 407] and among whom CHD incidence is falling at a slower rate, while CHD mortality rates (previously falling) may already be plateauing[52-54]. The results in chapter 8 show further the appreciable contribution of rising adiposity levels to the unfavourable rise in T2DM incidence, and, as shown in chapter 9, the rise in adiposity may have influenced the time trend in major CHD mainly through increasing in the incidence of T2DM. The relatively modest improvements in SBP and non-HDL cholesterol may also have been influenced by the unfavourable secular increase in adiposity levels, which is an important determinant of these clinical factors. That is, non-HDL and SBP may be pathways by which adiposity is restricting the decline in CHD. This emphasizes the need to address rising adiposity levels in the UK, and suggests that by controlling adiposity levels, there may be considerable potential for reducing levels of chronic disease in the population.

Chapter 8 also revealed however that rising adiposity levels alone do not appear to fully account for the rise in T2DM incidence. This is somewhat counterintuitive to

current perspectives; the public health messages in the media tend to focus on rising T2DM levels being linked to the growing obesity epidemic and that reducing obesity levels is the principal requirement for curbing the rise in T2DM. Instead, the results of this analysis suggest that other factors (for example diet) may be independently contributing to the rise in T2DM. In which case, broader public health interventions may be appropriate. For example, dietary factors associated with reducing T2DM risk include a high fibre diet[192, 195], and daily consumption of fibre declined between 1987 and 2000[376]. Also, the possible adverse impact on T2DM risk of certain drugs indicated for other conditions warrants further investigation[174, 385]. The presence of other contributing factors would suggest the need for a more multi-factorial approach to combat rising T2DM in the population.

Relationship between T2DM and major CHD trends

In chapter 9 it was shown that the excess risk of a major CHD event among patients with T2DM compared to those without may have been attenuated to a degree over time. The results indicate a modest success story, which may in part reflect improved management and treatment of T2DM patients[342]. Despite the attenuation of the relative risk, patients with T2DM remain at approximately double the risk of major CHD than those without T2DM. Thus there is still much room for improvement and a need for continued concerted efforts to manage T2DM. The need to better manage CHD risk in patients with T2DM is further emphasized by the increase in incidence of T2DM over time. Thus although the relative risk of CHD in those with and without T2DM has attenuated, as more patients develop T2DM, the proportion of all patients experiencing a major CHD event who have T2DM is likely to increase – that is, the

absolute contribution of T2DM to risk of a major CHD event is set to rise, as already demonstrated in the US population[395, 400].

Summary

In summary, the findings show that the rising T2DM prevalence in the UK reflects, at least in part, rising incidence, which warrants urgent attention. While CHD mortality rates are falling, in line with a decline in major CHD incidence, comparable declines are not occurring among all socio-demographic groups. There is some evidence of widening socio-economic inequalities in CHD incidence and in T2DM incidence that need to be addressed. The CHD trends appear to have been less favourable in younger groups, which suggests the potential for future resurgence of major CHD and that, despite the success in reducing CHD incidence and mortality to date, public health policy focus should not shift away from CHD. Public health policy to reduce CHD should include population-wide measures to improve the major modifiable coronary risk factors, which have considerable potential for reducing CHD incidence. In particular, a priority is to address the rising population adiposity levels, which appear to have had an appreciable adverse impact, both limiting the scale of the decline in major CHD incidence, and contributing appreciably to the rising T2DM incidence. Management of patients with T2DM is another important public health consideration, to reduce the continued substantial excess risk of major CHD among patients with T2DM, and in turn, prevent rising T2DM from curbing the decline in major CHD incidence.

10.2.2 Implications for other countries

As discussed in chapter 2, in line with the trends in major CHD in the UK, declines in CHD mortality and major CHD incidence have also been observed in North America[252, 254, 263] and other countries in Western Europe[249-251, 253, 255, 264], Australasia[265, 266] and Japan[267]. In contrast, in other regions of the world (Asia[10, 11], Eastern Europe[268]), in predominantly low and middle-income countries, CHD mortality rates have not been declining, and appear to even be increasing, leading to a growing CHD healthcare burden. The unfavourable rising CHD burden (along with other non-communicable diseases) in these countries is seen to reflect the phenomenon of "epidemiological transition" from the burden and priority of communicable diseases to non-communicable diseases[269, 270]. The extent of transition differs between countries; countries such as China and India, and parts of Eastern Europe are currently transitioning and as such are experiencing increased CHD mortality rates. Some countries in Sub-Saharan Africa are yet to transition and may be faced with a sizeable CHD burden in the future[273]. It has been estimated that the number of CHD deaths worldwide may almost double between 1990 and 2020[270]; CVD is already the leading cause of death worldwide and the third highest cause of disability[274].

Chapter 2 also highlighted the growing global prevalence of diabetes (primarily T2DM)[282-284]. Increases have been observed in many countries in both the developed and developing world. Current (2010) global prevalence is estimated to be 6.4% (285 million diabetic individuals) and predicted to rise to 7.7% in 2030, corresponding to 622 million people with diabetes[283]. India, China and the US come out top in terms of numbers of people with diabetes, while the Middle Eastern countries tended to have

the highest prevalence rates (estimated to be over 20% in the United Arab Emirates by 2030, and over 15% in Kuwait, Bahrain and Saudi Arabia)[283]. The projections are based primarily on the changing population demographics (population growth, ageing populations and urbanisation[285] being particularly implicated in the estimated increased prevalence rates). If adiposity or other aetiological factors are contributing to the rise in T2DM, the projected rates are likely to be underestimates.

The growing burden of CHD in other countries, and worldwide increase in T2DM prevalence, emphasizes the potential value of understanding and exploring the reasons for the trends in these conditions in the UK, as a means to inform how to reduce the burden of chronic disease in other countries. The thesis findings indicate that in the UK, favourable risk factor trends have made an important contribution to reducing major CHD incidence. This suggests that control of the major modifiable coronary factors (smoking, blood pressure and blood lipids including both HDL and non-HDL cholesterol) could also help to reverse the rising CHD epidemics in other countries.

Extrapolation of the results of the risk factor influences to trends in other populations however needs to be cautious. The potential benefit of favourable risk factor trends on the trends in incidence of major CHD and T2DM is likely to vary depending on initial levels of the risk factors, and the strength of the association between the risk factor and CHD or T2DM in the population. Considering the findings from studies worldwide analysing trends in CHD mortality (predominantly involving synthesis of aggregate data and dominated by the IMPACT model studies[249-255, 276]), where a decline in CHD mortality has occurred, risk factors have consistently tended to make a larger contribution than treatments. Three of the established major aetiological

exposures – cigarette smoking, blood pressure and total cholesterol - feature in most analyses, and favourable changes in these factors have made contributions to the CHD mortality declines in most of the countries. However, the relative size of the contribution of each of these factors appears to vary between populations. In the UK, declining smoking made a substantially larger percentage contribution (about 40%) to the CHD mortality decline than the other factors[12, 15], in line with the BRHS findings for major CHD incidence. While smoking also made important contributions to the mortality declines in Ireland[250] and Iceland[249] (>20%), the contribution of falling cholesterol levels in these populations was as high, if not higher (about 30%). In other Nordic countries (Finland[253] and Sweden[251]) the role of cholesterol was even larger (about 40%), relative to smoking and blood pressure. In the US[252] , Canada[254] and Italy[255], cholesterol was also the most important factor (almost 25% of the mortality decline explained), but blood pressure also made an appreciable contribution (~20%), compared to a more modest contribution from smoking (about 10%). Finally in Australasia, blood pressure tended to be the most influential[266, 296, 297]. Although predominantly populations of European origin, there will be some variations in ethnicity between populations and it has been suggested that there may be interactions between risk factors and genetic influences[270], such that the size of the risk factor associations could vary between different ethnic groups. However, other studies have shown that in fact the associations of these risk factors are broadly comparable between ethnic groups and populations[100, 103, 143]. An assumption of such comparability is made in the IMPACT studies, in which the estimates of the risk factor associations incorporated in the models applied to different populations are largely derived from the same studies anyway and so assumed to be same. The variations in the risk factor contributions to the CHD mortality declines between

countries are therefore more likely to reflect the different sized trends in the risk factors – where smoking levels have declined most dramatically, smoking is likely to have made the greatest contribution to the CHD mortality decline. Variations in the risk factor trends could reflect the different time periods covered, different starting levels of the risk factors and also different health policies, focussing on controlling different risk factors. For example, in Finland, concerted efforts have been made to improved diet in the population, as part of public health interventions such as the North Karelia Project, to reduce the very high CHD levels[368-370], and declining blood cholesterol was estimated to make the largest risk factor contribution to the CHD mortality decline in this population. Meanwhile, in the UK, where smoking made the greatest contribution, emphasis in the past has been on reducing the previously high smoking prevalence.

Ultimately, the overall broad comparability of the findings of the risk factor and treatment contributions to CHD *mortality* trends in the different countries, and the similarity in the associations of the risk factors with CHD between populations, suggests that the findings from the present study on *incidence* may be applicable to other countries. That said, the majority of the studies above on CHD mortality are of developed countries. The extent to which the results may be extrapolated to low or middle-income countries is less certain. There are factors unique to lower and middle income countries, such as urbanisation, and the political and economic environment, which may influence the extent of risk factor changes and so CHD incidence, and which therefore, which need to be taken into account[274]. Public health measures to prevent major CHD events through risk factor changes which work in one setting may not necessarily be applicable to another setting. While use of blood pressure lowering

medications or lipid-regulating medications may contribute to lower blood pressure and lipid levels in the UK, dispensing of such medications in lower or middle income countries may be limited by lack of infrastructure or prohibitive costs[274]. Instead, population level interventions such as tobacco control (for example the successful total ban in Bhutan[408]) or restrictions of levels of "hidden" dietary salt intake are seen to be more feasible measures to implement[274].

The adverse role of rising adiposity on the time trends in major CHD and T2DM incidence in the UK serves to emphasize the potential implications of rising adiposity worldwide, and the need to address worldwide obesity levels to reduce major CHD and T2DM incidence. This is particularly concerning for lower and middle income countries in which it is unlikely that the healthcare systems will have the necessary resources to provide the level of cardiovascular preventive treatment (particularly statins and blood pressure lowering medications) needed to compensate for the increasing prevalence of overweight and obesity already taking place.

10.3 Implications for epidemiology and epidemiological research

10.3.1 Epidemiological implications

The general approach in this thesis has been to make inferences about the role of different risk factors on the time trends in major CHD and T2DM, under the assumption of an aetiological association between the factors and CHD and T2DM. From an alternative perspective, the results themselves may be seen to provide further evidence of the size and extent of aetiological associations. The findings that declining blood pressure and lipid levels, and declining smoking may explain falling major CHD incidence, lends further support for the widely held assumption that these

relations are causal, particularly though showing reversibility (that reducing risk factor levels reduces CHD risk), which was highlighted in the original Bradford-Hill criterion for causality[409]. The finding that rising BMI is consistent with explaining one quarter of the rise in T2DM supports previous findings on the extent of the association between adiposity and T2DM risk, from studies assessing PARFs of adiposity in T2DM, which have reported PARFs similar in size[178, 181].

Moreover, the thesis findings provide further evidence that the effects of risk factor levels on CHD risk may be realised to some extent in a relatively short time-frame, supporting the small number of existing studies addressing time-lags to date[356-358]. That is, given the structure of the analysis, risk factor levels could be related to major CHD and T2DM risk within five years and eight years respectively of the risk factor exposure (the time between subsequent questionnaire time-points in the BRHS). This limited lag time modelled between the trends in the risk factors and trends in major CHD or T2DM indicates that changing risk factor levels may have a relatively immediate impact on subsequent major CHD or T2DM risk.

10.3.2 Lessons learnt from research methods

The principal method used to carry out the research for this thesis was statistical analysis of data from a combination of different data sources: two cohort studies of cardiovascular disease, with established follow-up, and a database of routinely collected general practice longitudinal data. The analyses were all carried out at the individual level, that is, relating an individual's risk factor exposure to their subsequent major CHD or T2DM risk, as opposed to ecological analyses. Key strengths and pitfalls of the methods, identified through the course of carrying out the

research, are discussed in this section. Suitable approaches for conducting related research in the future, based on the lessons learnt, are also considered.

Appropriateness of data sources

The first issue considered is the appropriateness of the data sources. For the main analyses in chapters 5, 6 and 8 (estimating the contributions of trends in aetiological exposures to trends in major CHD and T2DM), the benefits of the using the established BRHS and Whitehall II cohort studies are clear. These include the continuous and near-complete follow-up over an extended period for CHD and T2DM events and mortality, and the detailed information on aetiological exposures and medication use, recorded at repeated intervals. A particular strength here is that the risk factor (exposure) data has generally either been consistently collected or validation studies to compare the different ascertainment techniques have been possible (chapter 3), limiting bias in the estimates of the time trends in the risk factors and their roles in the trends in major CHD and T2DM.

The use of the BRHS and Whitehall II cohort studies for this research is not however without limitations. Numbers of events for some analyses are limited, and some of the confidence intervals (CIs) for the estimated risk factor contributions to the disease trends are very wide, indicating limited statistical power and precision. This is particularly evident in sub-group analyses, for example stratified by gender. Second, the representativeness of each cohort is limited by its restriction to certain sections of the UK population (BRHS comprises only men, while Whitehall II is restricted to men and women employed in the Civil Service in London). Further, in both the BRHS and Whitehall II cohorts, the participants are now reaching old age. This

renders the cohorts increasingly important data sources for the study of the health of the elderly (an area of medical research of growing importance, given the ageing of the UK population), especially since there are few other suitable data sources of comparable size. However, while the cohorts have proved suitable for the study of (and reflective of) UK time trends up to now (while the cohort participants were middle-aged), for future investigations of time trends, a younger sample of people may be preferred, as the results would provide a better indication of the future burden of disease, and because it is the apparent slowing of the decline in the CHD epidemic in the younger population that especially warrants further investigation.

Large well-conducted nationally representative cohort studies, which share the strengths of the BRHS and Whitehall II cohorts, but with younger age ranges, would therefore ideally be suited to future analyses of this type. However the availability of such data sources, with repeated risk factor information, and follow-up for CHD and T2DM, is limited, while the cost of setting-up and managing cohorts may act as a barrier to the formation of new suitable and sizable cohorts. An alternative is to consider the use of routinely collected data, such as The Health Improvement Network (THIN) primary care database. Other examples include similar primary care databases, such as the General Practice Research Database (GPRD) and QRESEARCH, hospital data from the Health Episode Statistics (HES), and disease registries. The notion of a very large amount of health-related data on the UK population, already available and being collected, is an exciting research prospect. Often, as in the case of the THIN database and other primary care databases, the data source comprises historical information while also being dynamic and continually updated, so that up-to-date data is also available. The data is also often at the

individual level, and longitudinal in nature, enabling individuals to be followed over time, and nested cohorts may be constructed from the data. Further, in the case of THIN (but also some of the other routine sources), key strengths are the very large number of patients contributing data, enabling precise estimation, and the nationwide scope, encompassing men and women of all ages, regardless of health status, and so including those (typically most vulnerable) groups of patients frequently ineligible to participate in randomised controlled trials and cohort studies. Thus the findings may be widely applicable and generalisable, and the data seen to be a reflection of current UK practice. Therefore tapping into routine data sources may yield considerable research potential.

The key drawback lies in the very essence of being routinely collected data, obtained primarily to assist with the day-to-day care of patients, and not collected specifically for research purposes. The implication is that the data is subject to incompleteness and inaccuracies, and there may be a lack of uniformity in how the data is entered (for example variations between practices). Also, with no choice over the data being collected, it may be that certain variables and factors of interest are simply not available at all. In addition, the format of the data is such that it generally presents formidable programming and data management challenges. Using the THIN data for this thesis (for the other more descriptive analyses) has made me aware of the great care and effort needed to prepare the data, extract the appropriate information, and make the data suitable for analysis. Challenges include defining the group of patients within the database for study, establishing time periods over which to follow patients, and defining outcomes of interest (through development of lists of Read diagnosis codes). In the THIN database, while diagnoses and prescriptions are generally well

recorded, opportunities for epidemiological or aetiological research have been limited so far by a lack of (timely) information on exposures. For example, in the case of the research in this thesis, the limited data on coronary and diabetic risk factors (smoking, adiposity, blood pressure, blood lipids etc), prohibited carrying out analyses comparable to those using the BRHS and Whitehall II cohorts, to explain disease trends. Instead, studies using THIN data to date tend to be mainly concerned with describing patterns of disease[410-412] (for example, describing disease trends as in chapter 4), or analysing health service use[313, 413]. However, while use of routine data may have been limited in the past, recent improvements in the collection of the data, and developments in the methods to handle the data, make the prospects for future research much more promising. In particular, as regards THIN and other primary care databases, the introduction of the Quality and Outcomes Framework (QOF) in the early 2000s, which includes specification of rewards for general practitioners for measuring and recording health indicators such as smoking status, has led to more complete and regular recording of these factors in the last few years. There is also a growing body of methodological research work on methods to manage and handle routine data, such as imputation of missing data[414], and identification of outliers[415] (to distinguish between extreme true values of continuous factors such as blood pressure, and mis-recorded erroneous data). Therefore routine data sources may prove a more and more useful resource in the future for epidemiological research in general, and it may subsequently be possible to carry out analyses of time trends in a manner similar to that used in the thesis on the BRHS and Whitehall II cohorts.

Arguably superior to using either a suitable cohort study or a routine database for subsequent research would be to use a combination of different data sources. One

option is for analyses to be repeated in different data sources, as in this thesis, where the analysis of major CHD incidence trends in the BRHS are replicated in the Whitehall II cohort. Consistent results from each data source increases confidence in the validity and robustness of the findings. Further, if only certain sections of a population are captured in one cohort/ data source, use of other data sources, representative of different sections of the population, enables the results to be generalised to a wider range of people. An alternative would be to be able to combine data from the different data sources at the individual level, on a patient-by-patient basis. That is, if certain information is not captured in a routine database, linkage to other data sources may enable additional information on a patient to be incorporated, thereby broadening the scope of possible analyses. For example, in the THIN database, for the analysis in this thesis, limited linked information, related to the patient's postcode, was available, enabling inclusion of area deprivation in the analyses. In the future, it is going to be possible to link THIN data to other data sources, such as the HES data or disease registries. Linkage to HES is an especially exciting prospect as it would entail combining primary and secondary care data, enabling tracking of a patient's care though both domains. A noted limitation of the analyses in this thesis is that the role of secondary care (such as surgical interventions) in the major CHD time trends could not readily be assessed – a linked database of primary and secondary care could then prove a rich source of data for analysis.

Use of individual-level analyses

The above discussion assumes the need for an individual-level analysis. As well as the choice of data sources for the different analyses, a second key methodological consideration in this thesis was the use of an individual-level analysis, over synthesis

of aggregate data sources, more often used to study time trends. As the data available allowed for an individual-level analysis, this method was chosen as it avoids ecological limitations, as outlined in chapter 2, section 2.6.1.3, thereby giving more confidence in the results and that the associations seen are true and not ecological fallacy. While an individual level analysis may still be the preferred means of analysis, it is worth noting (as shown in chapter 5, section 5.5.2) the broad consistency of the findings from the present analysis of CHD trends to those from the IMPACT model for Scotland and for England and Wales[12, 15], which are based on synthesis of aggregate data sources. Thus the thesis findings also serve to support and confirm the results of IMPACT and thereby suggest that ecological studies/ synthesis studies of this type in other populations may also be valid. This is reassuring, especially for populations/ countries where this type of group-level (ecological) analysis may be more readily carried out than an individual-level analysis, due to a lack of suitable individual level data resources.

Appropriateness of central statistical analyses methods

The central analyses carried out in the thesis were those relating the time trend in major CHD to the time trends in aetiological exposures in the two cohorts. The analysis is an adaptation of that used by Hu *et al* to examine time trends in major CHD incidence in the US Nurses Health Study[17]. The analysis methods used are described in detail in chapter 5, section 5.2.4. The strengths of the analysis include i) the fit to the format and extent of available data, making use of the repeated measures of the aetiological exposures in the cohorts, ii) the ability to distinguish between calendar trends and trends with age due to the ageing of the cohort, iii) that risk factor levels at each time-point are related to subsequent CHD incidence, thereby limiting

reverse causal mechanisms, and iv) that the analyses lead to "percentages explained" by each risk factor, such that the extent of the contribution of each risk factor to the CHD trend relative to each other may be quantified. The use of bootstrapping to derive CIs for the percentage explained estimates further enables estimation of the uncertainty around each estimate, which was not reported in the study by Hu *et al*.

Within the confines of this thesis, there is only space to consider certain aspects of time trends, and certain ways to model time trends. There are certainly other aspects of time trends not considered here and other analyses of time trends that may be carried out, such as exploration of cohort effects. The next section highlights some of the potential areas for further related research, towards a fuller understanding of chronic disease time trends.

10.3.3 Suggestions for further research

This thesis presents recent trends in the incidence of major CHD and T2DM and then goes some way towards explaining the trends seen. The relationship between the two incidence trends is also explored. However it is too broad a topic to be feasible to cover all aspects of the CHD and T2DM time trends in this thesis and as such there remain some unanswered questions. In addition new questions have arisen as a result of the findings. In this section, areas for further research, towards addressing these questions, are summarised.

Verification of observed incidence time trends

The results of chapter 4 showed a decline over time in incidence of major CHD in the UK, and a concurrent rise in T2DM incidence. It was discussed in section 4.6.5.1

that, while changes in diagnostic criteria for major CHD had occurred during the time-period of analysis, these changes are unlikely to have had a substantial impact on the major CHD incidence trends. For T2DM however, the situation may be somewhat different. While the rise in T2DM incidence in the 1990s may be seen to be independent of changes in case ascertainment or diagnostic criteria, beyond 2000, the extent to which the rise in incidence observed reflected changes in case ascertainment or diagnostic criteria was less certain. An important area for future research will be to try to disentangle the effects of changes in ascertainment and diagnostic criteria from estimates of the most recent T2DM incidence trends, to provide objective estimates of the extent of an epidemiological change in the population. One way to do this would be through analysis of data from a cohort, for whom blood glucose levels have been measured at repeated intervals over time (by the study personnel and using consistent methods each time). In this way incidence of T2DM may be ascertained from the blood glucose levels, unaffected by case ascertainment (no undiagnosed cases) and changes in diagnostic criteria (same methods used throughout; no reliance on GP diagnosis). With appropriate adjustment for the ageing of the cohort as in the thesis analyses, an unbiased trend in incidence of T2DM may be obtained. Repeated blood glucose measurements were not available in the BRHS data at the time of analysis. However, new glucose measurements are currently being taken in a 30-year follow-up examination, which, combined with one existing measurement, will make such an analysis a possibility in the future.

Prediction of future time trends

In chapter 4 recent past trends in major CHD and T2DM incidence were estimated, from which the current disease burden may be inferred. The analyses could be

extended to model and make predictions about future trends, in order to gauge future disease burden, which (if carefully interpreted) could help to inform future policy regarding health care provision. Such analyses are beyond the scope of this thesis. In the case of CHD, a particular priority would be to analyse and model future trends among younger men and women, to assess the future impact of the apparent slowing of the favourable CHD decline in this section of the population. In the case of T2DM, there are already some studies to date which have sought to predict future prevalence worldwide[7, 282-284, 286-288]. However most studies base future prevalence estimates on projected changes in the age-gender population structure alone, and do not take into account other factors such as rising obesity and therefore may underestimate the future disease burden. Further studies are needed which do incorporate likely future trends in adiposity, given the observed association between the adiposity and T2DM trends described here[286, 287].

Further exploration of socio-demographic variations in the time trends

Secondary analyses in chapter 4 revealed potentially widening socio-economic inequalities in major CHD and T2DM incidence over time. Further analyses would be useful to confirm these findings. The lack of data on ethnicity in THIN, and the predominantly white European ethnicity of the BRHS and Whitehall II cohort populations prevented study of time trends in incidence according to ethnicity. Given the variation in incidence rates by ethnicity, and observed variations in the trends in CHD mortality and T2DM prevalence by ethnicity[62, 73], outlined in chapter 2, sections 2.2.1.3 and 2.3.1.3, assessment of trends in incidence by ethnicity would also be of value.

Investigating the "unexplained" portions of the time trends

In subsequent chapters 5 and 6 it was estimated that a substantial portion (around 50%) of the decline in major CHD incidence may be attributed to trends in the measured major aetiological exposures. However, at the same time, an appreciable part of the incidence decline was not accounted for by risk factor changes. Further research is therefore needed to understand the reasons for this unexplained portion of the decline. The roles of factors not considered in this analysis, particularly hospital interventions, or early life and life course influences, need to be evaluated. Given the limited accuracy of self-reported dietary patterns and physical activity levels in questionnaires (the ascertainment methods in the two cohorts), further analyses using more objective measures of diet and physical activity to reassess the roles of trends in these factors would be of value, for example by means of pedometers or actigraphs for physical activity. The results from analyses stratified by gender and socio-economic status had limited precision due to a lack of power, and therefore need verifying through further research. In addition, subject to the availability of large enough population samples, comparable analyses of the time trends in incidence stratified by age group would be useful to understand why the decline in CHD appears to have been less marked in younger age groups.

In chapter 8 it was shown that one quarter of the rise in T2DM incidence could be attributed to rising BMI levels. This is apparently the first analysis of this kind. Further time trend studies in other populations are therefore needed to verify the findings and uncover reasons for the unexplained portion of the increase in incidence. In particular, studies with more precise measures of adiposity would be valuable.

Additional related research

Further research is also needed to identify the reasons for the attenuation of the excess risk of major CHD among T2DM patients (as identified in chapter 9) and establish whether the favourable change reflects the better management and treatment of T2DM or changed diagnosis and improved case ascertainment.

Suggestions for related research include investigation of the reasons for the trends in the contributory aetiological exposures. Chapter 7 addressed to an extent the reasons for the trends in blood pressure and lipid levels. It would also be of value to establish what have been the key drivers (including social, political and health policy influences) behind the trends in the other factors, in particular the smoking decline, and adiposity increase, to help inform future health policy.

Another suggestion would be to carry out age-period-cohort analyses to try to disentangle the effects of each of these factors on the overall time trends observed. In the present analyses, it is assumed that birth cohort effects are minimal; instead, changes over time in incidence are assumed to reflect age and period effects only. This is arguably a reasonable assumption as birth cohort effects have been shown to have limited influence on contemporaneous CHD and T2DM trends[52, 145-147, 217]. However it would be worth carrying out analyses to confirm the influence (or lack thereof) of birth cohort effects, which may in turn imply the influence of early life influences on the incidence trends.

Methodological research into how best to analyse time trends would also be useful. In addition, certain aspects of the current modelling methods warrant investigation,

which may improve future analyses of this type. For example, further research is needed to evaluate the extent of the time-lags between aetiological exposures and subsequent major CHD or T2DM risk[356-358]. The analyses of the time trends in major CHD incidence assumed only modest lag times between the aetiological exposures and major CHD incidence. The analyses of the time trends in T2DM incidence considered longer lag times. The predicted contributions of each exposure to the time trends from the models will depend on the time-lag allowed; the largest estimated contribution obtained when the correct lag time is incorporated in the model. The models may have underestimated the contributions of risk factors if an incorrect lag time is assumed.

Finally, this thesis considers time trends in major CHD and T2DM incidence, as contributing to the time trends in CHD mortality and T2DM prevalence. As discussed in chapter 2, time trends in case fatality following a major CHD event or in relative survival of patients with T2DM, may also have influenced the CHD mortality and T2DM prevalence trends. Therefore a logical next step in research would be to examine the time trends in major CHD case fatality and T2DM relative survival. In addition, this thesis research could be followed by analyses of time trends in other related conditions such as stroke and heart failure.

10.4 Concluding statement

Recent public health headlines in the UK have included the dramatic decline in CHD mortality in recent decades, and the contrasting apparent rise in T2DM prevalence. This thesis provides evidence of a contemporaneous decline in major CHD incidence and a contemporaneous rise in T2DM incidence, which have contributed to the CHD

mortality and T2DM prevalence trends. Analyses reveal that favourable time trends in major modifiable aetiological exposures (smoking and blood pressure and lipid levels) may explain much of the decline in major CHD incidence. Conversely, a rise in adiposity levels has had an adverse impact, limiting the scale of the decline in major CHD incidence, and explaining an estimated one quarter of the rise in T2DM incidence. The analysis of the decline in major CHD incidence highlights what can be achieved, and emphasizes the potential of population-wide public health measures to reduce exposure to modifiable risk factors to in turn reduce incidence of major CHD (and by extension CHD mortality rates). The results showing the sizeable adverse effects of adiposity underlines the urgent need to address rising obesity levels in the UK as well as in other countries, to reduce the future burden of these chronic diseases.

Appendix A Lists of Read codes to identify disease cases in The Health Improvement Network Database

A.1 Read codes[312] in THIN indicating forms of diabetes leading to exclusion from analysis of time trend in T2DM incidence:

Read code	Description
C10B.00	Diabetes mellitus induced by steroids
C10B000	Steroid induced diabetes mellitus without complication
C10H.00	Diabetes mellitus induced by non-steroid drugs
C10H000	DM induced by non-steroid drugs without complication
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10N.00	Secondary diabetes mellitus
C10N000	Secondary diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A200	Malnutrition-related diabetes mellitus with renal complicatn
C10A300	Malnutrit-related diabetes mellitus wth ophthalmic complicat
C10A400	Malnutrition-related diabetes mellitus wth neuro complicatns
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10A600	Malnutrition-related diabetes mellitus with multiple comps
C10A700	Malnutrition-related diabetes mellitus without complications
C10AW00	Malnutrit-related diabetes mellitus with unspec complics
C10AX00	Malnutrit-relat diabetes mellitus with other spec comps
Cyu2100	[X]Malnutrit-relat diabetes mellitus with other spec comps
Cyu2200	[X]Malnutrit-related diabetes mellitus with unspec complics
C10J.00	Insulin autoimmune syndrome
C10J000	Insulin autoimmune syndrome without complication
C10K.00	Type A insulin resistance
C10K000	Type A insulin resistance without complication
C10L.00	Fibrocalculous pancreatopathy
C10L000	Fibrocalculous pancreatopathy without complication
C10M.00	Lipoatrophic diabetes mellitus
C10M000	Lipoatrophic diabetes mellitus without complication
L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
L180000	Diabetes mellitus - unspec whether in pregnancy/puerperium
L180100	Diabetes mellitus during pregnancy - baby delivered
L180200	Diabetes mellitus in puerperium - baby delivered
L180300	Diabetes mellitus during pregnancy - baby not yet delivered
L180400	Diabetes mellitus in pueperium - baby previously delivered
L180800	Diabetes mellitus arising in pregnancy
L180811	Gestational diabetes mellitus
L180900	Gestational diabetes mellitus
L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium NOS
ZC2CB00	Dietary advice for gestational diabetes
66An.00	Diabetes type 1 review
C100000	Diabetes mellitus, juvenile type, no mention of complication
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma

C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108111	Type I diabetes mellitus with ophthalmic complications
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108311	Type I diabetes mellitus with multiple complications
C108312	Type 1 diabetes mellitus with multiple complications
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108611	Type I diabetes mellitus with gangrene
C108612	Type 1 diabetes mellitus with gangrene
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A11	Type I diabetes mellitus without complication
C108A12	Type 1 diabetes mellitus without complication
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C108D11	Type I diabetes mellitus with nephropathy
C108D12	Type 1 diabetes mellitus with nephropathy
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F11	Type I diabetes mellitus with diabetic cataract
C108F12	Type 1 diabetes mellitus with diabetic cataract
C108G11	Type I diabetes mellitus with peripheral angiopathy
C108G12	Type 1 diabetes mellitus with peripheral angiopathy
C108H11	Type I diabetes mellitus with arthropathy
C108H12	Type 1 diabetes mellitus with arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C10C.12	Maturity onset diabetes in youth type 1
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E011	Type I diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E200	Type 1 diabetes mellitus with neurological complications
C10E211	Type I diabetes mellitus with neurological complications

C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED11	Type I diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF11	Type I diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EG11	Type I diabetes mellitus with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EK11	Type I diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10y000	Diabetes mellitus, juvenile, + other specified manifestation
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
ZC2C900	Dietary advice for type I diabetes

A.2 Frequencies of Read codes[312] for incident major CHD in THIN by calendar year (patients aged 30 to 100 years):

Medcode	Description	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	All years
G30..00	Acute myocardial infarction	492	690	930	1030	1050	1379	1516	1624	1660	1654	1424	1292	1103	1006	16850
G30..15	MI - acute myocardial infarction	8	65	123	225	355	616	855	1168	1263	1083	901	750	672	573	8657
G30z.00	Acute myocardial infarction NOS	642	490	397	379	357	366	347	308	329	284	214	195	164	120	4592
G307100	Acute non-ST segment elevation myocardial infarction					1		4	4	101	276	446	679	891	1039	3441
G308.00	Inferior myocardial infarction NOS	5	27	40	74	105	113	115	113	114	118	114	104	92	77	1211
G30X000	Acute ST segment elevation myocardial infarction									9	33	93	172	241	302	850
G307.00	Acute subendocardial infarction	20	13	25	18	32	43	39	32	14	3	10	4	3	4	260
G301z00	Anterior myocardial infarction NOS		4	5	5	6	12	25	23	39	29	30	29	15	19	241
G30..12	Coronary thrombosis	14	11	18	18	26	29	13	32	20	10	8	12	6	3	220
G301.00	Other specified anterior myocardial infarction		4	4	10	11	19	21	24	26	17	6	14	18	10	184
G30..14	Heart attack	8	15	18	19	14	15	12	13	10	11	6	11	13	9	174
G307000	Acute non-Q wave infarction		1			1	9	30	39	25	7	9	4	3	6	134
G300.00	Acute anterolateral infarction			5	10	12	13	15	11	13	9	11	14	11	4	128
G302.00	Acute inferolateral infarction		1	3	5	11	11	16	13	12	10	13	10	9	12	126
G301100	Acute anteroseptal infarction		1	3	5	13	12	8	13	18	10	10	11	3	9	116
G304.00	Posterior myocardial infarction NOS		1	6	4	2	4	7	5	6	7	6	6	5	4	63
G30..17	Silent myocardial infarction				2	5	3	9	6	4	13	6	2	4	5	59
G30..16	Thrombosis - coronary		1	3	3	7	6	4	9	3	8	4	7	2	1	58
G303.00	Acute inferoposterior infarction			1	2	3	4	3	2	4	9	6	10	4	2	50
G305.00	Lateral myocardial infarction NOS			2	4	1	5	4	1	4	5	4	2	5		37
G30yz00	Other acute myocardial infarction NOS						7	4	2	5	3	6	6		1	34
G360.00	Haemopericardium/current comp folow acut myocard infarct		2	2	2	6	5	6	4	2	2	1	1	1		34
G38..00	Postoperative myocardial infarction				2	3	3	2	2	4	2	4	2	4	4	32
ZV71900	[V]Observation for suspected myocardial infarction			4	4	5	4	2	3	2	3	3	2			32

G310.11	Dressler's syndrome	1		2		4	1		3	1	9		4	3	3	31
G30A.00	Mural thrombosis					1	3	1	2	3	3	3	1	6	5	28
G30..13	Cardiac rupture following myocardial infarction (MI)		1	3	2	2	3	6	2	2	3	2			1	27
G30y.00	Other acute myocardial infarction					1	5	1	2	5		1	2	2	2	21
G30X.00	Acute transmural myocardial infarction of unspecif site		3	1	3	3	2	2	1	3					3	21
G35..00	Subsequent myocardial infarction			1	2				2	2	3	2	3	2		17
G30y200	Acute septal infarction			1		1		3	2	3		1	2	2	2	17
G310.00	Postmyocardial infarction syndrome				2					4	5					11
G309.00	Acute Q-wave infarct							1	3			3	2	1		10
G30..11	Attack - heart			1	1	1		1	1	1				1		7
G350.00	Subsequent myocardial infarction of anterior wall		1				1		1				2		1	6
G30y000	Acute atrial infarction			1		1		1	2			1				6
G301000	Acute anteroapical infarction					1	1						2	1		5
G30B.00	Acute posterolateral myocardial infarction										2	3				5
G306.00	True posterior myocardial infarction				1										2	3
G311000	Myocardial infarction aborted							1	1		1					3
G381.00	Postoperative transmural myocardial infarction inferior wall								2		1					3
G36..00	Certain current complication follow acute myocardial infarct							1	1					1		3
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn										1	1				2
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct			1								1				2
G38z.00	Postoperative myocardial infarction, unspecified											1			1	2
G384.00	Postoperative subendocardial myocardial infarction						1						1			2
G311011	MI - myocardial infarction aborted				1			1								2

G351.00	Subsequent myocardial infarction of inferior wall							1		1						2
G501.00	Post infarction pericarditis												1			1
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI				1											1

A.3 Frequencies of Read codes[312] for incident T2DM in THIN by calendar year (patients aged 30 to 100 years):

Codes include those relating specifically to T2DM, and codes for non-specific diabetes, assumed to indicate T2DM as patients are >30 years. Insulin-treated diabetes codes have been included as insulin, although predominantly associated with T1DM, may also be indicated for T2DM.

Medcode	Description	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	All years
C10F.00	Type 2 diabetes mellitus	174	263	435	590	934	1519	2253	3185	4375	5894	6748	7600	8375	8454	50799
C10..00	Diabetes mellitus	519	644	840	846	1094	1486	1785	1999	1657	1506	1251	786	581	675	15669
C109.00	Non-insulin dependent diabetes mellitus	42	65	97	176	262	482	764	912	747	472	359	197	97	75	4747
C100112	Non-insulin dependent diabetes mellitus	118	145	202	262	331	542	578	562	566	434	363	227	149	160	4639
C109.12	Type 2 diabetes mellitus	28	29	59	89	120	263	396	638	694	512	521	254	70	81	3754
66A3.00	Diabetic on diet only	21	27	30	53	81	107	116	124	110	84	62	43	46	48	952
C100111	Maturity onset diabetes	70	81	61	82	60	73	92	87	85	51	71	41	20	9	883
C109.13	Type II diabetes mellitus	1	5	2	8	15	25	75	52	49	17	21	8	9	3	290
66A4.00	Diabetic on oral treatment	2	3	4	17	11	28	43	30	30	27	18	14	15	11	253
C109.11	NIDDM - Non-insulin dependent diabetes mellitus				2	7	13	14	25	27	51	23	26	21	29	238
66A1.00	Initial diabetic assessment							8	10	27	24	24	30	31	24	178
C100100	Diabetes mellitus, adult onset, no mention of complication	12	14	14	8	11	18	13	6	11	16	9	6	2	3	143
C10F.11	Type II diabetes mellitus							2	3	9	6	5	15	33	26	99
C10FJ00	Insulin treated Type 2 diabetes mellitus		1	1	4	6	3	7	6	7	2	3	12	11	4	67
C108.00	Insulin dependent diabetes mellitus	3	1	1	5	7	11	6	11	8	4	2			2	61
C100011	Insulin dependent diabetes mellitus	3	3	5	8	7	9	6	2	6	6	1	3	1		60
66A5.00	Diabetic on insulin		3	11	3	5	4	5	3	5	5	2				46
C100.00	Diabetes mellitus with no mention of complication				7	6	2	4	1	4	2	2	2	6		36
66AQ.00	Diabetes: shared care programme					1	2		4	9	2	10	3	2	2	35
C101.00	Diabetes mellitus with ketoacidosis	1	3	1	2	5	3	3	3	2	1	4	1	3	2	34
C109J00	Insulin treated Type 2 diabetes mellitus			5	2	1	5	2	4	5	3		2	2	1	32
C10F900	Type 2 diabetes mellitus without complication					1	2	3		5	3	8	3	2	1	28
C108.11	IDDM-Insulin dependent diabetes mellitus				1	1		2	5	3	8	2		1		23

C10D.00	Diabetes mellitus autosomal dominant type 2										5	4	6	3		18
C10F911	Type II diabetes mellitus without complication										1	1		7	7	16
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus									1	1	4		3	2	11
C109900	Non-insulin-dependent diabetes mellitus without complication			1		1		3	3	1	1					10
C106.00	Diabetes mellitus with neurological manifestation						2	1				2	1	1	1	8
C10F700	Type 2 diabetes mellitus - poor control									1			1	1	2	5
C106.12	Diabetes mellitus with neuropathy						2			1	2					5
C10FN00	Type 2 diabetes mellitus with ketoacidosis					1							2	1	1	5
C102.00	Diabetes mellitus with hyperosmolar coma	1		1		1		1								4
C104.11	Diabetic nephropathy							2				1			1	4
C10FL00	Type 2 diabetes mellitus with persistent proteinuria												1	2	1	4
C105.00	Diabetes mellitus with ophthalmic manifestation	1						1		1						3
C100z00	Diabetes mellitus NOS with no mention of complication						1		1		1					3
66AV.00	Diabetic on insulin and oral treatment											1			1	2
C10C.11	Maturity onset diabetes in youth									1	1					2
C109700	Non-insulin dependent diabetes mellitus - poor control								1		1					2
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma									1		1				2
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria												1		1	2
C10F000	Type 2 diabetes mellitus with renal complications										1				1	2
C10F711	Type II diabetes mellitus - poor control														1	1
C107400	NIDDM with peripheral circulatory						1									1

	disorder															
C10E.12	Insulin dependent diabetes mellitus														1	1
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus								1							1
C10FB00	Type 2 diabetes mellitus with polyneuropathy									1						1
C10FJ11	Insulin treated Type II diabetes mellitus									1						1
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma											1				1
C10z100	Diabetes mellitus, adult onset, + unspecified complication										1					1
C104.00	Diabetes mellitus with renal manifestation			1												1
66AJ.11	Unstable diabetes					1										1
C10F311	Type II diabetes mellitus with multiple complications														1	1
C101z00	Diabetes mellitus NOS with ketoacidosis								1							1
C109J11	Insulin treated non-insulin dependent diabetes mellitus								1							1
C10F300	Type 2 diabetes mellitus with multiple complications														1	1
C109J12	Insulin treated Type II diabetes mellitus	1														1
C10F600	Type 2 diabetes mellitus with retinopathy						1									1
C107.12	Diabetes with gangrene					1										1
C108900	Insulin dependent diabetes maturity onset					1										1
C108800	Insulin dependent diabetes mellitus - poor control						1									1
C107.00	Diabetes mellitus with peripheral circulatory disorder						1									1
C10F611	Type II diabetes mellitus with retinopathy							1								1

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