We are living longer, but not healthier: evidence from the British birth cohorts and the Uppsala Birth Cohort Multigenerational Study

Dawid Gondek

A dissertation submitted in partial fulfilment

of the requirements for the degree of

Doctor of Philosophy

of

University College London.

Department of Social Science

Centre for Longitudinal Studies

University College London

March 26, 2020

Declaration

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

Abstract

Life expectancy has increased in the last decades of the 20th century and at the beginning of the 21st century, for instance, in the United Kingdom from 66.3 years in 1946 to 82.0 in 2015. However, the evidence on trends in other key health indicators, such as non-communicable conditions or disability, has been inconsistent.

The systematic review of 53 studies found no evidence for improvement in the age-standardised or age-specific prevalence of any of the studied major chronic conditions over the last few decades, apart from Alzheimer's disease. The evidence on trends in disability, expressed as prevalence or health expectancy was inconclusive.

In the secondary analyses of the 1958 and 1970 British birth cohorts, with the total sample of n=16,834, I found that the prevalence of multimorbidity was higher in the younger cohort: 24.3% vs 17.8% at age 42-48. Across both cohorts, early-life parental social class, birthweight, cognitive ability and body mass index at age 10/11, internalising and externalising problems at 16 were associated with multimorbidity at age 42-48. A higher prevalence of morbidity in younger birth cohorts was not limited to physical health. In the comparison across the 1946, 1958 and 1970 British birth cohorts (n=28,362), progressively younger birth cohorts had higher levels of mental health symptoms across adulthood.

Worsening health across progressively younger birth cohorts has also been observed in Sweden, in the analysis of the Uppsala Birth Cohort Multigenerational Study. Successively younger birth cohorts (1915-1972) had a higher prevalence of hospitalisation at overlapping ages, with inter-cohort differences emerging from early-

adulthood and increasing with age in absolute terms. Those with medium and low parental socioeconomic position (vs high) had respectively 13% and 20% higher odds of experiencing hospitalisation during the observation period (1989-2008)—when age, year-of-birth and gender were accounted for.

Hence, rising life expectancy has not translated into improving health and reduced hospitalisation, associated with non-communicable conditions, both in Great Britain and Sweden. This is likely to translate in greater demands on healthcare and public services.

Impact Statement

Rising life expectancy is undoubtedly one of society's greatest achievements. For instance, in the United Kingdom, life expectancy at birth increased from 66.3 years in 1946 to 82.0 in 2015 (1). In other countries, for instance, in Sweden—life expectancy at birth has increased by six years in the last five decades, whereas in the members of the Organization for Economic Co-operation and Development (OECD) by eleven years (2). However, one of its consequences is ageing of the population, with the proportion of those aged 80 years or older projected to increase by two and a half times between 2018 and 2100 in the European Union—from 5.6% to 14.6% (3). A progressively larger proportion of ageing population will lead to greater demands on the healthcare system and society in general. For instance, it will result in growing proportion of economically inactive individuals, which may require postponing retirement age and a greater adaption of workplace and environment. An important step in devising health policies aiming to improve population health is to understand historical trends in health, which have emerged alongside declining mortality. While the patterns in life expectancy have been well-studied, as historically it has been the main indicator of population health, trends in other health indicators are unclear.

This thesis shows that there is a clear increase in prevalence of non-communicable, mostly chronic conditions (e.g. diabetes, asthma, common mental disorders), with some conditions indicating stable prevalence (e.g. cancer, hypertension). Improvements have been found in very few morbidity outcomes, such as prevalence of Alzheimer's disease among older population and high blood pressure in mid-life individuals. Due to increasing life expectancy, only reduced morbidity in younger birth

cohorts can be considered as a positive scenario. Any other outcome translates into more years spent with morbidity during the life course and an increasing number of individuals experiencing morbidity in the population. Moreover, younger birth cohorts appear to experience higher rates of multimorbidity already in mid-life and are hospitalised at an increasingly younger age. This supports the assumption that the onset of morbidity happens at an earlier age in younger birth cohorts and emphasises the need for more preventative efforts, rather than merely focusing on treatment.

As higher rates have been observed across a range of morbidity outcomes, it is necessary to act on wider health determinants, likely to generally predispose to poor health. Such health determinants as parental social class, body mass index and cognitive abilities and mental health problems, particularly externalising ones, were found to be associated with mid-life chronic multimorbidity.

This thesis also found that individuals of disadvantaged background in childhood have been disproportionally affected by morbidity: in Great Britain—in form of multimorbidity in mid-life and in Sweden—expressed as hospitalisation throughout adult life. Reducing inequalities in health has been a priority for policy-makers in Europe in the last four decades. In Sweden, where the efforts to reduce the health gap have particularly intensive since the 1990s, inequalities have remained largely stable between the 1990s and late 2000s. In Great Britain, this health gap has not narrowed in mid-life between individuals born in 1958 compared with 1970. This emphasises that further efforts are needed in bridging the disparity between less and more advantageous groups of the population.

Table of Contents

Acknowledgements

Thank you to my primary supervisor Professor George B. Ploubidis and secondary supervisor Dr David Bann for their support and immensely helpful feedback throughout all my PhD. I also thank Professor Ilona Koupil for warmly welcoming me and providing me with the opportunity to conduct part of my research at the Centre for Health Equity Studies in Stockholm.

I also thank the study members of the British birth cohorts and the Uppsala Birth Cohort Multigenerational Study for their lifelong contribution to these high-valuable scientific resources. I also want to thank all the staff for their hard work making sure that these data resources are maintained to the highest quality and widely available to researchers. I am very grateful to the Economic Social Research Council for funding my research.

Thank you to all PhD students in our office for being such a lovely, fun and supportive group of people!

I dedicate this thesis to Coline, for all the love (and patience!).

.

List of Tables

List of Figures

Acronyms and Abbreviations

ADL	Activities of Daily Living
AIC	Akaike Information Criterion
ALSPAC	Avon Longitudinal Study of Parents and Children
APC	Age-Period-Cohort
AUC	Area Under the Curve
BCS70	1970 British Cohort Study
BHPS	British Household Panel Survey
BIC	Bayesian Information Criterion
BMI	Body Mass Index
BRHS	British Regional Heart Study
CI	Confidence Interval
CIS-R	Revised Clinical Interview Schedule
CMR	Continuous Morbidity Recording Project
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability-Adjusted Life Years
DARTS	Diabetes Audit and Research in Tayside
DIC	Deviance Information Criterion
DIN	Doctors' Independent Network
ELSA	English Longitudinal Study of Ageing
GBD	Global Burden of Diseases Study
GHQ	General Health Questionnaire
GHS/GLS	General Household Survey/General Lifestyle Survey
GP	General Practice
GPRD	General Practice Research Database
HLE	Healthy Life Expectancy
HSE/S	Health Survey for England/Scotland
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Disease
IQ	Intelligence Quotient
MAR	Missing At Random
MCMC	Markov chain Monte Carlo
MCS	Millennium Cohort Study
MI	Multiple Imputation
MICE	Multiple Imputation by Chained Equations
MLR	Multilevel Logit Regression
MRC	Medical Research Council
MRC CFAS	Medical Research Council Cognitive Function and Ageing Studies
NCDS	National Child Development Study
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSHD	National Survey of Health and Development
OECD	Organization for Economic Co-operation and Development
OR	Odds Ratio

PROSPERO	International Prospective Register of Systematic Reviews
PSE	Present State Examination
PSF	Psychiatric Symptom Frequency
QOF	Quality and Outcomes Framework
QUALY	Quality-Adjusted Life-Years
RR	Risk Ratio
SES	Socioeconomic Position
THIN	Health Improvement Network
TLE	Total Life Expectancy
UBCoS Multigen	Uppsala Birth Cohort Multigenerational Study
UK	United Kingdom
USA	United States of America

Definitions

In this section, I define concepts that appear throughout the thesis. These concepts have varying definitions in the literature, which may lead to confusion. Hence, they are defined here and have a consistent meaning throughout the thesis. I also provide references to publications where these concepts are discussed in more detail.

Age effects - variations linked to biological and social processes of ageing (4).

Chronic (condition or disease) - continuing or reoccurring for a long time (5).

Cohort effects - variations due to the unique experience of people born around the same time (cohort) as they move across time (6).

Condition - “[a] state of health, esp. one which is poor or abnormal; a malady or sickness” (7). (p309)

Comorbidity – co-existence of additional conditions in reference to an index condition (8).

Determinant (risk factor is used interchangeably) - a range of behavioural, biological, socio-economic and environmental factors that influence the health status of individuals or populations (9).

Gender – the term is used to emphasise socially constructed differences between men and women (as opposed to biologically determined males and females). Gender differences in studied outcomes (non-communicable long-term conditions, mental health problems, inpatient hospitalisation) are more often explained through social experience rather than biological factors, hence this term is preferred (10).

Health expectancy – a summary measure of a population’s health that expresses the average number of years that a person can expect to live in "full health" (11).

Health outcomes – an umbrella term for different measures of morbidity.

Mental health problems – an umbrella term for measures of diagnosed common mental disorders (depression, generalised anxiety disorder, panic disorder, phobias, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder (12)), their symptoms or general distress.

Morbidity – an umbrella term for any negative health outcomes (a general state of being in poor health) (13).

Multimorbidity – "two or more long-term health conditions where at least one of these conditions must be a physical health condition" (14; p. 17)

Non-communicable (condition or disease) - a condition or disease that is not transmissible directly from one person to another.

Period effects - result from external factors that equally affect all age groups at a particular calendar time (6).

Secular trends - changes over a long period of time, generally years or decades.

Chapter 1: Introduction

In the United Kingdom, life expectancy at birth increased from 66.3 years in 1946 to 82.0 in 2015 (1). In other countries, for instance, in Sweden—life expectancy at birth has increased by six years in the last five decades, whereas among the members of the Organization for Economic Co-operation and Development (OECD) by eleven years (2). Due to declining mortality from heart disease (15), recent increases in life expectancy have been particularly remarkable at older ages—with 65 year-olds in the United Kingdom (UK) having a longer life expectancy of 19.7 years in 2014 compared with 13 years in 1951 (1). It has to be noted, however, that despite a continuous increase in life expectancy, the current improvements are not as optimistic as they were—particularly among the older population (16). Rising life expectancy is undoubtedly one of society's greatest achievements. However, one of its challenges is ageing of the population, with the proportion of those aged 80 years or older projected to increase by two and a half times between 2018 and 2100 in the European Union—from 5.6% to 14.6% (3). A progressively larger proportion of the older population will lead to greater demands on the healthcare system and society in general.

As continuous improvements in life experience ought to remain a key priority, it is equally important to ensure that the additional years of life are spent in good health. Nonetheless, the focus is currently disproportionally placed on treating illnesses and prolonging lives, rather than preventing morbidity—the proportion of expenditure on prevention is only 5% in the UK out of total healthcare spending, compared with 65% on curative and rehabilitative care (the following 30% includes long-term care,

governance, ancillary services, governance, medical goods and other health services) (17). As ageing can be delayed (18, 19), a more holistic approach to population health, where prevention is of equal importance to treatment, could lead to further increases in life expectancy accompanied by equivalent improvements in health at older age (20). It is important, however, to lower multiple fatal and disabling disease risks simultaneously. Hence, we need policies and health interventions that target all stages of the life course—not only older age—with a particular focus on primary and secondary prevention. For instance, interventions at early-age should aim at delaying the onset of chronic morbidity, whereas intervening in mid-life could postpone the disabling impact of chronic conditions (15).

An important step in devising health policies aiming to improve population health is to understand historical trends in various morbidity outcomes, which have emerged alongside declining mortality. While the patterns in life expectancy have been well-studied, as historically it has been the main indicator of population health, it is unclear how health has evolved—as further discussed in Chapter 2. Understanding trends over time in various health indicators, including mortality, chronic health, disability and use of health services will help to be more proactive in planning for future healthcare and societal demands (21, 22). In this section, I outline the theoretical foundations for this thesis—the theories of population health change and life course epidemiology.

1.1 Theories of population health change

There are three main theories attempting to explain patterns in the population health over time: 1) compression of morbidity (23); 2) expansion of morbidity, also referred to as “failure of success” (24, 25); and 3) dynamic equilibrium (26) (Figure 1.1).

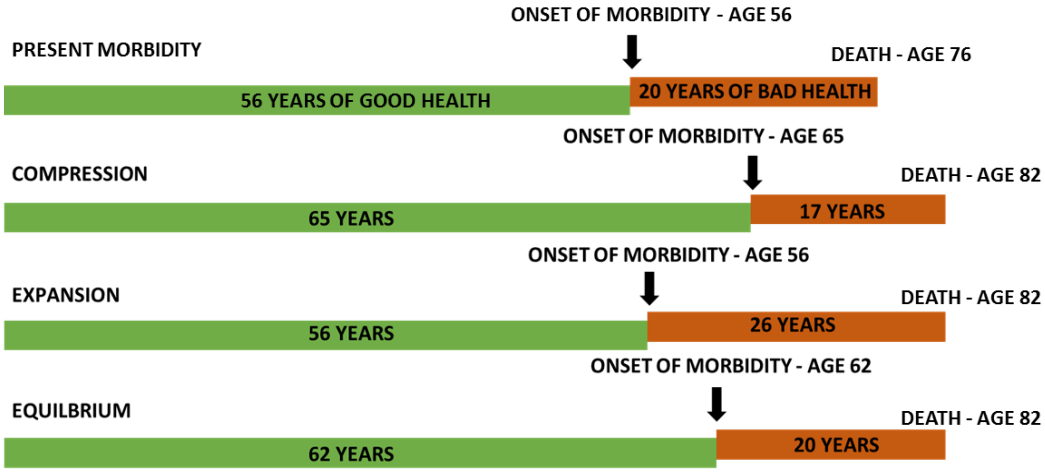


Figure 1.1 Visual representation of the population health change theories.

1.1.1 Compression of morbidity

According to the compression of morbidity theory, morbidity is postponed and "compressed" into the final years or even months of life (23). Fries argued that efforts leading to reductions in mortality have even greater preventative effects on morbidity than mortality resulting in its onset being delayed (27). Hence, younger generations experience better health at the same age or healthy life expectancy increases faster than life expectancy (27). This leads to contraction of morbidity into the end of life (27).

The theory was founded on several propositions:

1) All species, including humans, have a fixed lifespan. Fries proposed that most humans would be expected to live approximately 85 years.

2) Most chronic conditions have a common course, starting with the onset of the disease, followed by a period of morbidity or disability and ending with death.

3) The onset of chronic conditions has become delayed as a result of improved diet and lifestyle as well as medical innovations.

4) As the lifespan is believed to be fixed, delayed onset of disease results in “compression” of morbidity. This process leads to a “rectangularisation” of the survival curve. People live longer without chronic disease, the onset of which is followed by a short period of disability ending with—what Fries referred to as—the “natural death” occurring due to ageing-related causes (23).

The proposition that there is a generic linear process starting with a disease, leading to disability and ending with death was criticised—as severity, timing and course of disability or functional limitations are highly variable across health conditions (28). This criticism was based on the observation that certain conditions, such as osteoarthritis or cataracts, may result in disability but are not necessarily lethal (28). Thus, some argued that older people are more likely to avoid or survive chronic diseases and develop nonlethal, disabling conditions (24). Hence living longer may be associated with living more years with disability or functional limitations. Fries also seemed to ignore the possibility of comorbidity or multimorbidity, which are highly prevalent among older populations, in his formulations of disease, disability and death (28).

1.1.2 Expansion of morbidity

The expansion of morbidity theory proposes that additional years of life are spent in poor health, as the prolonged lifespan predominantly results from a reduction in mortality due to chronic conditions rather than by a decreasing their incidence or delaying their onset (24, 29). Thus, in contrast to the assertions of the compression of morbidity theory, more years would be spent in poor health during one’s lifespan.

This may occur if life expectancy is increasing faster than health expectancy (the number of years expected to live without disease/disability). The hypothesis is built on the assumptions that medical advances reduce the case fatality rates for conditions such as stroke, cancer and cardiovascular diseases, whereas time of their onset is not sufficiently delayed in proportion to increasing life expectancy. Thus, the age-specific prevalence rates for these diseases are stable or increasing and the older population spend more time with these conditions due to longer life expectancy (24). The theory also assumes that medical technology and public health improvements may be unable to prevent the disabling effects of certain degenerative diseases as they are simply manifestations of the ageing process.

The hypothesised driving mechanism of this theory is increased survival among those with morbidity that would have previously been fatal, mainly due to the increased capabilities of medicine (24, 27, 29). Hence, the core of the theory is an assumption that improvements in mortality may be somewhat independent of the improvements in morbidity (24, 25, 29). This would be supported by a greater reduction over time in prevalence of risk factors typically associated more strongly with mortality (e.g. smoking) rather than morbidity (e.g. obesity).

Overall, it appears unlikely that medical advancements are limited in their capabilities to reducing fatal complications of degenerative conditions, as modern medicine was found to be effective in secondary prevention—slowing down the progression of diseases and delaying the onset of their disabling effect (30).

1.1.3 Dynamic equilibrium

The dynamic equilibrium theory states that increases in life expectancy are due to delayed progression from less to more severe (and more disabling) disease states—

as opposed to the postponed onset of disease or medically-driven delay of death (26). The theory proposes that severity and the rate of progression of chronic diseases are directly related to mortality. Hence, slowed-down "ageing" of the vital organ systems has a corresponding effect on delaying morbidity and mortality. If this hypothesis is correct one would expect an increase in prevalence of less disabling disease states, leading to an increase of overall prevalence and stable (or decreasing) rates of severe conditions. Thus, the number of years spent in relatively stable productive state may increase, whereas the time with severe functional limitations or disability may remain relatively constant. The stability of the condition may be achieved through clinical efforts, for instance as in the case of hypertension or cholesterol control (31), as well as through promotion of healthy behaviours (32). More recent interpretations of the theory, using measures of health expectancy, also refer to dynamic equilibrium as a scenario where morbidity neither expands nor compresses as both mortality and morbidity are postponed by an equal number of years (33).

1.2 Contribution of this thesis

As it has been repeatedly emphasised, research on population health change has been inconsistent—with evidence supporting all three scenarios, depending on the definition of morbidity, population or studied period (30, 34-36). This has provided motivation for Chapter 2—a systematic review of the evidence on secular trends across a comprehensive set of morbidity outcomes and data sources in the UK. Subsequently, I aimed to understand how prospective longitudinal data can help to advance our understanding of population health change—addressing some of the gaps in the evidence identified by the systematic review (Chapters 4-6). In the UK, we are particularly fortunate to have access to rich longitudinally-collected data and these resources can be further exploited, adding to existing studies of trends in BMI (37), mental health (38) (see section 5.1.2), self-rated general health (39), or blood pressure (40). Most of the longitudinal studies share certain limitations, which are not as prevalent in routinely collected data, such as reliance on self-reported measures and attrition. Hence, I also used Swedish-based registry data (Chapter 6) to study secular trends in hospitalisation. In combination, these two types of resources can produce robust and comprehensive evidence on population health change—which is important for creating health policies and interventions.

In this section, I outline theoretical developments borrowed from life course epidemiology, which can accommodate prospective longitudinal research helping us to advance our understanding of population health change. Life course epidemiology is “the study of long-term biological, behavioural and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life or across generations” (page 285) (41).

As highlighted by Ben-Shlomo and Kuh, it is essentially an agnostic approach aiming to guide research on the most appropriate timing of intervention—including biomedical, individual or societal. Hence, it provides a flexible framework, which in combination with the theories of population health change, can facilitate our understanding of the trends in morbidity and mortality, including their driving mechanisms as well as preventative efforts required to improve health of future generations (42).

The life course models driving epidemiological research include: (1) the critical period model, (2) the critical model with later effect modifiers, (3) the accumulation of risk model/cumulative model, (4) the pathway model (chain of risk or trigger model). They encompass biological, behavioural and psychosocial pathways operating across one's life course or across generations, which influence development of morbidity. These models overlap to some extent in their conceptualisation and may operate simultaneously (41, 42).

The critical period, also referred to as the "latency model" describes exposures that act during a critical period of development, between being in utero and adolescence and have long-lasting effect on physical functioning that may later result in chronic morbidity (41, 42). The mechanism through which these exposures act is often referred to as "biological programming", forming the foundations for early versions of the hypothesis of foetal origins of adult morbidity (43). The critical period model proposes that an exposure acting during a critical period results in permanent and irreversible damage. Whereas outside of this period an exposure can still produce an effect that may be weaker and more likely reversible—this is referred to as a sensitive period. Sensitive periods may occur for various exposures during different

stages of the life course, for instance for social and cognitive development in adolescence or heavy drinking in mid-life (44, 45). The critical period model with later effect modifiers is an extension of the critical period model, adding the possibility that later physiological or psychological stressors may modify the effect of a given exposure on later disease risk (41, 42). For instance, obesity in adolescence or early adulthood may further increase the risk of chronic morbidity among those with low birthweight (48).

The accumulation of risk model (cumulative model) considers the total amount and sequence of exposures, which may accumulate during the life course (41, 42). Accumulation of risk may occur due to clustering of exposures, having cumulative damage to biological systems (41, 42). For instance, socioeconomically disadvantaged children may be more likely to have experienced low birthweight, have poor diets and be exposed to passive smoking (49). The model does not refute the possibility of critical or sensitive periods of development. The accumulation model is possibly the most prominent representation of processes leading to morbidity due to its advantageous predictive power, provision of aetiological insights and explanatory capacity of social inequalities in health (50). Kuh and colleagues described one's biological resources accumulated over the life course as "health capital", which determines current and future health (50).

The pathway (chain of risk/trigger) model deals with a sequence of linked exposures where one leads on to the next, these experiences are often socially stratified (51). For instance, children from more disadvantaged background may have fewer educational opportunities, which limit socioeconomic resources available later in life, associated with unhealthy behaviours and eventually leading to morbidity in later life

(52). This pathway model is to some extent similar to the accumulation model. However, the model additionally emphasises the importance of the timing of etiological exposure, which sets a person on a pathway to subsequent risk and it stipulates that the impacts of different life course exposures accumulate but do not necessarily interact (50).

This thesis does not aim to evaluate any of the aforementioned models of life course epidemiology, but it uses these models to provide theoretical and explanatory framework whose application may enhance our understanding of theories of population health change. As further explained, the theories of population health change have been focused mainly on studying periodical trends of morbidity prevalence in the context changing mortality rates. Adopting concepts from life course epidemiology, helps to study processes leading to morbidity and mortality and how these have changed over time.

1.2.1 Considering multifaceted aspects of morbidity

The theories of population health change have been developed around morbidity defined as disability or functional limitations associated with chronic conditions (53). As emphasised by recent literature reviews (15, 54), the focus of research on health expectancy since the mid-1990s has been on how chronic and acute conditions affect critical physical functions, represented by disability and functional mobility indicators—such as activities of daily living. More recently, there has been a rise of studies based on a self-rated general health question or an indicator if one suffers from longstanding illness or disability—due to availability of these health measures in population-based surveys (54).

Studying parallel trends of various aspects of population health, including disabilities, specific chronic conditions as well as other health indicators—for instance, biomarkers and mental health measures—would lead to more precise policy recommendations (55). For instance, increasing burden of chronic diseases would imply a greater need for medical care, whereas rising limitations in activities (e.g. in walking or lifting) would indicate a growing demand for rehabilitation, assistive technology and social services related to personal assistance as well as for a better-adapted environment (56). Moreover, costs of chronic conditions to an individual and society extend beyond their disabling effects—through medical costs, sub-clinical damage to health or psychosocial and stress-related burden associated with being labelled as diseased (53). Self-reported general health, which is often measured in population-based surveys, is another useful morbidity indicator as it has been demonstrated to be a strong predictor of mortality and disability even while controlling for a range of objective health measures (57, 58). This measure may capture a multifaceted nature of health—including morbidity as well as health awareness and expectations (57, 58). Whereas objective health measures—including biomarkers—are free from self-report biases, for instance, due to changing attitudes to health (59), hence they may provide information on "true", objective, aspects of health.

To holistically describe trends in morbidity, in the first research study (Chapter 2) I systematically reviewed the evidence on post-WWII trends in commonly-studied indicators of morbidity—including key chronic conditions, disability and functional limitations as well as self-reported general health. The following studies investigated trends in less-studied health measures, including: self-reported non-communicable diseases, objectively measured biomarkers and multimorbidity (Chapter 4), mental

health (Chapter 5) and inpatient hospitalisation due to non-communicable conditions (Chapter 6).

1.2.2 Studying age and cohort effects in morbidity

When studying trends over time in morbidity (and mortality), it is important to understand three types of time-related influences: age, period and cohort effects. Age effects refer to biological and social process related to ageing, which may include physiologic changes and accumulation of social experiences (60). Period effects are typically defined as external factors that equally affect all age groups at particular calendar time (60). Cohort effects are variations resulting from unique experiences of groups of subjects born at the same time as they move across time (60). As age, period and cohort effects are collinear (Cohort = Period − Age), they cannot be simultaneously estimated (61). However, different study designs are well-suited to estimate one or two of these time variables at a time—while assuming that the effects of the remaining variable can be omitted.

Cross-sectional studies allow for examining the age distribution of a health outcome. However, age and cohort are perfectly collinear in this type of studies and their generalisability over time is low as they provide a snapshot within a short calendar period (e.g. a single year). Repeated cross-sectional studies are more suited for describing age, cohort and period effects as they provide estimates over different periods and allow for conducting pseud-cohort analysis, where the same birth cohorts (but not the same individuals) are followed across time as they age. A longitudinal design is more powerful in studying age-related processes than cross-sectional designs. In longitudinal studies the same individuals are followed over time, where each person acts as their own control, ensuring that age trends are due to

intraindividual change. Nonetheless, when studying an individual birth cohort, age and period are perfectly collinear, thus their differential influences cannot be distinguished. Hence, an accelerated longitudinal study design, or combining several birth cohort studies, is more appropriate for investigating age, period and cohort effects, where the same individuals belonging to different birth cohorts are followed over time as they age. In such studies, the age-related processes can be attributed to intraindividual changes and cross-cohort comparisons can be made at overlapping ages (61). All empirical studies in this thesis (Chapters 4-6) use this design.

As explained, different types of studies may be more suited for examining age, period or cohort effects, however, there is no study design that would allow to statistically separate all three time variables (61). As Glenn put it “a continued search for a statistical technique that can be mechanically applied always to correctly estimate the effects is one of the most bizarre instances in the history of science of repeated attempts to do the logically impossible” ((62), p. 6). There are techniques, which attempt to statistically break the collinearity of age, period and cohort, but an interpretation of such estimates is problematic due to the logical impossibility of disentangling influences that can be attributed to ageing, periodical circumstances or environmental and historical influences accompanying different birth cohorts (62). A common strategy is to make a strong assumption about a time variable, whose effects are considered of lesser importance and estimate two other time variables. Such assumption depends on the research question of interest (61). In Chapter 5 and 6, I focus on studying age and birth cohorts, while informally considering potential period effects.

Younger birth cohorts are expected to live longer, which will translate into extended lifespan with morbidity, unless they experience a delayed onset of morbidity. Hence, when studying secular trends in morbidity in the context of population health change, age effects need to be accounted for. Most studies describing the epidemiology of morbidity over time use repeated cross-sectional surveys, where the prevalence of morbidity is compared over time after age-standardisation of the cross-sections of the population (see Chapter 2). This ensures that the obtained secular trends do not merely represent a greater proportion of older individuals in later-studied population. Age-specific comparisons, ideally covering a wide age distribution of the outcome (or focused on a narrow age group), help to recognise if specific age groups are at a greater risk of poor health. This may facilitate detection of risk factors disproportionally affecting those groups. In addition, investigating the age distribution of health outcomes is important in itself, even if the study mainly focuses on period effects, as this helps to identify high-risk life course stages (52).

When studying age-related processes in health outcomes, it is essential to consider cohort effects, which arguably may be more informative than focusing on period effects. Birth cohorts are likely to differ in their demographic composition, attitudes, values, beliefs and behaviours (63). Changes in education, politics, life conditions, socialisation, norms and technological innovation may all affect birth cohorts differently (63). This may lead to variations in ageing across birth cohorts. Members of different birth cohorts may enter social roles, experience key life course events (e.g. marriage, parenthood) or historical occurrences (e.g. an economic crisis) at different age (63). A universal age trend, despite these important differences across birth cohorts, suggests that change observed with age can be truly attributed to age effects. Hence, the finding of universal age trends across birth cohorts improves the

generalisability of the evidence, which facilitates the development of health policies and interventions (50). It is also possible that the age trajectories of a given health outcome have a similar shape across cohorts. However, the overall level of morbidity may differ across cohorts due to overall variation in the predisposition of a given birth cohort to experience poor health. Hence, we should aim to understand how changing socioeconomic and policy contexts have affected health over time and if these effects varied across different population segments—determined by their age and time of birth (52). Considering birth cohort differences in age trends also allows for more a precise inference regarding change in the length of lifespan spent with morbidity, as we can observe at what age secular changes start to emerge and if they persist over the life course. For instance, younger birth cohorts have been found to have worse mental health in mid-life (38), but these differences may converge at an older age—hence potentially leading to dynamic equilibrium in morbidity, as opposed to expansion.

Temporal trends in prospective longitudinal studies may also be attributed to period effects, which may confound age and cohort influences. Overall, regardless of period or cohort effects being at play—an increasing or stable trend in morbidity over time, after accounting for ageing, will lead to a greater proportion of individuals with morbidity in the population and longer time spent with morbidity during their lifetime. Overall, I focus on cohort effects—as it is difficult to imagine environmental, social or economic factors equally and simultaneously affecting health across the entire population. The exceptions here are changes in diagnoses of specific conditions, as these would result in the change of prevalence across all ages and birth cohorts. Such an example is lowering of plasma glucose threshold for diagnoses of diabetes

in 2000, which resulted in an initial sharp increase in diagnosis in the early-2000s (64).

Some social and economic changes may have a comparable effect on a range of age groups. For instance, a rapid increase in the popularity of foods high in sugar, fats and salt may be partially blamed for currently rising obesity across the entire population (65). Yet, these are still likely to have a distinct impact at different ages, leading to what epidemiologists define as cohort effects (resulting from period by age interaction) (6). As in the obesity epidemic example, cross-cohort differences in obesity emerged in early-adulthood in older cohorts (1946 vs 1958 vs 1970), whereas younger cohorts are more obese already in childhood (1991 vs 2000) (37).

In order to have a ubiquitous influence on the entire population, periodical factors would need to be extreme in nature—for instance resulting from famine or war. However, these events are well-documented and are likely to result in short-term fluctuations in morbidity trends (e.g. 2nd World War, Spanish flu, The Dutch famine of 1944–45). Hence, explicit statistical modelling of period effects is not needed to pick up these influences. In the age-cohort analysis, the same age across birth cohorts corresponds to different calendar years, thus simple replacement of age with period on X-axis (as in Chapter 5) would allow for detecting these periodical influences. Moreover, even population-level exposures extreme in nature would differentially affect groups in the midst of a critical developmental period, as they would increase their lifetime risk of disease, hence they may be more beneficial to consider as cohort effects (66).

In the UK, we are privileged to have the oldest and longest-running birth cohort—the 1946 Medical Research Council (MRC) National Survey of Health and Development

(NSHD). In addition, members of the other British birth cohorts—the 1958 birth cohort or the National Child Development Study (NCDS) and the 1970 British Cohort Study (BCS70)—are currently in middle-age. Combining these three cohorts allows for studying health processes across age and birth-cohorts—as in the accelerated longitudinal design, which is a gold standard for studying age and cohort effects. A similar set-up of the data can be done with the Swedish registries, as they include information collected over time on individuals born across many decades. Taking advantage of these data resources, I study age and cohort effects in mental health in the UK (Chapter 5) and inpatient hospitalisation in Sweden (Chapter 6).

1.2.3 Shifting from morbidity to "morbidity process"

The theories of population health change have been mainly focused on health trends in older age. However, availability of data collected over the life course allows for studying dynamic nature of health, which Crimmins referred to as the "morbidity process" (15, 67) and which has been emphasised by the life course models. At the population level, health-related processes start in early-life—or even prenatally—when early-life risk factors lead to physiological dysregulation, subsequently resulting in a diseased state that often translates into disability or functional limitations and eventually leads to death (15) (see Figure 1.2).

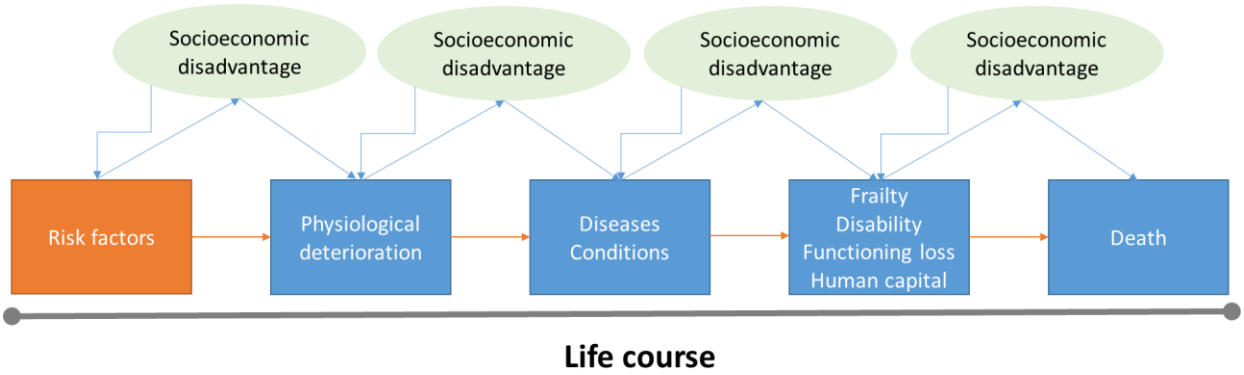


Figure 1.2 Visual representation of the morbidity process (adapted from Crimmins).

Life course models emphasise lasting effects of early-life circumstances—including illness, deprivation and cognitive development—on adult health (51). Crimmins describes the beginning of the morbidity process as physiological dysregulation (see Figure 1.2), however, life course epidemiology advocates for considering socially patterned exposures that precede physiological dysregulation, so-called “causes-of-causes” (68). These may predispose to clustering and accumulation of other risk factors over the life course having cumulative damage to biological systems—leading to morbidity (51). For instance, early-life social status may translate into less healthy diet, in turn leading to physiological dysregulation (e.g. high cholesterol) (69). Hence, investments in early-life are likely to produce the greatest long-term health benefits (15). Prospectively-collected longitudinal data allows for studying such temporal relationships, however, investigating complex causal chains remains methodologically challenging (e.g. see Joffe et al. (70) for discussion).

Mid-life, as early-life, has also been identified as a pivotal stage in the life course, which bridges young and older age and may be considered as a sensitive period of healthy ageing. Ageing starts to accelerate in mid-life, however middle-aged individuals still possess behavioural and neural plasticity that can be acted on to build

foundations for healthy ageing (71). Yet, research on population health theories or life course epidemiology has paid less attention to this life phase (see Chapter 2). This is a missed opportunity as existing evidence, for instance, based on a national longitudinal study—the Midlife in the United States—shows that supportive relationships, regular exercise and sense of control in mid-life help to maintain functional health and cognitive skills when entering older age (71). As depicted by the model of morbidity process (see Figure 1.2), acting in early-life is thought to have preventative effects in mid-life, whereas preventative interventions in mid-life lead to promotion of healthy ageing (72). In order to better understand the population health change, we may explore changes of morbidity process over time. For instance, we may investigate if the association between a risk factor and morbidity changed in magnitude over time (e.g. in younger birth cohorts compared to older ones). For example, Li and colleagues showed that the association between rising BMI trajectory and high adult blood pressure was stronger in the 1958 birth cohort compared with the 1946 cohort (73). This may suggest that chain of certain risk factors may have become stronger over time. The focus of the empirical studies of this thesis is on morbidity processes in early-life and mid-life. I investigate secular trends in multimorbidity in mid-life (Chapter 4), in mental health (Chapter 5) and in inpatient hospitalisation (Chapter 6) across adulthood. In addition, I examine the association between early-life risk factors and mid-life multimorbidity (Chapter 5) and adult inpatient hospitalisation (Chapter 6) and how these associations changed over time.

1.2.4 Importance of socioeconomic circumstances in morbidity process

Life course epidemiology emphasises the importance of the socioeconomic context in studying health outcomes—as depicted by the diagram of the morbidity process (Figure 1.2) and explained in more detail in section 1.2. Socioeconomic circumstances may act as risk factors for morbidity and mortality, for instance, via their direct impact on morbidity due to exposures during sensitive or critical periods and/or through their association with later health behaviours (e.g. diet, smoking or injury avoidance) (74). Moreover, they may act as modifiers of the effect of risk factors on health. They may cause disadvantaged individuals to be more vulnerable to the consequences of morbidity, for instance, having limited access to health services (75), or they may increase the propensity to being exposed to unhealthy environments (e.g. hazardous occupations) (76). Alternatively, socioeconomic position may mediate the effect of other risk factors on health. For example, previous work based on the British birth cohort studies has shown that the association between early-life characteristics—such as birthweight, cognitive ability, BMI and mental health problems—and adult morbidity as well as mortality, is mediated by adult characteristics—including education or socioeconomic status (77, 78). Finally, socioeconomic characteristics may act as confounders of the effect of other exposures on health resulting in spurious association—for instance, birthweight may be associated with morbidity due to socioeconomic circumstances leading to both low birthweight and morbidity. Hence, socioeconomic context is an important aspect of the morbidity process and it should be appropriately operationalised, depending on the research question of interest.

In the thesis, socioeconomic circumstances are treated as exposures (Chapters 4-6) as well as potential confounders of the association between early-life characteristics and adult morbidity (Chapters 4-5). Studying life course trajectories across birth cohorts is particularly important, as socioeconomic context sets up the cadence of developmental processes (15). Hence, I examine socioeconomic differences in adulthood hospitalisation in Sweden (Chapter 6).

1.3 Structure of the thesis

The following chapters include the systemic review (Chapter 2), description of the data used for the primary analyses (Chapter 3)—the British birth cohorts and the Uppsala Birth Cohort Multigenerational Study—and the empirical studies (Chapters 4-6). Each chapter corresponding to a research study includes a more detailed discussion of the relevant literature—identifying gaps that the studies aim to address. The empirical studies are followed by the general discussion (Chapter 7)—bringing main findings together, highlighting contributions as well as limitations of the research conducted within this thesis and suggesting avenues for future research. The last chapter of the thesis (Chapter 8) includes information about publications and conference presentations relevant to outputs of the thesis. The document also contains supplementary material providing additional information relevant to each research study. Below I outline the aims of each empirical chapter and key contributions to the literature within the themes discussed in section 1.2.

Chapter 2: Post-war (1946-2017) population health change in the United Kingdom: A systematic review

Aim(s): To systematically review the evidence on trends in multiple health outcomes—expressed as prevalence rates and health expectancy—including chronic conditions, disability, self-reported general health among adults in the UK during the period of 1946-2017.

Key contributions: This chapter addresses the need to focus on multi-faceted definition of morbidity when studying trends over time—as outlined in section 1.2.1. I considered two sources of evidence, which have been rarely interpreted

simultaneously in the context of the theories on population health change: trends in age-standardised or age-specific prevalence rates as well as in health expectancy.

Chapter 4: Prevalence and early-life determinants of mid-life multimorbidity: evidence from the 1958 and 1970 British birth cohort studies

Aim(s): (1) To estimate the prevalence of multimorbidity in mid-life (age 46-48) in the 1970 British birth cohort, according to the definition provided by the National Institute for Health and Care Excellence; (2) to examine the association between early-life characteristics and mid-life multimorbidity in the 1970 British birth cohort and (3) to compare the estimates of multimorbidity and the magnitude of associations across the 1958 and 1970 British birth cohorts.

Key contributions: This study contributes to our understanding of population health change (section 1.2.1) by focusing on multimorbidity, which is associated with elevated risks of polypharmacy, complex health needs, healthcare utilisation and costs. In addition, I attempted to identify modifiable early-life risk factors potentially linked with multimorbidity, such as parental social class at birth, birthweight, BMI as well as cognitive and emotional development. As proposed by the Department of Health, these were identified due to being associated with a wide range of health outcomes commonly included in the definition of multimorbidity. These variables are believed to act at the origins of the morbidity process, hence they are particularly important for prevention (see section 1.2.3). The study compares health outcomes in mid-life across the birth cohorts, as it is a key life phase when preventative efforts can be implemented to delay age-related health decline (see section 1.2.3).

Chapter 5: Mental health morbidity from adolescence to early old age: Evidence from the 1946, 1958 and 1970 British birth cohorts

Aim(s): (1) To investigate the age trajectory of mental health over time in three British birth cohorts (1946 – NSHD, 1958 – NCDS and 1970 – BCS70), including—to the best of my knowledge—the longest continuous follow up of this outcome within the same individuals from age 36 to 69; (2) to examine cohort differences in mental health across three representative British birth cohorts: 1946 (NSHD), 1958 (NCDS) and 1970 (BCS70).

Key contributions: This study contributes to the theories of population health change by investigating age and cohort effects in mental health (see sections 1.2.2). Mental health morbidity has rarely been considered in the context of these theories. This is despite mental health disorders increasing in prevalence over the last three decades and being the leading cause of non-fatal disease burden.

Chapter 6: Inequality in hospitalisation due to non-communicable diseases in Sweden: age-cohort analysis of the Uppsala Birth Cohort Multigenerational Study

Aim: To examine cohort differences in age trajectories of hospitalisation due to non-communicable conditions and if these varied by paternal socioeconomic position.

Key contributions: This research contributes to the literature by focusing on inpatient hospital admissions, which indicate a direct demand on health services and can be considered as a quasi-objective measure of severe morbidity burden (see section 1.2.1). Hospital admissions are also closely associated with other health measures, such as self-reported health, as well as quality of life. Inpatient care constitutes one-fourth of total health expenditure in Sweden, particularly due to cancer and heart

disease. A large proportion of inpatient admissions, for conditions such as asthma or diabetes, could be managed in primary care or community settings—which would reduce the costs and improve effectiveness of healthcare. Hence, hospital admissions are a particularly useful outcome to monitor over time. The national registries allow setting up the data as an accelerated longitudinal design—which is a gold standard for studying age and cohort effects (see section 1.2.2). Studying cohort effects in age trajectories in admissions can help to project future demand and better understand at what age these demands may be particularly increased. In addition, I investigate changes over time in the socioeconomic inequality in hospitalisation, which is a useful indicator of effectiveness of social policies leading to health equity (see sections 1.2.2 and 1.2.4).

Chapter 2: Post-war (1946-2017) population health change in the United Kingdom: A systematic review

Chapter objectives:

- To systematically review the evidence on secular trends in key chronic conditions, disability and self-assessed general health among adults in the United Kingdom, as reported in primary/secondary care databases and population-based surveys conducted between 1946 and 2017.

Key findings:

- There was no evidence for improvement in the age-standardised or age-specific prevalence of any of the studied major chronic conditions over the last few decades, apart from Alzheimer's disease.
- The evidence on trends in disability, expressed as prevalence or health expectancy, was mixed, but also appeared to support the expansion of morbidity theory among those aged 65 or over.
- Evidence for trends in morbidity measures, particularly disability, in those aged under 65 is lacking.

2.1 Introduction

As elaborated in more detail in section 1.2.1, it is important to study trends in a range of morbidity outcomes. In this review, I focus on non-communicable conditions with the greatest impact on overall ill-health, disability or early death. In addition, this review considers trends in other morbidity outcomes, such as disability or functional limitations and self-rated health. As mentioned in section 1.2.1, disability measures are a good indicator for demand for rehabilitation, assistive technology and social services related to personal assistance as well as for a better-adapted environment (56). Self-reported general health is a strong predictor of mortality and disability even while controlling for a range of objective health measures (57, 58) and it captures various aspects of health—including morbidity as well as health awareness and expectations (57, 58). Hence, this review will provide a holistic overview of trends in a range of morbidity outcomes and help to identify gaps in the literature that are to some extent addressed in this thesis and can be further investigated in future research.

This review considered two sources of evidence that have been rarely investigated simultaneously in the context of the theories of population health change: trends in age-standardised or age-specific prevalence rates as well as in health expectancy and total life expectancy (see Table 2.1 for interpretation). The most pessimistic scenario, the expansion of morbidity theory, alludes that gains in unhealthy years are greater than those in healthy ones (27). Hence, due to rising life expectancy, stable or rising age-specific prevalence rates would lead to expansion. The theory of expansion of morbidity will also be supported, if we observe an increase or no change in age-specific/age-adjusted prevalence of morbidity between two different

periods. Individuals born later are expected to live longer, hence if they experience worse and or similar health at the same age (the average age of onset of morbidity is not postponed), they are likely to spend more of their lifespan with morbidity. This scenario can be assessed, for instance, by comparing morbidity across two birth cohorts at overlapping age (e.g. at age 42 born in 1958 vs 1970 as in Chapter 4). This is an indirect test of the expansion of morbidity, as it does not allow for the exact estimation of the number of years spent with morbidity.

The most optimistic theory—compression of morbidity—states that health expectancy is rising faster than total life expectancy; meaning that age-specific prevalence of morbidity is declining over time (27). Hence, more recently born individuals would need to experience better health than their earlier born counterparts when age differences are accounted for. This would mean that the morbidity onset is delayed, leading to a shorter lifespan with morbidity—under the condition that the delay is substantial enough to offset rising life expectancy.

The third theory, dynamic equilibrium, proposes that there is an overall increase in prevalence and years of morbidity, which however, has a mildly disabling effect (33). Dynamic equilibrium also occurs when morbidity neither expands nor compresses as both mortality and morbidity are postponed by an equal number of years (see Table 2.1) (33).

Without explicitly quantifying joint progress of health and life expectancy over time, we are not able distinguish between compression of morbidity and dynamic equilibrium scenarios. For instance, a modest improvement in the prevalence of age-adjusted (or age-specific) morbidity over time, may lead to either compression of morbidity or dynamic equilibrium depending on whether this improvement keeps up

with (dynamic equilibrium) or exceeds (compression of morbidity) the decline in mortality. For simplicity, decrease in age-adjusted (or age-specific) prevalence of morbidity over time is considered as supportive evidence for compression of morbidity. Hence, a somewhat strong assumption is made that the improvement in age-adjusted (or age-specific) prevalence of morbidity over time is large enough to offset the rise in life expectancy.

Interpreting evidence from the perspective of these theories helps to emphasise the necessity to improve population health to compensate for the consequences of increasing lifespan—since only reduction in morbidity over time can be considered as a positive scenario for public health.

Table 2.1 Interpretation of findings in the context of the main theories of population health change.

Study findings	**Interpretation**
• Decrease in age-specific/age-adjusted prevalence of morbidity • Greater increase in health expectancy than in total life expectancy	Compression of morbidity
• Increase or no change in age-specific/age-adjusted prevalence of morbidity • Greater increase in total life expectancy than in health expectancy	Expansion of morbidity
• Increase or no change in age-specific/age-adjusted prevalence of mild morbidity and decrease in age-specific/age-adjusted prevalence of severe morbidity • Equal increase in health expectancy and total life expectancy	Dynamic equilibrium

Overall, there is little consensus on which—if any—of these stylised scenarios best describes recent trends and, it seems that much depends on the health conditions used to operationalise morbidity. Two systematic reviews of this topic have been conducted. One in the USA, which found overall declines in mild old-age disability between 1990 and 2002, whereas conflicting findings were observed for more severe

long-term disability (34). The second review was also limited to older population and period between 1991 and 2011, but did not make any geographical restrictions (35). It concluded that chronic morbidity measures tended to point towards expansion of morbidity, whereas disability-related measures somewhat inconsistently produced evidence for compression of morbidity (35). Other European studies investigating trends in the last three decades have found evidence for all three scenarios: compression in fair or poor self-perceived health (79, 80) and disability (81), expansion of morbidity due to chronic diseases, moderate mobility limitation (82) and mild disability (83, 84) and dynamic equilibrium in disability due to chronic morbidity (85). Available non-systematic reviews of the evidence in the UK tend to emphasise the inconclusive and scattered nature of the evidence (30, 36). The Global Burden of Disease Study (GBD), using a vast array of data including both published literature and primary sources, produced evidence supporting expansion of morbidity theory in the UK (86, 87). It concluded that people spent more years in poor health in 2010 compared to 1990, as the number of years in good health increased to a lesser extent compared to life expectancy at birth (86). This was mainly due to reductions in age-specific mortality and largely unchanged prevalence of major health conditions (weighted by an estimate of how disabling those were) (80). Nonetheless, the GBD study included information on trends only from 1990 and provided little evidence on health outcomes other than chronic conditions, such as self-rated general health or disability.

Hence, I aimed to systematically review the evidence on trends in multiple health outcomes—expressed as prevalence rates and health expectancy—including main chronic conditions as well as disability and self-reported general health among adults in the UK during the period of 1946-2017. This would provide a holistic picture of

population health trends in the UK and further our understanding of the inconsistencies in the evidence. This review included information from both primary/secondary care databases and population-based surveys, which have different strengths and sources of bias. For instance, routinely collected data may be more sensitive to introduction of screening programmes or changes over time in health awareness, as they rely on the subpopulation presented to health services. Whereas population-based surveys may mitigate this bias by studying the same, pre-defined population over time. On the other hand, population-based surveys are likely to have data available in sporadic points in time, compared with routinely collected data that have yearly information. Triangulation of information from these sources allowed for attaining more reliable evidence on population health trends (88). This review also includes a wider period of time (1946-2017) than the previous reviews, considering long-lasting population health changes that have taken place in the UK

2.2 Methods

2.2.1 Search strategy and selection criteria

In order to evaluate post-war trends in morbidity among adults (16 years old or older), two types of primary outcomes were retrieved: (1) estimates of trends in age-specific or age-standardised prevalence of major chronic non-communicable conditions, disability and self-reported general health and (2) estimates of trends in health expectancy—which were not defined based on any specific health measure due to an overall small number of studies estimating health expectancy.

Studies including an estimate of prevalence of morbidity (or health expectancy) at one time point were not included. This was due to a large volume of such evidence, which would make this review infeasible due to available resources. For instance, not adding key terms for “trend” in the search strategy resulted in over 100.000 potentially relevant studies indicated by the search engines. In addition, the manuscripts rarely provided enough details on the methodology (e.g. age structure of the sample, measures of morbidity) to assess the comparability of the studies, which provided estimates at one time point. Whereas the comparability of methodology tended to be well-described in studies investigating trends in morbidity over time.

In addition, studies of trends in incidence were retrieved as a secondary outcome. They, however, did not provide direct evidence on the theories of population health change but may help to explain current and predict future, trends in prevalence (see Appendix 1A for a brief summary of the evidence on incidence). In the current study, morbidity was defined as (1) chronic morbidity (i.e. a persistent condition or otherwise long-lasting in its effects), (2) disability and (3) self-reported poor health. Additionally, studies using a question on limiting longstanding illness or disability were included,

as they are typically used in health expectancy estimates. The review focused on major contributors to chronic morbidity, accounting for at least 1% of disability-adjusted years of life (DALYs) in the UK from non-communicable diseases (84): coronary heart disease, stroke, chronic obstructive pulmonary disease, asthma, diabetes, Alzheimer's disease migraine, cirrhosis, musculoskeletal pain. Colorectal and breast cancer, as well as osteoarthritis, were also included, however studies of trends in prevalence have not been found.

The included disability measures followed a wide definition of disability by the World Health Organisation, which covers impairments (i.e. a problem in body function or structure) and activity limitations (a difficulty in executing a task or action) (55). Indicators of disability included: activities of daily living (ADLs), often considered as severe disability (e.g. difficulties with bathing) and instrumental activities of daily living (IADLs), an indicator of mild disability (e.g. difficulties with shopping) (55). Measures of self-reported general health were also included as they have been found particularly useful for population health monitoring due to being highly predictive of mortality and use of health services (89).

I conducted separate searches for studies of health expectancy and incidence/prevalence (example in Table 2.2). In addition, reference lists of all included studies, Google Scholar and OpenGrey Repository were screened to identify any other eligible research. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42017069291).

2.2.2 Data collection

Titles and abstracts were screened independently by two reviewers (DG & KN) according to exclusion/inclusion criteria. To meet the inclusion criteria, studies (1) drew on population-based probability samples (having longitudinal or cross-sectional design) or primary/secondary care databases and other routinely collected data, (2)

Table 2.2 The search strategy in OvidSP (including EMBASE AND MEDLINE).

Search structure for studies capturing trends in the **prevalence/incidence**					
Concept	*Trends*		*Health indicators*		*Study design*
Examples of key words	change in incidence OR change in prevalence OR trends in incidence	AND	self-rated health OR SRH OR stroke	AND	cohort* OR prospective OR retrospective OR panel
Search structure for studies capturing trends in the **health expectancy**					
Concept	*Trends*		*Health expectancy*		
Examples of key words	increase* OR rise* OR gain* OR difference*	AND	health* life expectanc* OR health expectancy OR active life expectanc*		
Searched fields	abstracts, key words, titles, text word, keyword heading word				
Limits applied	13+; English only; Article only, human only, removed duplicates				
Truncation command used	'root word*': captures alternative word endings				

To note. Searches were conducted in MEDLINE (from 1946), EMBASE (1980-2017) and EMBASE Classic (1947-1973) via OvidSP interface and Web of Science (from 1946).

An asterisk (*) was used to truncate search terms.

were conducted in the UK and (3) were published in English. Studies providing estimates of incidence/prevalence at a single point in time were excluded. Full texts were retrieved for all citations that were included by either reviewer and their eligibility was also assessed by two reviewers (DG & KN). Any disagreements were resolved by discussion. Subsequently, I extracted the key information from all publications. In addition, the information from 20% of all the publications was extracted by the second reviewer (KN) to ensure reliability and discrepancies were discussed.

2.2.3 Risk of bias assessment

Two reviewers independently assessed the risk of bias within all sources of data according to the criteria broadly based on the Newcastle-Ottawa Quality Assessment Scale (Appendix 1B) (90). These criteria included: (1) sample being representative of the UK population; (2) high validity and reliability of outcome assessment; (3) consistency in methodology over time. Other potential biases—not related to the data source itself—were discussed in relation to each outcome. An example could be ascertainment bias resulting from the introduction of screening programmes. The evidence was considered of high quality (free of major biases) if all three criteria were met, two met criteria indicated moderate quality and evidence with one or none met criterion was considered of low quality. Tables 2.3 – 2.4 indicate data sources used for each outcome as well as overall quality of body of evidence. The detailed assessment of quality of each data source can be found in Appendices 1C – 1E.

2.2.4 Synthesis of evidence

Meta-analysis of trends or cumulative reporting of year-by-year estimates were not feasible due to vast differences across studies in reporting of the estimates (e.g.

prevalence rates per 100,000 person years at risk, estimates of proportion of the population who have the condition, annual % change over the studied period), as well as in definition of health outcomes and lack of information on year-by-year estimates. Hence, this review reports on consistency in the overall trends across studies, focusing on the comparability of methodology over time. The evidence is summarised narratively and the estimates of trends are provided throughout the study from the data sources of the highest quality. Findings are reported separately for periods 1950s-1990s and 1990s-2010s as well as for each morbidity outcome, either based on health expectancy or prevalence. A majority of the studies provided age-standardised estimates for entire adult population ("All" in Age column of Tables 2.3 - 2.4) or older individuals (65 years old or older)—hence reporting of the results is focused on those two age groups.

2.3 Results

2.3.1 Study selection

The literature searches identified 6141 publications examining trends in prevalence and incidence and 2186 for trends in health expectancy (see Figure 2.1). After removing duplicates and studies conducted outside of the UK, the initial screening of titles and abstracts was conducted by two reviewers—reaching a high agreement (Kappa=0.78). This narrowed the number of full texts for retrieval to 65 for prevalence/incidence and 56 for health expectancy. These papers were assessed for eligibility by two reviewers (Kappa=0.69), the main reason for exclusion was ineligibility of the outcome. Twenty papers reported incidence trends exclusively and were excluded at this stage. After inclusion of papers from other sources (see Figure 2.1), the total sample included 39 studies reporting trends in prevalence and 15 in health expectancy.

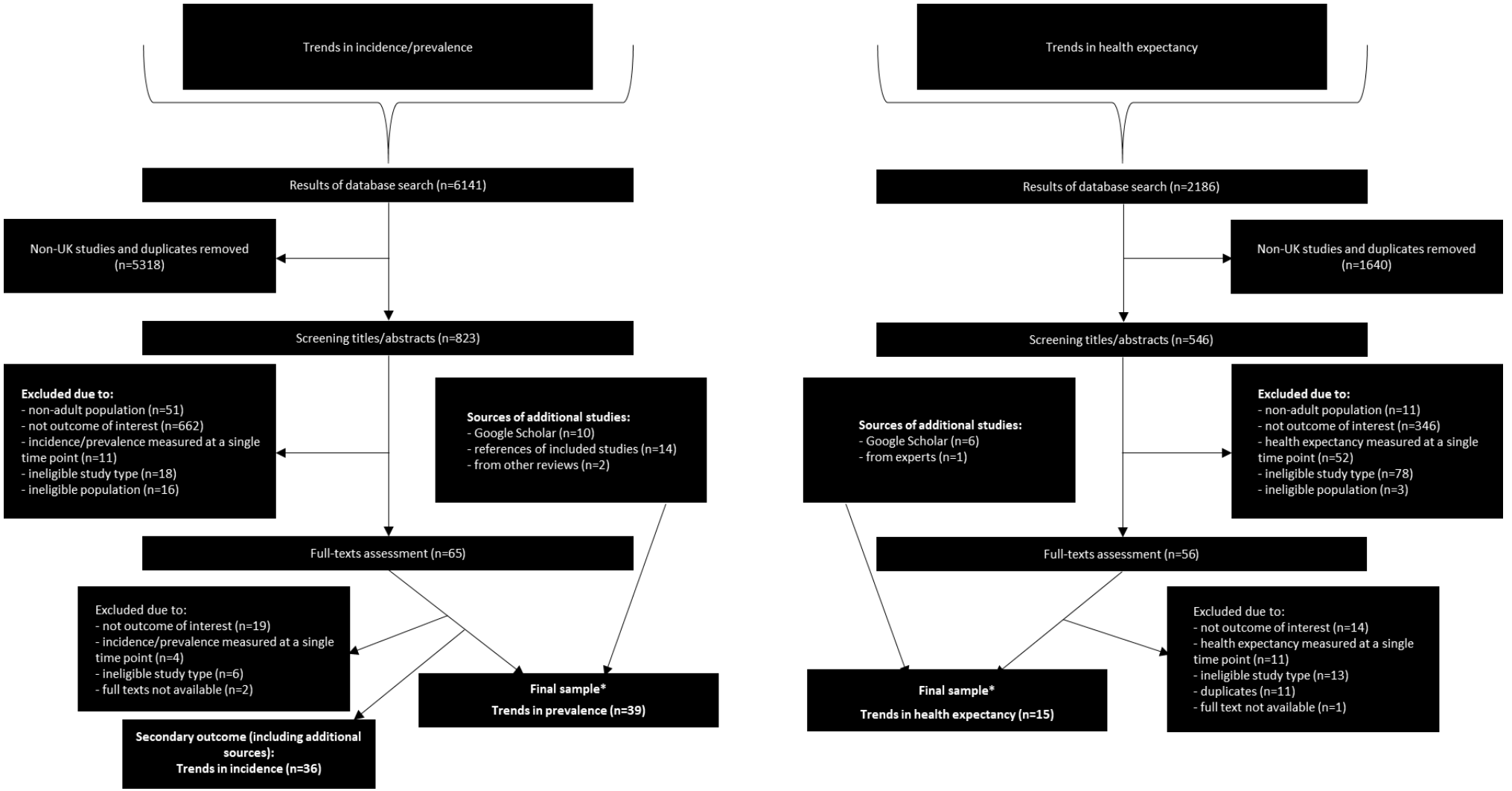


Figure 2.1 Flow chart for selection of papers and sources included in the review.

*One study reported both prevalence and health expectancy.

2.3.2 Period 1950s – 1990s

The trends in prevalence of chronic morbidity clearly support the expansion of morbidity scenario for the period of 1970s-1990s, across all ages and genders. There was evidence pointing towards expansion in coronary heart disease occurring from as early as 1950s (see Table 2.3). Similarly, the evidence consistently shows expansion in limiting longstanding morbidity (including illness or disability), self-reported general health expressed as health expectancy at birth and among older people for the period of 1970s-1990s and of more severe disability (with stable prevalence trends) between early-1980s and mid-1990s (see Table 2.3). However, there is some evidence that more severe disability may have declined among the oldest participants (75 or older) between early-1980s and mid-1990s, supporting compression of morbidity for that period (see Tables 2.3 - 2.4).

2.3.2.1 Chronic morbidity

All included studies for this period reported trends in prevalence rates of chronic morbidity (none in health expectancy). Studied chronic conditions were coronary heart disease, stroke, musculoskeletal pain and diabetes. The National Morbidity Survey, including a representative sample of General Practitioners (GPs), reported increasing prevalence of angina from mid-1950s to 1990s, particularly among those aged 65 or older (e.g. it increased by 128% for the period of 1972-1992) and of stroke between 1971 and 1991 in all age and genders (increased by 40%) (91). The overall trends in the prevalence of myocardial infarction were inconsistent: prevalence rates increased slightly between 1971 and 1981 (by 15%) and subsequently fell between 1981 and 1991 (by 31%) (91). One study also reported a higher point prevalence of self-reported musculoskeletal pain (e.g. cervical, dorsal) in

1994-95 compared with 1956-58 (92). However, representativeness of the study was limited to a small north-eastern region of England and the measure of musculoskeletal pain as well as demographic characteristics somewhat varied between the surveys (92). In another study—representative for the population and with identical methodology over time—gender- and age-standardised prevalence of self-reported back pain (lasting for at least 24 hours in previous 12 months) increased between 1987-8 and 1997-8 (by 12% in absolute terms) (93). However, severe back pain (self-reported ability to put on hosiery) fell minimally—by 0.7% (-0.1%, 1.5%) among 29-59-year-olds (93). The increase in age- and gender-standardised prevalence was also seen in diabetes between 1978 and 1996 in two large surveys conducted in primary care practices (94, 95). According to the British Regional Heart Study, which is a representative cohort of 7722 British men aged 40-59, the annual age-adjusted rate of diabetes rose by 4.3% (0.4%, 8.2%) in the period of 1978-1985 and 5.5% (3.0%, 8.1%) in the period of 1985-1992 (95). In the same study, the lifetime prevalence of coronary heart disease stayed stable in the period of 1978-1985 and increased (annual % change in odds: 1.9%, 0.5% to 3.3%) in 1985-1992 (96).

2.3.2.2 Limiting longstanding morbidity

The proportion of older individuals (age 60-89) reporting a limiting longstanding illness, disability or infirmity in the General Household Survey increased from late-1970s until late 1980s and tailed off in the 1990s—averaging at 42% (97). Due to rising life expectancy, this resulted in an increase of over three years in life expectancy with limiting long-term ill-health (98). A greater increase in life expectancy than the total number of years without a limiting long-standing illness or disability was

also seen in other studies for overlapping periods, both at birth and at age 65 or over (99-101).

2.3.2.3 Disability

The analysis of the General Household Survey showed largely stable rates in ADLs (i.e. self-reported ability to independently bath, shower or wash all over) and mobility measures (i.e. self-reported ability to manage stairs and steps)—among aged 75 or older—between 1980 and 1994 (97, 98). However, there was evidence for reductions in disability among participants 85 years old or older, particularly among men (97, 98). For instance, 18% of men reported one or more ADLs in 1994 compared with 31% in 1980 (98). The increase in health expectancy was comparable with the total life expectancy—hence the overall number of years expected to be lived with disability remained stable (98). A repeated cross-sectional survey including only 75 years old or older population of Melton Mowbray (Leicestershire, UK), also found a decrease in age-adjusted prevalence of most ADLs (i.e. getting in and out of bed/a chair, dressing, getting to and from the toilet, bathing) between 1981 and 1988 (102). However, the study may not be representative of the UK population.

2.3.2.4 Self-rated general health

Life expectancy increased more than health expectancy with self-rated “good” or “fairly good” health—by 0.4 years—for those aged 65 for the period between 1981 and 1995 (99). Likewise, more recently born cohorts had a greater proportion of elderly people who rated their health as “less than good” between 1981 and 1988 (e.g. by 17% among those aged 75-81) (103). The estimates were also robust due to effects of migration over time (103). Similar results were found for the period of 1981-1995 for health expectancy at birth, when the expected number of years lived in poor

health increased by 1.3 years (99) and for 1994-1999 among individuals aged 15—with the increase by 0.9 years (104).

2.3.3 Period 1990s – 2010s

The trends in chronic morbidity consistently pointed towards expansion of morbidity across all ages, with rising prevalence in all studied conditions except for dementias, especially Alzheimer's disease (decreasing trend in prevalence in 1990-2010) and coronary heart disease (stable in 2000-2010) (see Table 2.3 and Fig 2.2). The expansion of morbidity was apparent due to long-standing illness or disability (as a self-reported one item indicator)—particularly among those aged 65 or older, where increase in health expectancy did not compensate for the increase in total life expectancy. Overall, expansion of morbidity in disability was also more apparent among older population (65 years old or older), however there was a considerable inconsistency in the evidence, with trends varying depending on specific measures used. Studies on disability trends among younger population were lacking. There was a clear trend for expansion of morbidity in self-reported general health for the entire period and across all ages and genders. Finally, the evidence appears to support compression of morbidity for cognitive impairment among women (but expansion among men).

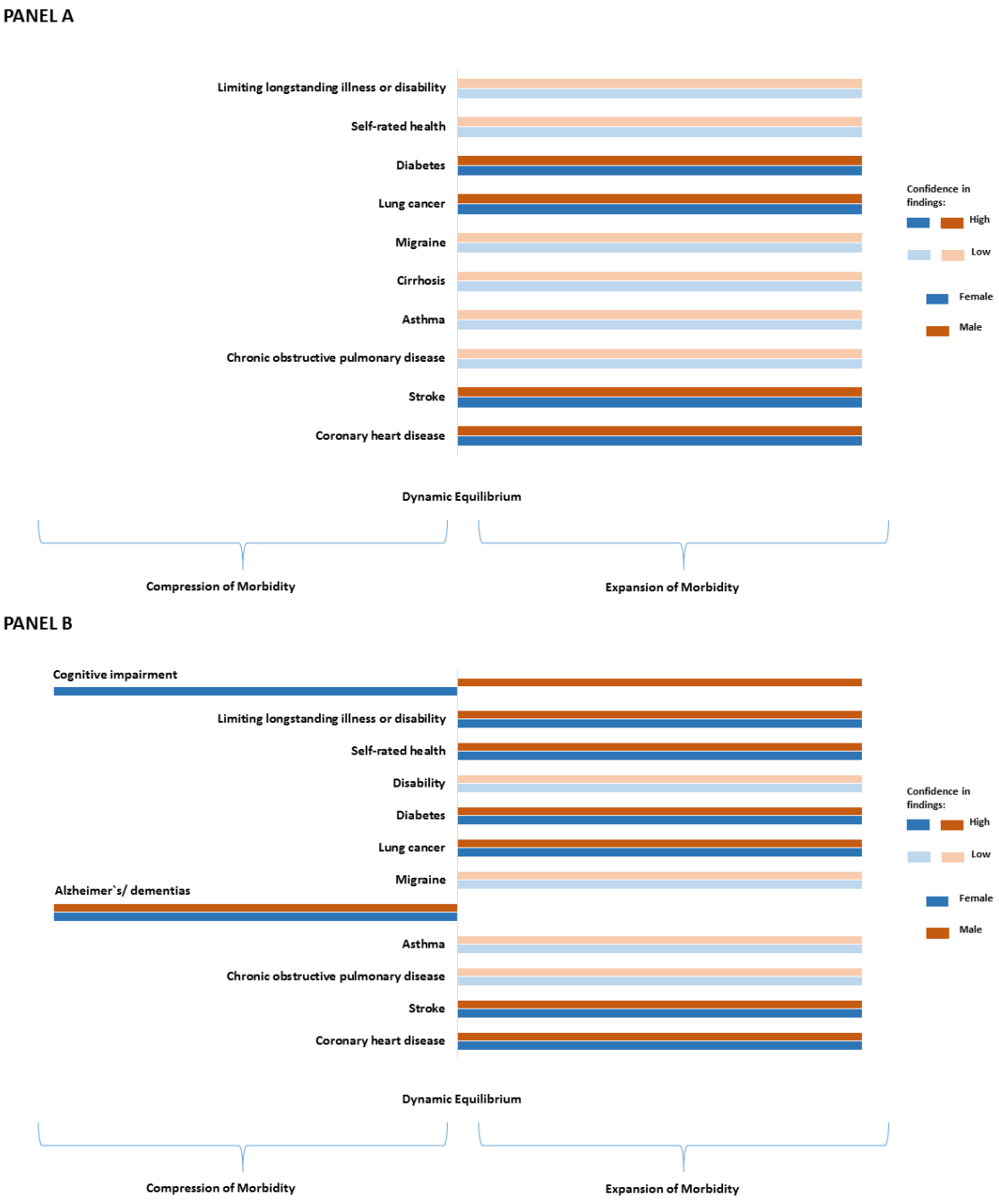


Figure 2.2 Summary of the evidence for the period (1990 – 2010), for those aged 16-64 (Panel A) and 65 or older (Panel B).

*Each bar indicates compression/dynamic equilibrium/expansion of morbidity in a given health condition for either men or women. Darker shades represent high confidence in findings, with evidence being consistent and of high quality (see Tables 2.3 – 2.4). Lighter shades represent inconsistent evidence or of low quality.

2.3.3.1 Chronic morbidity

All included studies reported trends in prevalence rates, rather than in health expectancy. Chronic conditions found for this period were coronary heart disease, stroke, lung cancer, COPD, asthma, Alzheimer's disease and other dementias, migraine, cirrhosis, low back pain and diabetes.

According to the British Regional Heart Study, the age-standardised prevalence of coronary heart disease declined minimally (the trend was not statistically significant) among 40-59-year-old men in the period 1992–1996 (annual % change in odds: -1.4%, -3.0% to 0.2%) (96). High-quality evidence—based on large primary/secondary care databases and population-based surveys, with consistent methodology over time—indicated increasing age-standardised prevalence rates between mid-1990s and mid-2000s in all ages and genders for coronary heart disease (91, 105-107), stroke (91, 107-109) and diabetes (94, 95, 110-118). Based on large primary care databases—the Health Improvement Network (THIN) and the General Practice Research Database (GPRD)—average percentage change in age-standardised prevalence of coronary heart disease increased by 1.5% for the period 1996-2005 (105); unstandardised stroke prevalence increased by 13%, from 6.40/1000 in 1999 to 7.20/1000 in 2008 (109); and crude prevalence of diabetes prevalence increased from 2.8% in 1996 to 4.3% in 2005 (age- and gender-standardisation did not make a substantial difference) (111).

More recently, studies of trends in coronary heart disease between early-2000s and early-2010s, based on both general practice records (the Quality and Outcomes Framework) and population-representative annual cross-sectional surveys (the National Health Surveys and the General Household Survey), concluded that the

prevalence of coronary heart disease remained largely stable (91, 96, 105, 106, 119), whereas rates of stroke (119) and diabetes (64) increased respectively by 13% and 123% in relative terms.

Similarly, high-quality evidence, based both on primary/secondary databases and population-based surveys, indicated an increase in prevalence of chronic respiratory diseases (asthma and chronic obstructive pulmonary disease) from early-1990s to mid-2000s (112, 120-123). For instance, according to the QRESEARCH, there was a relative increase in the standardised prevalence of COPD (by 24%) and of asthma (by 20%) between 2001 and 2005 (122, 123). The British Household Panel Survey (BHPS) also reported an increase in self-reported migraine between 1991 and 1998 in both men and women across most of the age groups, particularly 65 or older (112). A study using THIN showed that age- and gender-standardised prevalence rates of lung cancer rose by 23% between 2004 and 2012, mainly due to increases among women (124). I found two high-quality prospective longitudinal studies, the English Longitudinal Study of Ageing (ELSA) and the Medical Research Council Cognitive Function and Ageing Studies (MRC CFAS I and II), both representative of the older population, aged 50 or older and 65 or older respectively (125, 126). Both studies showed a relative decrease in age and gender-standardised prevalence of dementia by 30% for the period of 2002/3-2012/3 and by 40% for 1989-2011 (125, 126).

2.3.3.2 Limiting longstanding morbidity

Large population-based surveys, representative for the UK population and with consistent methodology over time (GHS/GLS, the Integrated Household Survey, Continuous Household Survey and the UK census data), all found that the total life expectancy has increased by a greater number of years than life expectancy without

a limiting longstanding illness or disability at age 65 or older for the period between early-1990s and early-2010s (127-129). For instance, estimates based on the National Census showed an increase of 0.4 years for 85-year-olds between 1991 and 2001 (129). However, there is some evidence that between 2002 and 2012, those born after 1924 experienced lower odds of having a long-standing illness, disability or infirmity, whereas the prevalence was stable for women (130). However, among people who reported longstanding morbidity, the number of disabilities increased (e.g. mobility, manual dexterity) for each successive cohort (incidence rate ratio 1.03), suggesting greater severity of morbidity (130).

The findings for trends at younger ages were inconsistent, however overall pointing towards a greater increase in total life expectancy than health expectancy. Wohland and colleagues (129) found total life expectancy increased by 1.3 years more than health expectancy in the period of 1991-2001. Similar findings were obtained for the period of 2001-2011, based on the UK National Census data from London only (expansion of morbidity by 1.7 years) (131). On the contrary, estimates based on the GHS/GLS showed a greater increase in health expectancy than total life expectancy—for men only (with no difference among women)—in the period of 2000-2011 (by 0.9 years) (127, 128). Finally, a study based on repeated annual cross-sections of the Health Survey for England from 1991 to 2014 (participants aged 25-64), found an equal increase in health expectancy and total life expectancy (107).

2.3.3.3 Disability

There was an increase of 2.5 years with self-reported ADLs (e.g. putting on shoes and socks) and IADLs (e.g. shopping) in the period of 1991-2011 among 65-year-olds (132). The findings were somewhat mixed among studies that provided age-

standardised prevalence rates. These inconsistencies were found despite overlapping study periods, comparable populations and definitions of disability. The analysis of the Health Survey for England indicated increasing rates of severe disability (e.g. washing/bathing, dressing) among 65-year-olds, up from 13.5% in 1995 to 15.3% in 2001 (114). By contrast, the results from the General Household Survey indicated a decline in severe disability rates among people aged 65 and over, from 21% in 1994-95 to 18% in 2001-2 (114). The reasons for the diverging results are not clear. In studies with multiple indicators of disability, the trends were also mixed—regardless of severity of disability or type of activity. For instance, a repeated cross-sectional study in England, conducted between 1998 and 2008, found reductions in gender-standardised disability rates among those aged 75 or older in outdoor mobility, washing difficulty, ability to prepare a meal, joint pain and requiring help with nail care, whereas differences were not found in dressing difficulty, indoor mobility and prevalence of falls (133). Similarly, a study using the HSE—conducted among individuals 65 years old or older in 1992-2007—found decreasing age-adjusted prevalence in usual activities, stable rates in limitations in self-care activities and increasing rates in limitations in walking 200 yards and climbing stairs (134). Chatterji and colleagues found a declining proportion of people aged 50-75, but not 75 or older, with severe disability (ADLs) in 2002-2008 (35). Whereas the proportion of individuals with mild disability (IADLs) increased over the period across all ages, with a sharper rise among 75-year-olds or older (35). In the only study with a younger population, a greater proportion of 25-year-olds or older reported problems or disability related to arms, legs, hands, feet, back or neck (112).

2.3.3.4 Self-rated general health

The findings somewhat consistently showed that life expectancy increased more than expected years with self-reported “good” health for those aged 65 for the period between early-1990s and mid-2010s (by 0.6 years) (127, 132). Similar findings were obtained for individuals at age 15 in 1994-1999—with a greater increase in life expectancy than health expectancy by 0.9 years (104). Contradictory findings were produced by a study using the GHS/GLS, which showed that years from birth with self-rated good health increased by 1.3 years more than total life expectancy in 2000-11 (127). However, the response option changed during the observation period, hence the reliability of the findings is questionable (127). The inconsistencies in the methodology were accounted for statistically in another study, which focused on England only and included a longer observation period (2000-2014) (135). The study showed that total life expectancy increased more at birth than years with self-rated good health by 0.9 years (135). A greater increase in total life expectancy than health expectancy was also found by Jivraj and colleagues, for the period of 1991-2014 among participants aged 25-64 (107).

2.3.3.5 Measures of cognition

A study estimating health expectancy without cognitive impairment between 1991 and 2011 at age 65 found that health expectancy increased more than total life expectancy among women (by 0.8 years) (132). Whereas for men, the number of years without cognitive-impairment lagged behind increase in life expectancy (by 0.3 years) (132).

Table 2.3 The characteristics of evidence on prevalence of each health outcome, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of findings on trends**	**Overall quality of evidence † †**
Coronary heart disease (n=6): QOF (n=1)[119] HSE/S (n=2)[91, 119] GLS/GHS (n=1)[119] National Morbidity Survey (n=1)[91] BRHS (n=1)[96] CMR (n=1)[106] THIN (n=1)[105] MRC CFAS (n=1)[108]	1955-6-2013-4	All	Expansion for the entire period (mixed findings on trends: stable or increasing prevalence)	High + representative of the population; + low risk of bias related to outcome assessment, combination of both self-reports and linkage of medical records; + highly comparable methodology over time; = lack of strong evidence on other biases
Stroke (n=4): QOF (n=1)[119] HSE/S (n=2)[91, 119] GLS/GHS (n=1)[119] National Morbidity Survey (n=1)[91] MRC CFAS (n=1)[108] GPRD (n=1)[109]	1970-1-2013-4	All	Expansion for the entire period (mixed findings on trends: stable or increasing prevalence)	High + representative of the population; + low risk of bias related to outcome assessment combination of both self-reports and linkage of medical records; + highly comparable methodology; = lack of strong evidence on other biases

Table 2.3 (cont.) The characteristics of evidence on prevalence of each health outcome, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of results**	**Overall quality of evidence † †**
Lung cancer (n=1): THIN (n=1)[124]	2004-2012	All	Expansion for the entire period (consistent findings on trends: increase in prevalence)	High + representative of the population; + low risk of bias related to outcome assessment, based on linkage of medical records; + highly comparable methodology; = lack of strong evidence on other biases
COPD (n=2): QRESEARCH (n=1)[123] GPRD (n=1)[120]	1990-2005	All	Expansion for the entire period (consistent findings on trends: increase in prevalence)	Low + representative of the population; + low risk of bias related to outcome assessment, linkage of medical records; however spirometry data not available for checking reliability of diagnoses = no information on comparability of methodology over time; - possible ascertainment bias due to introduced incentives to create and maintain a registry of patients with COPD
Asthma (n=3): QRESEARCH (n=1)[122] GPRD (n=1)[121] BHPS (n=1) [112]	1990-2005	15+	Expansion for the entire period (consistent findings on trends: increase in prevalence)	Low + representative of the population; + low risk of bias related to outcome assessment, based on linkage of medical records; however spirometry data not available for checking reliability of diagnoses = no information on comparability of methodology over time; - publicity and awareness campaigns on asthma in the lay and medical arenas and diagnostic bias, might play a role in the reported increase in asthma prevalence

Table 2.3 (cont.) The characteristics of evidence on prevalence of each health outcome, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of results**	**Overall quality of evidence † †**
Alzheimer's disease/other dementias (n=2): MRC CFAS (n=1)[126] ELSA (n=1)[125]	1989-2013	50+	Compression for the entire period (consistent findings on trends: decrease in prevalence)	High + representative of older population; + low risk of bias related to outcome assessment, based on cognitive assessment; + highly comparable methodology over time; = possible non-response bias, however, it was addressed by sensitivity analyses = lack of strong evidence on other biases
Migraine (n=1) BHPS (n=1)[112]	1991 - 1998	All	Expansion (increase in prevalence)	Low + representative of the population; - no detailed information on the outcome assessment, based on self-reports; = no information on comparability of the methodology over time = lack of strong evidence on other biases
Cirrhosis (n=1): GPRD (n=1)[136]	1992 - 2001	25+	Expansion (increase in prevalence)	Moderate + representative of the population; + no information on the outcome assessment, based on linkage of medical records; = no information on comparability of the methodology over time = lack of strong evidence on other biases
Low back pain (n=2): Arthritis Research Campaign (n=1)[92] Randomly selected from lists of GPs (n=1)[93]	1956 - 1997-8	18-64	Expansion for the entire period (consistent findings: increase in prevalence of less disabling back pain, no difference in prevalence of more disabling back pain)	Low - representativeness limited to the northwest region of England; - no information on possible biases due to outcome assessment, based on self-reports; - changes to mode of data collection and definitions of the outcome; = lack of strong evidence on other biases

Table 2.3 (cont.) The characteristics of evidence on prevalence of each health outcome, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of results**	**Overall quality of evidence † †**
Diabetes (n=13): MRC CFAS (n=1)[108] DIN (n=1)[115] DARTS (n=1)[110] Routine hospital data (Cardiff/Vale of Glamorgan) (n=1)[116] Hospital diabetes register (n=1)[94] THIN (n=2)[64, 111] GPRD (n=1)[117] HSE/S (n=6)[113, 114, 118, 137] BRHS (n=1)(95) GLS (n=1)[114]	1979-1984 2013	All	Expansion for the entire period (consistent findings on trends: increase in prevalence)	High + representative of the population; + low risk of bias related to outcome assessment, combination of both self-reports and linkage of medical records; + highly comparable methodology over time; = lowered criteria for diagnosis of diabetes by fasting plasma glucose values from ≥7.8 to 7.0 mmol/l in 2000, however, the rate of increase in incidence is similar before and after 1999; = possible ascertainment bias due to, introduction of incentives for general practitioners to better detect cases (the Quality and Outcomes Framework in 2004), however sensitivity analyses showed little impact and the increase too large to be explained solely by ascertainment bias
Self-rated general health (n=2): BHPS (n=1)[112] General practices in Leicestershire (n=1)[103]	1981-2008	75+	Expansion (increase in prevalence)	Low + representative of the population; = no detailed information on the outcome assessment; = no information on comparability of the methodology over time = lack of evidence on other biases

Table 2.3 (cont.) The characteristics of evidence on prevalence of each health outcome, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of results**	**Overall quality of evidence † †**
<u>Disability (n=7):</u> MRC CFAS (n=1)[108] ELSA (n=1)[35] General practices in Gloucestershire (n=1)[133] General practices in Leicestershire (n=1)[102] GHS (n=2)[97, 114] Family Resource Survey (n=1)[130] HSE (n=2)[114, 134]	1979-2012	50+	Expansion in 1979-1994 (consistent findings on trends: stable prevalence) Expansion in 1994-2012 (mixed findings on trends)	High + representative of the population; + low risk of bias related to outcome assessment, based on self-reports; + highly comparable methodology over time; = lack of evidence on other biases

Note. QOF = Quality and Outcomes Framework; HSE/S = Health Survey for England/Scotland; GHS/GLS = General Household Survey/General Lifestyle Survey; BRHS = British Regional Heart Study; CMR = Continuous morbidity recording project; THIN = The Health Improvement Network; MRC CFAS = Medical Research Council Cognitive Function and Ageing Studies; GPRD = General Practice Research Database; COPD = chronic obstructive pulmonary disease; UK = United Kingdom; ELSA = English Longitudinal Study of Ageing; BHPS = British Household Panel Survey; GP = General Practice; DIN = Doctors' Independent Network; DARTS = Diabetes Audit and Research in Tayside.

† Some studies included more than one data source.

†† Quality criteria were representativeness of the sample of the UK population; risk of bias due to outcome assessment; comparability of the methodology over time; other biases affecting comparability of trends. Meeting three criteria indicates high quality of evidence, 2 moderate, 1/0 low quality of evidence (high risk of bias in comparability of trends),

"+" = no risk of bias

"-" = risk of bias

"=" = no information on risk of bias

*There were no studies estimating trends in prevalence of other health outcomes meeting inclusion criteria: other musculoskeletal disorders, neck pain, colorectal cancer, breast cancer, osteoarthritis.

Table 2.4 The characteristics of evidence on health expectancy, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of results**	**Overall quality of evidence † †**
Limiting long-standing illness or disability (n=10): GHS/GLS (n=7)[98-101, 107, 127, 128] UK Census (n=2)[129, 131] MRC CFAS (n=1)[132]	1976 - 2014	All	At birth: Expansion in 1976-1995; expansion in 2001-2014 (consistent) Age 65/85: Expansion for the entire period (consistent)	High + representative of the population (includes institutionalised population); + low risk of bias related to outcome assessment; + consistent methodology over time; = lack of evidence on other biases.
Self-rated general health (n=6): HSE (n=1)[104] MRC CFAS (n=1)[132] GHS/GLS (n=4)[99, 107, 127, 138]	1981 - 2014	0, 15, 65, 85	At birth/15: Expansion in 1981-1999 (consistent); expansion in 2000-2011 (inconsistent) Age 65/85: Expansion for the entire period (consistent)	High + representative of the population (includes institutionalised population); + low risk of bias related to outcome assessment; + consistent methodology over time; = lack of evidence on other biases.
Disability (n=2): GHS/GLS (n=1)[98] MRC CFAS (n=1)[132]	1985 - 2011	65+	1980-1994: Compression among 75-year-olds or older 1991-2011: Expansion among 65-year-olds or older	High + representative of the population (includes institutionalised population); + low risk of bias related to outcome assessment; + consistent methodology over time; = lack of evidence on other biases.

Table 2.4 (cont.) The characteristics of evidence on health expectancy, with the emphasis on size, consistency and quality.

Health outcome and data source (n studies)†	**Period**	**Age (range)**	**Conclusion & consistency of results**	**Overall quality of evidence † †**
Measures of cognition (n=1): MRC CFAS (n=1)[132]	1991-2011	65+	Compression of morbidity for women and expansion for men	High + representative of the population (includes institutionalised population); + low risk of bias related to outcome assessment, based on cognitive assessment; + consistent methodology over time; = lack of evidence on other biases.
Summary health variable (n=1): BHPS (n=1)[112]	1991-1998	20-80	Expansion of morbidity for all ages	Low + representative of the population; = no detailed information on the outcome assessment; = no information on comparability of the methodology over time; = lack of evidence on other biases.
Other health outcomes (n=1): HSE (n=1)[107]	1991-2014	25-64	Expansion of morbidity for all ages	High + representative of the population (includes institutionalised population); + low risk of bias related to outcome assessment, based on cognitive assessment; + consistent methodology over time; = lack of evidence on other biases.

Note. GHS/GLS = General Household Survey/General Lifestyle Survey; UK = United Kingdom; MRC CFAS = Medical Research Council Cognitive Function and Ageing Studies; ADL = activities of daily living; HLE = healthy life expectancy; TLE = total life expectancy; QUALY = quality-adjusted life-year; BHPS = British Household Panel Survey; HSE = Health Survey for England.

† Some studies included more than one data source.

†† Quality criteria were representativeness of the sample of the UK population; risk of bias due to outcome assessment; comparability of the methodology over time; other biases affecting comparability of trends. Meeting 3 criteria indicates high quality of evidence, 2 moderate, 1/0 low quality of evidence (high risk of bias in comparability of trends).

"+" = no risk of bias

"-" = risk of bias

"=" = no information on risk of bias

2.4 Discussion

2.4.1 Summary of findings

This is the first systematic review of evidence on the joint progress of health and mortality in the UK. I assessed trends in morbidity, based on large population-based surveys and primary/secondary care databases or other routinely collected data. The trends in the prevalence of chronic morbidity support the expansion of morbidity scenario for the entire period of 1970s to mid-2010s across all ages, with some evidence pointing towards expansion in coronary heart disease occurring already from the 1950s. Rising prevalence was observed in all studied conditions except for coronary heart disease that appears to have been stable in the period of 2000s-2010s (still supporting the expansion of morbidity scenario) and Alzheimer's disease and other dementias (1989-2013)—reflecting compression of morbidity in severe cognitive impairment (particularly among women) (132). Likewise, the evidence consistently points towards expansion in limiting longstanding morbidity (including illness or disability) and self-reported general health, when life expectancy is considered both at birth and at older people, for the period of 1980s-2010s. An increase in health expectancy based on those measures lagged behind the rise in total life expectancy, hence supporting expansion of morbidity. The evidence based on measures of disability, such as daily activities (e.g. mobility, self-care) was inconsistent. It appears that there was expansion of morbidity in severe disability (with stable prevalence trends) between the early-1980s and mid-1990s. Overall, expansion of morbidity in disability among the older population appears to be the more likely scenario in the period 1990s-2010s. The evidence on disability measures at younger age is lacking, with one study pointing towards expansion of morbidity.

2.4.2 Comparison with other evidence

Findings from this review were largely consistent with the Global Burden of Disease (GBD) study, which is currently the most comprehensive research project, with over 1,800 researchers from 127 countries, looking at worldwide secular trends in various morbidity outcomes (84). This review, in line with the GBD study, found supportive evidence for expansion of morbidity for diabetes, lung cancer, stroke, asthma, chronic obstructive pulmonary disease and migraine (86, 87). Inconsistencies were found for Alzheimer's and other dementias as the GBD found no difference in prevalence rates over time (expansion of morbidity), while studies included in this review suggested a decrease (compression of morbidity) (86, 87). This, however, may be due to the different age distribution of the sample (all vs 50-year-olds or older) and definition of caseness. As far as coronary heart disease is concerned, the GBD found no difference among women (expansion of morbidity) and decrease among men (compression of morbidity) over time, whereas this review suggested an increase in both genders (expansion of morbidity). Overall, findings of this review seem to be consistent with the GBD study, which found that health expectancy—based on the overall prevalence of a range of health outcomes multiplied by disability weights—has increased to a lesser extent than total life expectancy (3.2 vs 4.2 years) (86). This finding holds for all EU15+ countries, although the difference between the increase in life expectancy at birth and health expectancy varied from 0.5 years in Greece to 1.7 years in Luxembourg (86). Chatterji and colleagues also found expansion of chronic morbidity for the period of 1991-2011 in worldwide studies, whereas no discernible patterns emerged in disability (35).

2.4.3 Explanations of the findings

There are several potential explanations for findings of this review. The improved survival (e.g., from stroke and some cancers), due to more effective disease management (36, 64, 105, 106, 115), appears to have led to a higher prevalence of morbidity and an increase in the number of people living with disorders that previously would have been fatal (86, 87). Although there is some evidence for declining incidence in coronary heart disease or stroke, these decreases appear to lag behind improvements in survival (see Appendix 1A). For other conditions, such as diabetes, the incidence has increased in the last three decades—hence further expansion of morbidity is expected (Appendix 1A).

It is also likely that more effective screening, combined with greater health awareness—rather than the actual burden of chronic diseases—have contributed to the rising rates. For instance, there have been some concerns that asthma may be currently overdiagnosed in primary care, after years of underdiagnosis (139). Also, the quality of recording tends to improve over time, particularly after adopting new computer systems, which may lead to higher estimates (140). Moreover, rising rates of morbidity may be partially caused by programmes incentivising accurate maintenance of registers of patients with diseases such as asthma or diabetes (e.g. the New General Medical Services Contract (141)). However, studies that limited their analysis to services with highly accurate data—as a sensitivity check—tended to find similar trends—for instance in diabetes (115). Interpretability of trends in diabetes specifically is also limited by lowering of plasma glucose threshold for diagnoses of diabetes in 2000, which did result in an initial sharp increase in diagnosis in early-2000s (64). Nonetheless, the rising trends in diabetes have been consistently observed before and after 2000. Moreover, the prevalence of diabetes

also increased as indicated by haemoglobin A1c (HbA1c), in addition to self-reported diagnosis (107, 137).

The trends in chronic health should also be considered in the context of trends in risk factors. These, however, are inconsistent over time with some important risk factors decreasing since 1990s, for instance, systolic blood pressure, total cholesterol, smoking or heavy drinking (91, 107, 134, 137, 142) and others increasing—obesity, hypertension and sedentary lifestyle (91, 107, 137). It also appears that, overall, there was a greater decline in risk factors more strongly associated with mortality (e.g. smoking) than morbidity (e.g. obesity), hence providing a partial explanation for the observed expansion of morbidity (54).

It is also important to note that people's knowledge about health may have improved over time, due to better education (63), which might have raised the propensity to report health problems and to have higher expectations from health services. However, empirical research testing this hypothesis is lacking. There are still inconsistencies regarding reports of IADL (e.g. independence in shopping) and, more severe, ADL disability (e.g. independence in bathing). Declines in IADLs should be expected, partially due to improvements in the environment, for instance, wheelchair access or availability of ready-made meals or microwave ovens (56). However, similar aids are difficult to implement for ADLs (56). Hence declines in this type of disability may be less likely to occur, unless secondary and tertiary care is more successful in offsetting disabling effects of rising chronic diseases, for which there is currently no evidence.

2.4.4 Limitations and future research

The main limitation of the review is that it relies on a narrative summary of the evidence, as opposed to using a formal quantitative analysis in which uncertainty and potential bias in estimates could be quantified. As explained in section 2.2.4, this is due to differences in reporting of the estimates (e.g. prevalence rates per 100,000 person years at risk, estimates of the proportion of the population who have the condition, annual % change over the studied period), as well as in definition of health outcomes and lack of information on year-by-year estimates. This limitation partially results from the approach I took to review trends in a wide range of morbidity outcomes and over a long observation period. This decision was made to address the limitations of previous reviews that were limited to individual health outcomes (see section 2.1) and to provide a wider literature background for this thesis.

In a similar vein, it was deemed infeasible to review studies providing an estimate of prevalence of morbidity or health expectancy at one time point. This was due to a large number of such studies and often lack of sufficient amount of details on the methodology in the manuscript, which would allow for comparisons of the estimates over time. However, this may have resulted in excluding evidence from data sources, which are well-documented and comparison over time could be possible. For instance, this includes routinely collected data by the Office of National Statistics or THIN database.

Research on disability suffers from methodological inconsistencies across studies, mainly around how disability was measured, leading to mixed findings. This has been repeatedly pointed out in the literature (34, 54). Also, as it is the case in the USA, data on changes in the prevalence of disability and functioning problems are scarce

and generally limited to the older population (36). Disability can occur at any time in life and research on disability at all ages is needed (143, 144). For instance, 44 million people aged 15-64 (14.0 % of that age group) reported a basic activity difficulty in 2011 among the EU-28 countries. Further research could focus on objective measures of disability as these are not affected by response bias and are more comparable over time. Moreover, disability measures are often based on a single question, thus the use of instruments with a finer gradation of disability severity should be more common (143, 145). This would allow for testing of the dynamic equilibrium theory and a better understanding of the reasons underlying disability trends. Furthermore, future research could study changes over time in the magnitude of the association between health indicators obtained within the same individuals, such as chronic conditions and disability (112). This would help to understand if improving disease management over time also leads to one's better functioning—in addition to prolonging survival. Another limitation of the literature was that very few studies included the institutionalised population (126), as the changes in the prevalence of institutionalisation over time may lead to under-/overestimation of the prevalence of certain diseases. A few studies that took that into account did not, however, find any difference in estimates—due to the overall low proportion of the institutionalised population (<5%) (126, 130).

2.4.5 Conclusion and implications

This review is the first one conducted systematically, which provides a comprehensive and critical insight into the existing evidence on the post-war population health trends in the UK. Overall, the rates of morbidity as well as time spent in morbid states, have increased in the last three decades. This is, partially,

due to remarkable improvement in survival with most chronic conditions. The evidence on trends in prevalence of chronic conditions strongly suggests expansion of morbidity in the last few decades in the UK. The increasing prevalence of chronic morbidity may to some extent reflect better diagnostics, but as rising trends occur within short studied periods, it is unlikely to be the sole explanation for the observed trends. The trends in disability are less conclusive. However, even if the length of life with disability remains the same or is reduced but the length of life requiring treatment for disease increases, lifetime health costs will increase unless the costs of health care are reduced. Thus, there is an urgent need for preventative efforts that would delay the onset of morbidity. As the prevalence of morbidity is projected to increase in the next decade, it is also necessary to consider how the additional years of life can be managed to ensure good quality of life and reduce financial consequences of already existing morbidity (146). For instance, McCormick and colleagues (147) argued that we should move beyond focus on healthcare and pensions, creating more innovative practices leading to harnessing everyday relationships, enabling older individuals to continue paid or unpaid work, encouraging lifelong learning and building environment that helps to connect older people to services, activities and other people (147). Such practices have been successfully implemented around the world and could be adapted to the UK context (e.g. Healthy Ageing Evidence Review (148)).

Chapter 3: Data used in the thesis

In this chapter, I provide a general overview of data used for the empirical studies (Chapters 4-7). Specific information about the samples and measures used in each study is given in corresponding chapters. The data used in the thesis come from the 1946 Medical Research Council (MRC) National Survey of Health and Development (NSHD) (Chapter 5), the 1958 National Child Development Study 1958 (NCDS) (Chapters 4-5), the 1970 British Cohort Study (BCS70) (Chapters 4-5) and the Uppsala Birth Cohort Multigenerational Study (Chapter 6).

3.1 The 1946 Medical Research Council (MRC) National Survey of Health and Development (NSHD)

The MRC NSHD initially included all 13,687 births in England, Wales and Scotland from one week in March 1946 (149) and it aimed to investigate fertility rates, infant health and maternity services. It was not feasible to follow-up all births at that time, hence the sampling strategy was devised to include participants from all eligible births to women with husbands in non-manual and agricultural occupations, as well as one-fourth of all births to women with husbands in manual occupations, which constituted the majority of the workforce (149). This resulted in the social class-stratified, nationally representative, sample of 5,362 children of married mothers only. The participants have been followed up on 24 occasions (150). During their childhood, interviews with the mothers were regularly conducted by health visitors and additional assessments were made with school doctors and teachers (151). The main aim of data collection was to investigate the effect of the home and school environment on physical and emotional development and educational attainment

(151). During adulthood, research nurses conducted home visits at ages 26, 36, 43, 53 and 69, with additional detailed clinic visit between ages 60-64 (150). There have also been a number of postal questionnaires. The participation rate at the latest home visit (age 69) was 57.2% (N=2,149) of the original productive sample after excluding those who died or permanently emigrated (150). The NSHD is largely representative of the population of older adults in Great Britain despite some losses to follow-up, meaning that results are likely to be generalisable to this generation (150, 152). The NSHD was granted ethical approval from the Greater Manchester Local Research Ethics Committee and the Scotland Research Ethics Committee and all participants have provided informed consent. In the thesis, I used the data sweeps at age 0 (at birth), 15, 36, 43, 53, 60-64 and 69 in Chapter 5.

3.2 The 1958 National Child Development Study (NCDS)

The NCDS follows the lives of 17,415 people born in England, Scotland and Wales in a single week of 1958 (153). It has collected information on physical and educational development, economic circumstances, employment, family life, health behaviours, wellbeing, social participation and attitudes. Since the first survey at birth in 1958, there have been ten further data collection points at ages 7, 11, 16, 23, 33, 42, 44-46, 50 and 55 years. There was a considerate drop in the sample size at age 23 (n=12,537, compared with n=14,647 at age 16) due to participants moving to a new address and inability to trace them. Refusal rates have been relatively low: 7.1% at age 23, 11.1% at age 33, 13.2% at age 42 (154). At the latest data sweep, at age 55, 8,670 participants (58.7% of the original sample after excluding those who died or permanently emigrated) took part in the survey. The NCDS was designed to be representative for cohorts born around the same (it included 98% of all the births in

Great Britain in a single week), hence the participants nearly exclusively white (153). The NCDS has been granted ethical approval for each sweep from 2000 by the National Health Service (NHS) Research Ethics Committee and all participants have given informed consent. In the thesis, I used the data sweeps at age 0 (at birth), 7, 11, 16, 23, 33, 42, 44-46, 50 in Chapter 4 and at age 0 (at birth), 23, 33, 42, 44-46, 50 in Chapter 5.

3.3 The 1970 British Cohort Study (BCS70)

The BCS70 follows the lives of 17,196 people born in England, Scotland and Wales in a single week of 1970 (155). The BCS70 has collected information on factors such as health, physical, educational and social development and economic circumstances. Since the first survey at birth in 1970, there have been nine other surveys at ages 5, 10, 16, 26, 30, 34, 38, 42 and 46-48 years. There was a considerate reduction in sample size between ages 16 and 26 due to teacher's strike (sweep at age 16) and cohort members not successfully traced by a postal survey (sweep at age 26). This resulted in a reduction in the productive sample from 13,774 (80.1% of the original sample) at age 10, to 8,332 (48.5% of the original sample) at age 26. Refusal rates have been relatively low, for instance, 7.3% at age 30 and 7.6% at age 34 (156). At the latest data sweep, at age 46-48, 7,951 participants (50.3% of the original productive sample after excluding those who died or permanently emigrated) took part in the survey. The BCS70 was designed to be representative for cohorts born around the same, hence the participants nearly exclusively white (155). The BCS70 has been granted ethical approval for each sweep from 2000 by the National Health Service (NHS) Research Ethics Committee and all participants have given informed consent. In the thesis, I used the data

sweeps at age 0 (at birth), 5, 10, 16, 26, 30, 34, 38, 42, 46-48 in Chapter 4 and at age 0 (at birth), 26, 30, 34, 38, 42, 46-48 in Chapter 5.

3.4 The Uppsala Birth Cohort Multigenerational Study

The Uppsala Birth Cohort Multigenerational Study (157, 158)—follows a cohort of 14,192 men and women born in the Uppsala University Hospital (Uppsala, Sweden) between 1915 and 1929 and their children, identified through the Multi-Generational Register. Among the members of the original sample of the study, 12,168 were living in Sweden in the late 1940s, hence they received unique personal identification numbers (159), which remain unchanged and allow for the linkage across national registers. They also allowed for a linkage of information on descendants of the original cohort members obtained from routine registers. In 2007-2011, the study was further developed by including information collected manually from church parish records, school archives and records from the Census in 1930. This resulted in multigenerational study spanning five generations: 14,192 original cohort members, their 22,559 children, 38,771 grandchildren and 25,471 great grandchildren born up to 2009. The data on two generations, original cohort members and their children, were used in the Chapter 6. The UBCoS Multigen includes rich information on social background, family characteristics, morbidity and mortality. The sample of initial study members is nationally representative of Sweden in terms of infant mortality and fertility (160), with a marginally higher proportion of births to single mothers (161) and infants from urban areas (162). The study was approved by the Regional Ethics board in Stockholm.

Chapter 4: Early-life predictors of mid-life multimorbidity: evidence from the 1958 and 1970 British birth cohorts

Chapter objectives:

- To estimate the prevalence of multimorbidity in mid-life (age 46-48) in the 1970 British birth cohort.
- To examine the association between early-life characteristics and mid-life multimorbidity in the 1970 British birth cohort.
- To compare the estimates of multimorbidity and the magnitude of associations across the 1958 and 1970 British birth cohorts.

Key findings:

- The prevalence of multimorbidity in mid-life (age 46-48) was 33.8% in the 1970 British birth cohort.
- Early-life parental social class, birthweight, cognitive ability, body mass index at age 10, internalising and externalising problems at age 16 were associated with multimorbidity at age 46-48.
- The prevalence of multimorbidity was higher in the 1970 birth cohort compared with the 1958 birth cohort, using a comparable multimorbidity definition across cohorts: 24.3% vs 17.8%.
- The association between early-life characteristics and mid-life multimorbidity remained stable across both birth cohorts in relative terms.

4.1 Introduction

Multimorbidity has increased in the last two decades in high-income countries and the rise is projected to continue (163-165). In addition, a study conducted in Canada suggests that multimorbidity tends to emerge at an increasingly earlier age and in younger birth cohorts (166). This presents a challenge to the quality of life and safety, due to increased risks related to polypharmacy and complex health needs among those with multimorbidity (165). Multimorbidity is also associated with high healthcare utilisation and costs, which increase with the number of co-occurring conditions (167). However, research on multimorbidity is still relatively sparse—particularly among the younger (middle-aged) individuals, who will constitute the future older population (168). Hence, the Academy of Medical Sciences published an international policy report in 2018 outlining recommendations for future research that will facilitate public health policies and interventions (168). These include estimating the burden and nature of multimorbidity and how it changes over time as well as studying modifiable risk factors across common clusters of diseases (168).

4.1.1 Estimating the prevalence of multimorbidity and trends over time

A key challenge of estimating the prevalence of multimorbidity is a lack of agreement on its definition (168, 169). Typically, multimorbidity is defined as the presence of two or more long-term conditions (168, 170). However, the approaches vary greatly in terms of the types of conditions included, their number and how they are measured (168, 170, 171). For instance, inconsistencies in the definition include limiting multimorbidity to physical health conditions, as opposed to considering both physical and mental health, excluding (or not) conditions that are often seen as risk factors, such as obesity or substance dependency (163-165, 168). In order to resolve these

discrepancies, the National Institute for Health and Care Excellence (NICE) (172) specified in 2016 that multimorbidity ought to comprise at least one physical health and mental health long term conditions and these can include:

• Defined physical and mental health conditions such as diabetes or schizophrenia,

• Ongoing conditions such as a learning disability,

• Symptom complexes such as frailty or chronic pain,

• Sensory impairment such as sight or hearing loss,

• Alcohol and/or substance dependency.

The inconsistent approaches to studying multimorbidity led to a wide range of estimates of multimorbidity. For example, a systematic review of 39 observational studies across twelve countries reported prevalence from around 13% to 95% (173). Another systematic review found similarly varied estimates in the general population ranging from 13% to 72% (174). It is highly challenging to disentangle the variation reflecting true differences in the prevalence between populations and attributable to differences in definition. Certainly, the higher number of included conditions in the definition results in higher estimates (175, 176). For instance, a retrospective cohort study in the UK showed prevalence ranging from 16% to 58%, depending on whether multimorbidity was defined according to the UK Quality and Outcomes Framework pay-for-performance programme or the wider Johns Hopkins University Adjusted Clinical Groups Case-Mix System (177). More recent sources also provide widely varying estimates due to the aforementioned reasons. For instance, the GP Patient Survey estimated the prevalence of multimorbidity to be around 31%, while the Health Survey of England found 15% (178). The most comprehensive estimate of

multimorbidity in mid-life in the UK is 30.4%, reported among over 1.7 million general practice patients aged 45-64 in 2007 (179). Prevalence among middle-aged individuals (age 40-60) in high-income countries was found to range between around 15% and 80% in the period of 1961-2013 (173).

The estimates of the prevalence of multimorbidity vary greatly and most of the estimates in the UK are somewhat outdated. Furthermore, studies of trends over time using consistent methodology are lacking and are mostly limited to the older population (168). Hence, the Academy of Medical Sciences identified estimating the prevalence of multimorbidity using an agreed definition, as their main research priority (168). In addition, the need for studying age-specific trends over time using consistent methodology was emphasised (168). Estimates in younger, middle-aged populations, would be of particular benefit due to a gap in the literature and as they would help to project future healthcare and societal demands (168).

4.1.2 Early-life determinants of multimorbidity

Due to the high prevalence of multimorbidity, there is an urgent need to gather high-quality evidence about its determinants (168). Such evidence may help to identify populations at elevated risk, guide the development of health interventions and optimise allocation of resources (168). The report by the Department of Health proposed that at this early stage of research, we ought to focus on wider determinants of a range of health conditions occurring throughout the life course (180). This is in recognition that people may experience multimorbidity due to greater exposure to personal or societal risk factors, such as persistent and accumulating socioeconomic disadvantage (180). As alluded to in section 1.2.3, such factors tend to emerge early in childhood, setting a life course trajectory of adverse exposures—

linked through biopsychosocial pathways—which are predisposing to adult morbidity (181, 182). This may be due to physiological reactions, such as altered neuroendocrine hormone levels, toxic stress and increased allostatic load, which leads to damage in metabolic, cardiovascular, immune and nervous systems (183, 184). This early damage may directly result in loss of functioning, in accordance with sensitive or critical period theories of life course (41, 42). In addition, early cognitive and social disruptions may increase the risk of harmful behaviours such as smoking or alcohol consumption adopted as coping mechanisms and leading to further damage—as proposed by the chain of risks life course models (184, 185). Therefore, as explained in section 1.2.3, acting in this life phase is likely to bring the greatest benefits.

There is also a methodological advantage of studying exposures occurring early in the causal chain. The earlier the exposures are observed, the fewer factors potentially confound their relationship with adult health outcomes. In addition, potential confounders are likely to be related to parental and household characteristics that are widely measured in the British birth cohorts. For instance, when studying the link between socioeconomic status at birth and multimorbidity in adulthood, this relationship cannot be confounded by later education or income as they fall on the causal pathway. Moreover, early-life exposures are less likely to suffer from reverse causality. As in the above example, experiencing multiple health conditions can limit one's participation in the labour market in adulthood (186), however, it cannot affect one's socioeconomic position in childhood. Naturally, there is a range of potential confounding factors that need to be considered, related mainly to parental and household characteristics (see Appendix 2A for the list of confounders controlled in related studies).

Some childhood exposures may act primarily through their direct effect on later health, while other factors may mainly act through indirect pathways. For instance, cognitive development and educational performance, are believed to shape socioeconomic circumstances in adulthood, which in turn influence health (187). Whereas exposure to poor mental health in childhood may have a more direct impact on adult's health through physiological dysregulation (188). Hence, early-life risk factors may operate either via social chains of risk or by causing physiological dysregulation at earlier life stages which form part of long-term biological or psychological chains of risk (187).

In this study, I focus on early influences on later health across a range of domains including physical health and growth (birthweight and BMI at age 10/11), emotional development (internalising and externalising problems at age 16), cognitive function (cognitive ability at age 10/11) and socioeconomic circumstances (father's social class at birth). These characteristics are potentially malleable, hence they may serve as foundations for health interventions. However, it has to be recognised that social class may not be directly modifiable but it can be thought of as a proxy for socioeconomic disadvantage whose immediate consequences can be mitigated (189)—for instance through family-wide educational interventions (190). Likewise, it has been debated if cognitive ability can be modified (191). The evidence suggests that at least certain aspects of it are malleable (192, 193). These include verbal and performance skills (192), whose improvement may lead to better educational outcomes or greater vocational skills (194).

Another criterion in identifying relevant exposures was that there are existing systematic structures, such as schools or primary care, which can be used to act on

those exposures. The evidence for the effectiveness of approaches implemented in these settings is promising (195, 196). For instance, schools have been considered as the right settings for addressing child or adolescent mental health problems, with the most effective interventions involving parents (197, 198). Finally, the selected exposures have been widely studied in the context of adult health, but not multimorbidity and there were clear theoretical reasons to believe that they may affect a wide range of morbidity outcomes—hence increasing the plausibility of their causal effect on multimorbidity (199). These potential mechanisms are briefly described in the discussion section.

Finally, I studied the selected early-life exposures across two different British birth cohorts—the NCDS (born in 1958) and BCS70 (born in 1970). Examining the associations across changing contexts, for instance, related to demographic composition or education, will lead to a greater generalisability of the findings and further understanding of the process of social change and its impact on health (63). Whereas changes in the magnitude of the association over time will indicate varying morbidity processes, where certain risk factors may be more or less harmful over time. For instance, it has been found that obese adults experienced the largest increase in multimorbidity over-time (Odds Ratio=1.65; $p<0.001$ for 2012–13 vs. 1996–97) (200). Likewise, Li and colleagues showed that the association between BMI trajectory and adult blood pressure was stronger in the 1958 birth cohort compared with the 1946 cohort (73). There is also some evidence that child mental health problems have become more strongly associated with negative social, educational and mental health outcomes over a 40-year period (201). This is contrary to the association between childhood cognitive ability and mental health, which weakened in the 1970 birth cohort compared with the 1958 birth cohort (202).

4.1.2.1 Studying multimorbidity clusters

Multimorbidity can encompass many different combinations of conditions and there is evidence that certain conditions are more likely to cluster than others (173, 203). Hence, at this early stage of research it has been suggested to study specific clusters of health outcomes, which occur frequently or have particularly severe implications on lives of multimorbid individuals (168). The most common clusters of conditions comprise depression, cardiometabolic, respiratory and musculoskeletal conditions (173, 203, 204). Co-occurring mental health and physical health conditions appear to have particularly detrimental effects on quality of life, clinical outcomes and premature mortality compared with having physical or mental health conditions only (205-207). In addition, mental health and physical health conditions tend to co-exist to a greater extent in younger adults than in those over 50 years of age (208, 209), hence may be particularly relevant for the population of this study. Therefore, I selected clusters of conditions including mental health as well as diabetes, asthma, hypertension and arthritis.

4.1.3 Evidence on early-life determinants of multimorbidity

Reports commissioned to summarise evidence on multimorbidity emphasised that research on the determinants of multimorbidity is “sparse, conflicting and mainly limited to cross-sectional studies” (168, p. 43), with few studies of factors associated with multimorbidity (168). Other limitations of evidence include using definitions of multimorbidity derived for specific studies, as opposed to employing an agreed definition (200, 210-213), not accounting for a wide range of confounders—particularly family characteristics (200, 210, 211, 213) and being rarely representative of the target population (200, 210) (Appendix 2A includes details of key relevant

studies). The evidence (if available) is discussed in the order of 1) longitudinal studies of the association between the exposure and multimorbidity; 2) systematic reviews of the association between the exposure and individual health conditions typically used in defining multimorbidity; 3) longitudinal studies, using the British birth cohorts, of the exposure and individual health conditions typically used in defining multimorbidity. The literature was identified by searching reference lists of key publications (mainly systematic reviews) and retrieving studies that cited those publications. I did not conduct systematic searches of the literature in this chapter due to a large number of terms related to the exposures and morbidity outcomes, which result in a very higher number of identified publications by search engines.

4.1.3.1 Birthweight

One study examined the association between birthweight and multimorbidity (at age 64-68) longitudinally, in the Hertfordshire Cohort Study in England, showing a lack of association in an unadjusted model (as well as multivariate model) (OR=1.29, 0.58 to 2.89) (212). Similar findings were obtained for infant growth in the study. The main limitations of this study are relatively small sample size (<2000) and lack of information on potential bias due to missing data, potentially limiting generalisability of the findings to the population of Great Britain (212).

As far as the association with other adult health outcomes is concerned, Belbasis and colleagues conducted a large umbrella review including 39 systematic reviews and meta-analyses, which indicated “highly suggestive evidence” for the association of low birthweight with all types of leukaemia, overweight or obesity (214). The review also emphasised the importance of accounting for gestational age in studying the relationship between birthweight and later health (214).

The relationship between birthweight and adult health outcomes has been studied in the British birth cohorts (215-217). These studies tended to be well-adjusted due to the availability of rich information on potentially confounding factors occurring throughout the life course. There was evidence for the association between birthweight and self-reported fair/poor general health at age 30/33 in the NCDS and BCS70 (OR=1.16, 0.99 to 1.36), but not with long-standing illness at the same age—after adjustment for a range of mainly socioeconomic, family-related variables (215). Cooper and Power also found evidence for the association between lower birthweight and higher cholesterol among women, but not men at age 44/45 in those cohorts (216). However, the study controlled for a range of variables potentially lying on the causal pathway in each multivariate model. For instance, minimally adjusted models included growth or current BMI, whereas fully-adjusted controlled for characteristics such as physical activity and lifetime socioeconomic position, all of which may result in underestimation of the relationship.

There was also evidence for the association between lower birthweight and systolic blood pressure (but not diastolic) in the older birth cohort (1946 - NSHD) (217). The study, however, limited their adjustment to childhood social class.

4.1.3.2 Childhood socioeconomic position

One study recently examined the association between parental social class at birth and multimorbidity in adulthood, in the Aberdeen Children of the 1950s cohort (Scotland), showing that children of father's in unskilled social class at birth had higher odds of multimorbidity (OR=1.43, 1.06, 1.93) (211). After adjustment for educational attainment, gender, cognition at age seven and school type, this association highly attenuated (OR=1.20, 0.91, 1.70) (211). However, again these

variables are likely to lie on the causal pathway between parental social class and multimorbidity, rather than acting as confounders, hence they do not provide reliable estimates of adjusted direct effect of the exposure on the outcome (218).

In a systematic review, including 40 studies published up to 2006, childhood socioeconomic position was found to be associated with a higher risk of cardiovascular and coronary heart diseases (219). This association was only partially explained by adult socioeconomic position. Childhood manual social class was found to be associated with early-life and mid-life systolic blood pressure, but not diastolic, after adjustment for gender and birthweight in the NSHD (217). In a longitudinal prospective cohort study of over 7,000 British civil servants in England (the Whitehall II study), low childhood socioeconomic position at age 16 was found to be associated, independently from adult cognitive ability, with a greater risk of a range of mid-life health outcomes (at age 47-69): coronary heart disease (RR=1.95, 1.36 to 2.81), self-rated poor health (RR=1.69, 1.17 to 2.44), psychological distress measured by the General Health Questionnaire (RR=1.52, 1.14 to 2.03), physical (RR=1.30, 0.98, 1.74) and mental (RR=1.69, 1.26, 2.26) component scores of the Short Form 36 General Health Survey scales (220). Cognitive ability in mid-life explained some of the relation between socioeconomic position and health: 17% for coronary heart disease, 33% for physical functioning, 12% for mental functioning and 39% for self-rated health (220).

4.1.3.3 Childhood and adolescence body mass index

To the best of my knowledge, there is no study of the association between childhood BMI or obesity and multimorbidity, however, two studies investigated the link between adult obesity and mid-life multimorbidity (200, 210). A cross-sectional study

of the National Population Health Survey (conducted in 1996-7) and Canadian Community Health Surveys (conducted in 2012–13) found an association between obesity and multimorbidity in both surveys after adjustment for age, gender, marital status, immigrant status, home ownership, rural residence, education, income quintile, smoking status and alcohol consumption (200). The relationship appeared to strengthen over time. For instance, those with obesity class II/III (vs without obesity) had 48% (OR=1.48, 1.13, 1.95) higher odds of multimorbidity in 1996-7 compared with 391% in 2012-3 (OR= 3.91, 3.06, 4.99). Another cross-sectional study—adjusted for age, gender, socioeconomic deprivation and smoking—found an association between obesity and multimorbidity in the sample of 30-year-olds or older, using the Clinical Practice Research Datalink (2005-2011).

Childhood BMI or obesity was not studied in the context of multimorbidity, however, there is an extensive literature on the association with other health outcomes. In a systematic review of 39 studies conducted until 2012, Park and colleagues found strong evidence for an association between BMI or obesity up to age 19 and diabetes, hypertension and coronary heart disease. These associations were robust to adjustment of a variety of potential confounders (221). More recently, an analysis of the British birth cohorts—NSHD and NCDS—revealed that BMI at ages 7-16 was positively associated with systolic blood pressure and this relationship appeared to strengthen over time (73).

4.1.3.4 Childhood and adolescence cognitive ability

There were no studies of the association between childhood cognitive ability and multimorbidity. I identified one study that found a link between higher cognitive ability at age 10/11 and lower odds of long-term sickness at age 34-53 after adjusting for

gender and social class in NSHD, NCDS and BCS70 (222). There was some evidence for a stronger relationship between the exposure and the outcome in the more recent cohort: BCS70 (OR=0.80, 0.66 to 0.97), compared with NSHD (OR=0.70, 0.56 to 0.86) or NCDS (OR=0.69, 0.61 to 0.77) (222). However, the outcome was measured at different ages across the cohorts (34 in BCS70 vs 42 in NCDS and 53 in NSHD) and cohort membership, as an effect modifier, was not formally tested in this study.

4.1.3.5 Childhood and adolescence emotional development

Childhood emotional development, defined as internalising and externalising problems, has not been studied in the context of multimorbidity. However, longitudinal studies conducted in the UK have been used to examine the association between emotional development and both mental and physical health outcomes. Neeleman and colleagues found an association between negative affect, aggression as well as anxiety at age 13-15 and count of both somatic and psychiatric symptoms at age 43 (213). This study, however, only adjusted for gender, not considering any other potential confounding variables (213). In the NCDS, externalising problems (e.g. “antisocial”) at age seven but not internalising ones (e.g. “neurotic”), were associated with psychological distress at age 33, after adjusting for a wide range of potential confounders: including parental socioeconomic status at birth and parental mental health (223). More recently, Henderson and colleagues studied one specific internalising problem in the Aberdeen Children of the 1950s—often appearing to be miserable or unhappy at age 6-12—and found that it was strongly associated with being permanently sick or disabled at age 46-51 (OR=3.81, 1.01 to 14.4), when year-

of-birth, gender, IQ (Intelligence Quotient) and father's social class in childhood were accounted for (224).

4.1.4 Aims and hypotheses

Due to the aforementioned limitations of the evidence, the main objectives of this study are: (1) to estimate the prevalence of multimorbidity in mid-life (age 46-48) in the BCS70 (14); (2) to examine the association between early-life characteristics and mid-life multimorbidity in the BCS70. I hypothesised that birthweight, father's social class at birth, BMI at age 10, cognitive ability at age 10, internalising and externalising problems at age 16 will all be associated with multimorbidity (age 46-48). As an association between exposures and multimorbidity may be driven by mechanisms of action related to specific components of multimorbidity, I additionally studied associations between the exposures and the most common clusters of conditions and their individual components (168). As a secondary objective, I compared the estimates of multimorbidity and the magnitude of associations across two cohorts, born 12-years apart (1958 vs 1970): the NCDS and the BCS70. This will improve generalisability of findings across different birth cohorts. Finally, as the evidence on cross-cohort trends in mid-life morbidity is limited (see Chapter 2), I also present relative risk difference across the cohorts for experiencing individual health conditions.

4.2 Methods

4.2.1 Participants

Details about the history, design and features of the NCDS and BCS70 have been previously described (149, 155, 225-227) and more details are provided in Chapter 3. In brief, both surveys included all surviving children born in England, Scotland and Wales in a single week: NCDS in March 1958 (n=17,415) (226), BCS70 in April 1970 (n=17,196) (155). The analytical sample included those who participated in the biomedical sweeps of BCS70 at age 46-48 (data collection lasted two years) (n=7,951) and NCDS at age 44-46 (n=8,883) (data collection lasted two years) (Figure 4.1). In order to facilitate cross-cohort comparison of NCDS and BCS70, multiple comparable biomedical measures were included in both sweeps.

The age 46-48 sweep (conducted in 2016-2018) of BCS70 included many data collection elements, such as 45-minute core interview (topics covered: relationships, children, parents, place of residence, economic activity, income, qualifications and training, physical and mental health, smoking, drinking, exercise), cognitive assessments, self-completion paper questionnaire (topics covered: physical health, mental health and well-being, physical activity and leisure activities), anthropometric measurements (height, weight, body-fat, waist/hip circumference), blood pressure measurement, grip strength assessment, balance assessment, blood sample collection, activity monitor, online dietary diary (228). Bio-measures were administered by a nurse, who also collected contextual information about each measurement (228).

Likewise, the age 44-46 sweep (conducted in 2002-2004) of NCDS comprised a range of measures, including a computer-assisted self-completion interview (topics

covered: drinking, mental health), vision, blood pressure measurement, hearing, anthropometric measurements (height, weight, body-fat, waist/hip circumference), lung function, sight, paper self-completion questionnaires (sun exposure, physical activity connected with work, hearing, eyesight, pain, working conditions, household circumstances, social support general health and diet, leisure exercise, employment, partnership status and children life events) (229).

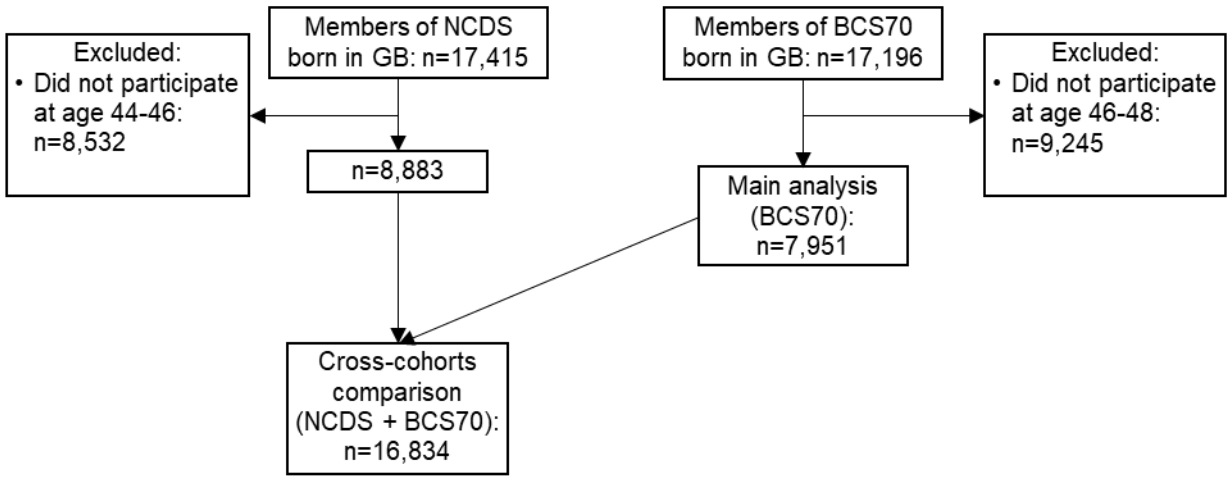


Figure 4.1 Flow diagram of the study sample.

4.2.2 Measures

Details on the measures of all variables used in the study can be found in Tables 4.1 – 4.4.

4.2.2.1 Multimorbidity

Multimorbidity was defined as presence of “two or more long-term health conditions where at least one of these conditions must be a physical health condition” (14; p. 17). These can include physical and mental health conditions, symptom complexes (e.g. chronic pain), sensory impairment, alcohol and substance misuse (14).

For the analyses using BCS70 exclusively, multimorbidity comprised self-reported conditions diagnosed since the previous interview (four years or more) (e.g. asthma, heart problems; see Table 4.1 for the full list), alcohol problems (Alcohol use disorders identification test; primary care ≥ 5), mental health problems (Malaise Inventory ≥ 4), hypertension (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or taking medications) and diabetes (Glycated Haemoglobin of 48 mmol/mol ≥ 6.5% or taking medications). Tables 4.1 and 4.2 provide details on how these variables were measured.

For cross-cohort comparisons, the definition of multimorbidity was derived using health outcomes comparable across the NCDS and BCS70. The multimorbidity outcome was a binary indicator of having two or more health outcomes. The multimorbidity comprised lifetime prevalence of self-reported (at age 42) migraine, asthma/bronchitis, convulsions/epileptic seizures or fits, any cancer, mental health problems (using the Malaise Inventory in both cohorts (230)); objectively measured hypertension and diabetes at age 44-48. Table 4.2 provides details on how hypertension and diabetes were measured in NCDS and BCS70.

While NCDS asked about ever having a given condition (lifetime prevalence), BCS70 asked about having a condition since the last interview. Thus, lifetime prevalence variables were derived by combining four (complete) waves of the BCS70, age 42 (4-year period prevalence), age 38 (point prevalence), age 34 (4-year period prevalence) and age 30 (lifetime prevalence). Table 4.3 and Appendix 2B provide more details on how these variables were harmonised. I also comment on cross-cohort differences in obesity, as BMI measure was available in biomedical sweeps and it is considered an important risk factor for major long-term conditions (231).

4.2.2.2 Exposures

The same exposures were used in the main analyses of BCS70 only and in pooled analyses of NCDS and BCS70. Birthweight (kg) was recorded in the birth survey by a midwife who attended the delivery. BMI at age 10/11 was derived from a measure of weight and height obtained by a range of different health practitioners. Father's social class at birth (SES) refers to the occupation of the father coded according to the Registrar General's classification (I – professional, II – managerial and technical, III – skilled non-manual/manual, IV – partly-skilled and V – unskilled) (232). Cognitive ability was assessed by the General Ability Test (233) in NCDS (age 11) and a modified version of the British Ability Scales (234) in BCS70 (age 10). Following the approach used in previous studies, I performed a principal components analysis for each of the verbal and nonverbal sub-tests, in order to obtain scores indicating a general cognitive ability factor (g) and to ensure similar relative ranking in the latent unmeasured trait (202, 235). The scores were standardised to a mean of zero and a standard deviation of one. Internalising and externalising problems were captured with the modified version of the Rutter A scale, completed by mothers of the participants as part of the home interview (230). See Table 4.4 for details on measures of exposures.

4.2.2.3 Confounders

A range of child and family characteristics were controlled, which have been suggested in previous research to confound an association between early-life exposures and adult health (see Appendix 2A for the list of studies; Table 4.4 and Appendix 2C for details on measures of confounders). These included gestational age, birthweight and father's social class at birth—when they were not used as

exposures, whether mother ever smoked during pregnancy, mother breastfeeding, mother's height, mother's marital status at birth, mother being a teen at birth, household tenure (age 5-11), overcrowding (age 5-11), parental interest in child's education (age 10/11), length of time absent from school due to illness (age 10/11), parental divorce (age 16) (see Appendix 2C for more details).

Table 4.1 Description of self-reported outcome variables under multimorbidity definition in BCS70.

Variable	Type of variable	Age	Description
Self-reported chronic morbidity	Outcome	46-48	Questionnaire was self-administered with the computer-assisted personal interviewing (CAPI). The question was: “Since the last interview/4 years ago have you had any of the health problems listed on this card? Please include any health problems that had already started before that date.” - Asthma or wheezy bronchitis; convulsion, fit, epileptic seizure; recurrent backache, prolapsed disc, sciatica or other back problem; cancer or leukaemia; problems with hearing; problems with eyes (do not include problems which are resolved by wearing glasses or contact lenses – e.g. short sightedness, long sightedness or astigmatism); heart problems; chronic fatigue syndrome (ME); liver disease including viral hepatitis B or C; arthritis; stroke.
Drinking	Outcome	46-48	Drinking behaviours were measured with the Alcohol use disorders identification test for primary care (AUDIT PC), including five questions (236). A score of five or more indicates high-risk drinking (237). The test was found to have 98.3% sensitivity 90.9% specificity for detecting hazardous drinkers in randomly selected primary care patients (237).
Mental health problems	Outcome	46-48	BCS70 at age 46-48 used the Malaise Inventory (230), which was self-administered with the computer-assisted personal interviewing (CAPI). A shorter 9-item version (as opposed the full 24 items version) was used, with a binary (“yes-no”) response scale. It showed robust psychometric properties when tested in general population: Cronbach’s alpha = 0.70 – 0.80; all items identify a common factor; AUC against self-reported diagnosed psychiatric morbidity = 0.77–0.79) (238).

Table 4.2 Description of outcome variables used under both definitions of multimorbidity – in BCS70 only and in NCDS and BCS70 for cross-cohort comparisons.

Variable	Type of variable	Age	Description
Obesity	Outcome	44-46 (NCDS)/ 46-48 (BCS70)	Obesity was derived as BMI equal 30 or higher (239). I calculated body mass index (BMI, kg/m^2) at age 44-46 using height and weight measurements obtained with Leicester portable stadiometers and Tanita solar scales, while participants were lightly clothed and unshod. In NCDS, the values were derived as a part of the larger work package by the Cohort and Longitudinal Studies Enhancement Resources (CLOSER) aiming to facilitate comparisons of the British cohort studies (240). For consistency, the protocol was followed to derive BMI values in BCS70. A standardised data cleaning protocol was applied (240): a) This involved removal of biologically implausible values using sensible yet arbitrary cut-offs (e.g., weight > 250 kg and height > 3 m); b) Inspection of a connected scatter plot of serial weight or height against age (i.e., a trajectory) for persons with a measurement or change in measurement between two consecutive ages greater than five standard deviations from the gender and study stratified mean. This resulted in two values being replaced with missing in BCS70.

Table 4.2 (cont.) Description of outcome variables used under both definitions of multimorbidity – in BCS70 only and in NCDS and BCS70 for cross-cohort comparisons.

Variable	Type of variable	Age	Description
Hypertension	Outcome	44-46 (NCDS)/ 46-48 (BCS70)	Hypertension was defined as SBP≥140 mmHg or DBP≥90 mmHg or taking medications for high blood pressure. These medications included β-blockers, drugs affecting the renin–angiotensin system, calcium channel blockers and diuretics. Medications were self-reported. The name of each medication was recorded and where possible nurses asked to see the medication packaging to increase accuracy. Systolic and diastolic blood pressure was measured in a seated position, after 5 min rest, using automated oscillometric devices (NCDS: Omron HEM 705; BCS70: OMRON HEM 907). Both cohorts used a large cuff for participants with a mid-upper arm circumference 32 cm. The measurement was repeated three times and all successful and reliable measures were averaged to obtain final blood pressure values (NCDS: n=8,740; BCS70: n = 6,970) (241). The measurement was taken on the left arm in BCS70 and the right arm in NCDS, which however should not introduce any bias as shown by the studies reporting on double-arm measurements (242). Pregnant women were excluded from both studies.

Table 4.2 (cont.) Description of outcome variables used under both definitions of multimorbidity – in BCS70 only and in NCDS and BCS70 for cross-cohort comparisons.

Diabetes	Outcome	44-46 (NCDS)/ 46-48 (BCS70)	Diabetes was indicated as Glycated Haemoglobin (HbA1c) of 48 mmol/mol (6.5%) or over or taking medications for diabetes (243). Medications were self-reported. The name of each medication was recorded and where possible nurses asked to see the medication packaging to increase accuracy. Glycated haemoglobin is an integrated measure of the level of sugar in the blood over the previous eight to 12 weeks before measurement. HbA1c it is regarded as a useful screening tool for detecting diabetes in general population (244). In NCDS, HbA1C was measured on whole citrated blood by ion exchange high performance liquid chromatography, using the Tosoh A1c 2.2 Glycohemoglobin Analyser HLC-723GHb. In BCS70, HbA1C was measured using whole blood supplied in an ethylenediaminetetraacetic acid (EDTA) tube and was analysed using the Tosoh G8 analyser. Exclusion criteria included: people with clotting or bleeding disorder; people who were currently on anticoagulant drugs, e.g. Warfarin therapy; people who had had an epileptic fit in the last three years (NCDS); or who have ever had a fit (BCS70); people who were not willing to give their consent in writing; in BCS70 only – pregnant women; respondents who were HIV positive or who have hepatitis B or C.

Table 4.3 Description of self-reported outcome variables under multimorbidity definition in the NCDS and BCS70 – for cross-cohort comparisons.

Variable	Type of variable	Age	Description
Self-reported chronic morbidity	Outcome	42	The lifetime prevalence of any of the conditions: migraine/headaches, asthma/bronchitis, diabetes, convulsions/epileptic seizures/fits and any cancer. While NCDS asked about ever having a given condition (lifetime prevalence), BCS70 asked about having a condition since the last interview. Thus, lifetime prevalence variables were derived by combining four (complete) waves of the BCS70, age 42 (4-year period prevalence), age 38 (point prevalence), age 34 (4-year period prevalence) and age 30 (lifetime prevalence). The studies used the computer-assisted personal interviewing to collect the data for NCDS and for all waves within BCS70 apart from the age 38 (telephone interview). The wording of the items varied slightly, for instance NCDS at age 42 asked about having fits, convulsions or epilepsy, whereas BCS70 included convulsion, fit, epileptic seizure at ages 42, 38, 34 and fits, convulsions or epilepsy at age 30 (see Appendix 2B for details).
Mental health morbidity	Outcome	42	Both the NCDS and BCS70 at age 42 used the Malaise Inventory (230), which self-administered with the computer-assisted personal interviewing. A shorter 9-item version (as opposed the full 24 items version) was used, with a binary (“yes-no”) response scale. It showed robust psychometric properties when tested in general population: Cronbach’s alpha = 0.70 – 0.80; all items identify a common factor; AUC against self-reported diagnosed psychiatric morbidity = 0.77–0.79) (238).

Table 4.4 Description of covariates.

Variable	Type of variable	Age	Description
Birthweight	Exposure/confounder	0	Birthweight of each cohort member was measured in ounces and converted into kilograms.
Cognitive ability	Exposure/confounder	10/11	The cognitive ability was assessed by the General Ability Test (233) in NCDS (age 11), comprising tests of both verbal and non-verbal skills. Scores from this test correlate strongly with IQ-type test scores (r=0.93), hence providing a good proxy for IQ scores (233). The BCS70 used a modified version of the British Ability Scales (234) comprising four sub-scales: word definitions and word similarities were used to measure verbal ability and recall of digits and matrices was used to measure non-verbal ability. For both cohorts, a principal components analysis (PCA) was conducted for each of the verbal and nonverbal sub-tests, in order to attain a general cognitive ability factor (g). Following the protocol of previous studies, I saved scores from the first unrotated factor for each valid case (235). As previously, the first component accounted for 90% of the total variance in the NCDS (235). For the BCS70 cohort, I summed up the individual items to derive an overall score for each sub-test and I conducted a PCA on these four variables, again saving the first components score (accounting for 57% of total variance). The scores were standardised to a mean of 0 and a standard deviation of 1.
Body mass index (BMI)	Exposure/confounder	10/11	Height and weight were measured by trained medical personnel using standard protocols at ages 11 (NCDS), 10 (BCS), 16 (NCDS/BCS70). The weight and height measures were harmonised by the CLOSER consortium to facilitate comparisons across cohorts (240).

Table 4.4 (cont.) Description of covariates.

Variable	Type of variable	Age	Description
Externalising problems	Exposure/confounder	16	The modified version of the Rutter A scale, a measure of mental health capturing conduct problems, hyperactivity, emotional and peer problems, was completed by mothers of the participants as part of the home interview in both NCDS and BCS70 (230). As in previous studies (245); two scales were created: 1) externalising problems (five items, e.g. “destroys own or others belongings”) and internalising problems (three items, e.g. worries about many things). Each item has a 3-point response scale (“Not true”=0, “Somewhat true”=1, “Certainly true”=2). Hence, higher score reflects more externalising or internalising problems. The measure was tested in general population; acceptable inter-rater reliability (r = 0.64) and retest reliability (r = 0.74) (230).
Internalising problems	Exposure/confounder	16	
Father’s social class at birth	Exposure/confounder	0	Occupation of the father at the time of the participants’ birth was coded according to the classification Socio-economic Groups (SEG) classification introduced in 1951. in both NCDS and BCS70. Current or most recent jobs of participants’ fathers were classified as: I (professional), II (managerial and technical), III (skilled non-manual/manual), IV (partly-skilled) and V (unskilled); with those classified as “missing” who had unclassifiable occupation/had insufficient information/served in armed forces/were unemployed or sick or retired.

Table 4.5 Description of self-reported outcome variables under multimorbidity definition in the NCDS and BCS70 – for cross-cohort comparisons.

Variable	Type of variable	Age	Description
Self-reported chronic morbidity	Outcome	42	The lifetime prevalence of any of the conditions: migraine/headaches, asthma/bronchitis, diabetes, convulsions/epileptic seizures/fits and any cancer. While NCDS asked about ever having a given condition (lifetime prevalence), BCS70 asked about having a condition since the last interview. Thus, lifetime prevalence variables were derived by combining four (complete) waves of the BCS70, age 42 (4-year period prevalence), age 38 (point prevalence), age 34 (4-year period prevalence) and age 30 (lifetime prevalence). The studies used the computer-assisted personal interviewing to collect the data for NCDS and for all waves within BCS70 apart from the age 38 (telephone interview). The wording of the items varied slightly, for instance NCDS at age 42 asked about having fits, convulsions or epilepsy, whereas BCS70 included convulsion, fit, epileptic seizure at ages 42, 38, 34 and fits, convulsions or epilepsy at age 30 (see Appendix 2B for details).
Mental health morbidity	Outcome	42	Both the NCDS and BCS70 at age 42 used the Malaise Inventory (230), which self-administered with the computer-assisted personal interviewing. A shorter 9-item version (as opposed the full 24 items version) was used, with a binary (“yes-no”) response scale. It showed robust psychometric properties when tested in general population: Cronbach’s alpha = 0.70 – 0.80; all items identify a common factor; AUC against self-reported diagnosed psychiatric morbidity = 0.77–0.79) (238).

4.2.3 Missing data

Multimorbidity was missing in 3,793 out of 7,951 participants and the extent of missing data was greater in the BCS70 than in NCDS (see Appendix 2D). To preserve sample representativeness and reduce selection bias, I used multiple imputation with chained equations generating 50 datasets (246). Multiple imputation returns unbiased results under the missing at random (MAR) assumption, which implies that systematic differences between the missing and observed values can be explained by the observed data (247, 248). All variables used in the analysis were included in the imputation model. Some of these variables (e.g. BMI at age 10, mental health at age 16) were predictive of missingness (see Appendix 2D for the estimates) and having them in the imputation model increased the plausibility of the outcome being MAR. The precision of the model was further improved by inclusion of variables with very little missing data (less than <1%) collected at birth (e.g. smoking during pregnancy, birth marital status, gender). Finally, I enriched the imputation model and further maximised the plausibility of the MAR assumption with auxiliary variables (self-perceived general health, individual health conditions under multimorbidity outcome and smoking), which were not part of the substantive model of interest, but they were related to the probability of missingness and/or related to the incomplete outcome itself (see Appendix 2D).

In order to investigate sensitivity of the estimates due to missing information, the estimates of multimorbidity prevalence are also presented under different missing data generating mechanisms (see Appendix 2E for estimates)—complete cases where information is assumed to be missing completely at random (MCAR)—and across imputations based on samples with varying missing data due to different

inclusion criteria. All analyses were conducted in Stata 14.2 (249) and the results of analyses run on each dataset were pooled according to Rubin's rules (250).

4.2.4 Analysis

4.2.4.1 Exposures—multimorbidity association

The associations between exposures (birthweight, father's social class at birth, cognitive ability at age 10, BMI at age 10, externalising as well as internalising problems at age 16) and multimorbidity (age 46-48) in BCS70 were estimated with a multivariate Poisson regression. I present gender-adjusted estimates and further adjusted models that account for a range of child and family characteristics. I did not control for any covariates occurring in adulthood, for instance health behaviours or socioeconomic status, as they may mediate the association between early-life exposures and multimorbidity.

As a sensitivity analysis, the confounder-adjusted models were also re-run using a count of health conditions as an outcome. I also tested—using the Wald test—for non-linear associations between continuous exposures and outcome by including squared and linear terms (e.g. birthweight^2 and birthweight) in unadjusted regression models, but there was no evidence of departure from linearity. Likewise, using a similar approach no evidence of gender*exposure interaction was found.

In order to examine potential benefits of targeting each exposure, assuming a causal effect with multimorbidity, I estimated the proportion of multimorbidity cases that might have been avoided if the exposure among the most vulnerable 20% (i.e. scoring in the lowest/highest 1-2 decile) had had an average value of a given exposure equal to the one among the more favourable 80%. Hence, I estimated the difference between two marginal prevalences (the population attributable risk or PAR (251)), expressed as predicted probabilities: (1) the baseline scenario—with actual

prevalence of multimorbidity among the most vulnerable 20%; (2) the alternative scenario—with prevalence of multimorbidity among the most vulnerable 20% if they had the value of a given exposure equal to the one among those in other 80% of the sample, keeping other covariates constant. The predicted probabilities in both scenarios were obtained from the confounders-adjusted models using *mimrgns*, a user-written Stata command that applies Rubin's rules to pool estimates across multiply-imputed samples from Stata's built-in margins command (252).

4.2.4.2 Exploratory analysis – multimorbidity as clusters of conditions

Due to heterogeneous definitions of multimorbidity, it has been suggested that the focus of the initial research should be on the determinants of the most common clusters of conditions or those of the greatest impact (168). Based on the literature (204), I identified five most common combinations of conditions that can be paired using health outcomes included in this study: mental health morbidity and hypertension, mental health morbidity and arthritis, mental health morbidity and diabetes, mental health morbidity and asthma/bronchitis, diabetes and hypertension. Subsequently, I ran the confounders-adjusted model for each exposure and each cluster. As the clusters used in these analyses were derived from the multimorbidity outcome, they are likely to be closely-related hence increasing family-wise error rate. Thus, I present the findings considering a more stringent p-value threshold of 0.003—using the Bonferroni correction ($\alpha = 0.05$ divided by 20 tests) (253). In addition, I re-ran the confounders-adjusted models including individual components of these clusters as the outcomes. This helped to assess if the associations with the clusters were stronger in magnitude than with their individual components.

4.2.4.3 Cross-cohort comparisons

Relative difference across cohorts in prevalence of multimorbidity (and its individual components and obesity) was estimated using Poisson regression, where year-of-birth (or cohort membership) was used as the exposure. Ignoring or excluding participants on medication can bias associations (254), hence in cross-cohort comparison of levels of blood pressure and Glycated Haemoglobin (HbA1c): corrections were made for those: treated for hypertension (n=574: +10 mmHg for diastolic blood pressure and systolic blood pressure (254)) and taking oral medication for type 2 diabetes (n=210: +1% in absolute terms for Glycated Haemoglobin (HbA1c) (255)).

I used the Wald test to assess cohort differences in the association between the exposures and outcome in a series of unadjusted models including the year-of-birth*exposure interaction term. To facilitate interpretation of the interaction effects, fully-adjusted cohort-specific probabilities of multimorbidity were obtained across different values of each exposure. The values were obtained using *mimrgns* Stata command (252).

4.3 Results

4.3.1 Prevalence of multimorbidity

The prevalence of multimorbidity was 33.8% at age 46-48 in the BCS70. The most prevalent conditions were high-risk drinking (26.3%), recurrent back problems (20.9%) and mental health problems (19.1%) (see Table 4.5). Among the most prevalent chronic physical health conditions were asthma/bronchitis (11.7%) and arthritis (7.7%).

Table 4.6 Descriptive summary of the health variables and early-life exposures in the 1970 British birth cohort (BCS70).

	N=7,951
Outcomes (age)	%
Multimorbidity (46-48)	33.8 (32.6, 35.0)
Chronic fatigue syndrome (46-48)	1.5 (1.2, 1.7)
Arthritis (46-48)	7.7 (7.1, 8.3)
Stroke (46-48)	0.5 (0.4, 0.7)
Heart problems (46-48)	3.0 (2.6, 3.4)
Eyes problems (46-48)	4.9 (4.5, 5.4)
Hearing problems (46-48)	5.8 (5.2, 6.3)
Recurrent back problems (46-48)	20.9 (20.0, 21.8)
Drinking problems (46-48)	26.3 (25.3, 27.4)
Hypertension (46-48)	15.7 (14.8, 16.6)
Diabetes (46-48)	4.7 (4.1, 5.2)
Mental health morbidity (46-48)	19.1 (18.3, 20.0)
Asthma/bronchitis (46-48)	11.6 (10.9, 12.3)
Convulsion, fit, epileptic seizure (46-48)	1.1 (0.8, 1.3)
Cancer or leukaemia (46-48)	1.6 (1.4, 1.8)
	Mean (standard error)
Multimorbidity (46-48)	1.24 (0.02)
BMI (46-48), $kg.m^{-2}$	28.30 (0.08)
Systolic blood pressure, mmHg (46-48)	125.39 (0.19)
Diastolic blood pressure, mmHg (46-48)	77.73 (0.13)
HbA1C, % (46-48)	5.59 (0.01)
Malaise Inventory (46-48)	1.76 (2.12)
AUDIT-PC (46-48)	3.88 (2.58)
Exposures (age)	Mean (standard error)
Birthweight (0)	3.31 (0.01)
Cognitive ability (10)	0.16 (0.01)
Body mass index (10)	16.9 (0.03)
Internalising problems (16)	0.93 (0.02)
Externalising problems (16)	0.68 (0.02)
	%
Father's social class at birth (0)	
I – professional	6.1
II – managerial and technical	13.8
III – skilled non-manual/manual	60.8
IV – partly-skilled	13.9
V – unskilled	5.5

*Note. The outcome data were collected over the two year period when participants were 46-48 year old.

AUDIT-PC = Alcohol use disorders identification test; primary care.

4.4 Exposures—mid-life multimorbidity association

In gender-adjusted models, all exposures were associated with a greater risk of multimorbidity at age 46-48: lower birthweight, lower cognitive ability at age 10, higher BMI at age 10, more internalising and externalising problems at age 16 as well as a more disadvantaged father's social classes at birth ($p<0.001$): with unskilled class having 43% higher risk of multimorbidity (risk ratio; RR=1.43, 95% confidence interval 1.15 to 1.70) (Table 4.6).

Adjustment for potential confounders had little effect on the strength of the association. An additional kilogram of birthweight was associated with 10% reduced risk of multimorbidity (RR=0.90, 0.84 to 0.96); an increase of one point on BMI scale was associated with 3% higher risk (RR=1.03, 1.01 to 1.05); one standard deviation higher score on cognitive ability measure corresponded to 4% lower risk (RR=0.96, 95% CI 0.91 to 1.00); increase of one internalising problem was equated with 4% higher risk (RR=1.04, 1.00 to 1.08) and of one externalising problem with 6% higher risk (RR=1.06, 1.03 to 1.09). Findings based on the count of health outcomes, as opposed to a binary indicator, were largely consistent with the main analysis.

Table 4.7 Association between early-life exposures and multimorbidity at age 46-48 in BCS70.

N=7,951	Relative risk (95%CI)	
	Gender-adjusted	Confounders-adjusted
SES at birth (age 0)		N/A*
I – professional	Reference	-
II – managerial and technical	1.14 (0.94, 1.40)	-
III – skilled non-manual/manual	1.30 (1.09, 1.55)	-
IV – partly-skilled	1.43 (1.18, 1.74)	-
V – unskilled	1.43 (1.15, 1.77)	-
Birthweight (age 0)	0.86 (0.80, 0.91)	0.90 (0.84, 0.96)
Cognitive ability (age 10)	0.91 (0.87, 0.95)	0.96 (0.91, 1.00)[1]
BMI (age 10)	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)[2]
Internalising problems (age 16)	1.07 (1.04, 1.11)	1.04 (1.00, 1.08)[3]
Externalising problems (age 16)	1.09 (1.07, 1.12)	1.06 (1.03, 1.09)[4]

*Not adjusted for any other variables as they may potentially lie on the causal pathway.

All confounders-adjusted models included: gender, father's social class at birth, birthweight, mother ever smoked during pregnancy, mother breastfed, mother's height, mother's marital status at birth, mother being a teen at birth, household tenure (5-10), parental interest in child's education (10), overcrowding (5), length of time absent from school due to illness (10), parental divorce (16), mother's mental health (10).

[1] Additionally adjusted for BMI at age 10;
[2] Additionally adjusted for cognitive ability at age 10, externalising and internalising problems at age 16;
[3] Additionally adjusted for cognitive ability and BMI at age 10 and externalising problems at age 16;
[4] Additionally adjusted for cognitive ability and BMI at age 10 and internalising problems at age 16.

4.4.1 Population attributable risk

Among 20% with the highest mean of externalising problems (mean=2.84, standard error=0.05), 41.5% experienced multimorbidity. If their mean of externalising problems was reduced to the average of those in the other 80% (mean=0.04, standard error=0.004), while keeping other characteristics constant, 34.8% would have developed multimorbidity—hence 6.7% of cases might have been avoided assuming causality. The difference between such scenarios (PAR) might have resulted in 4.5% avoided cases of multimorbidity in regards to BMI, 3.8% to internalising problems, 1.6% to birthweight and 1% to cognitive ability. If cohort members whose father had partly-skilled/unskilled social class were “shifted” to one of the higher social classes, 5% cases of multimorbidity might have been prevented.

4.4.2 Exploratory analysis—multimorbidity as clusters of conditions

The prevalence of pairs of conditions were: mental health morbidity (MH)/hypertension (4.1%), MH/asthma (3.3%), MH/arthritis (2.5%), diabetes/hypertension (2.1%), MH/diabetes (1.4%).

There was strong evidence (at the Bonferroni corrected $p<0.003$) for the association between father’s SES at birth and clusters including mental health problems: MH/hypertension (for unskilled vs professional class: RR=2.92, 1.23 to 6.94) and MH/arthritis (RR=3.41, 1.46 to 7.95) (Table 4.7). These associations were stronger than for the individual conditions: arthritis (for unskilled vs professional class: (RR=1.86, 1.19 to 2.91), hypertension (RR=1.52, 1.05 to 2.20) and mental health problems (RR=1.54, 1.11 to 2.10; with p-value being slightly above the Bonferroni threshold: p=0.005) (Table 4.8).

Birthweight was associated with diabetes and hypertension, with 1kg higher weight being linked with 31% (RR=0.69, 0.54 to 0.87) and 21% (RR=0.79, 0.71 to 0.88) lower risk of having these conditions respectively (Table 4.8).

Cognitive ability was associated with MH/arthritis (RR=0.75, 0.63 to 0.89) and mental health problems (RR=0.89, 0.84 to 0.95) (Table 4.7). Externalising problems were not found to be linked with any cluster or individual condition. Whereas internalising problems were linked with clusters including mental health problems: MH/hypertension, MH/arthritis, MH/asthma and with mental health problems as an individual condition (Table 4.7). BMI at age 10 had the strongest association with diabetes/hypertension clusters (RR=1.25, 1.16 to 1.34) and it was linked with diabetes and hypertension as individual conditions and their clusters with mental health (Tables 4.7 – 4.8).

Table 4.8 The association between early-life risk factors and multimorbidity clusters at age 46-48.

N=7,951	MH + hypertension	MH + arthritis	MH + diabetes	MH + asthma	Diabetes + hypertension
	Relative risk (95%CI)				
Father's SES at birth[1]					
I – professional (reference)	-*	-*	-	-	-
II – managerial and technical	1.27 (0.53, 3.04)	1.19 (0.51, 2.80)	2.69 (0.35, 20.83)	1.67 (0.78, 3.56)	2.04 (0.52, 7.99)
III – skilled non-manual/manual	2.32 (1.11, 4.87)	1.53 (0.72, 3.26)	4.40 (0.67, 29.13)	1.68 (0.83, 3.40)	3.01 (0.85, 10.61)
IV – partly-skilled	2.96 (1.36, 6.44)	1.92 (0.85, 4.35)	5.13 (0.56, 30.32)	2.03 (0.97, 4.26)	3.59 (0.97, 13.35)
V – unskilled	2.92 (1.23, 6.94)	3.41 (1.46, 7.95)	5.92 (0.78, 44.64)	2.04 (0.85, 4.89)	3.60 (0.92, 14.09)
Birthweight[2]	0.82 (0.65, 1.04)	0.84 (0.64, 1.10)	0.99 (0.63, 1.55)	0.84 (0.65, 1.08)	0.69 (0.47, 1.00)
Cognitive ability (age 10)[3]	0.92 (0.75, 1.11)	0.75 (0.63, 0.89)*	0.76 (0.57, 1.01)	0.85 (0.72, 1.00)	0.78 (0.56, 1.08)
BMI (age 10)[4]	1.11 (1.05, 1.18)*	1.03 (0.96, 1.12)	1.17 (1.06, 1.28)*	1.04 (0.98, 1.11)	1.25 (1.16, 1.34)*
Internalising problems (age 16)[5]	1.21 (1.09, 1.34)*	1.17 (1.03, 1.33)*	1.09 (0.86, 1.38)	1.25 (1.12, 1.39)*	0.97 (0.79, 1.19)
Externalising problems (age 16)[6]	1.00 (0.90, 1.11)	1.06 (0.95, 1.19)	1.04 (0.88, 1.24)	1.02 (0.92, 1.14)	1.04 (0.89, 1.22)

[1] Adjusted for gender.

[2] Adjusted for gender, father's social class at birth, mother ever smoked during pregnancy, mother breastfed, mother's height, mother's marital status at birth, mother being a teen at birth, household tenure (5-10), overcrowding (5), length of time absent from school due to illness (10), parental divorce (16), mother's mental health (10).

The following models included the above confounders and were additionally adjusted for:

[3] birthweight, BMI at age 10;

[4] birthweight, cognitive ability at age 10, externalising and internalising problems at age 16;

[5] birthweight, cognitive ability and BMI at age 10 and externalising problems at age 16;

[6] birthweight, cognitive ability and BMI at age 10 and internalising problems at age 16.

*significant at p-value (after the Bonferroni correction) = 0.003 (for father's SES at birth, it refers to all categories combined)

Table 4.9 The association between early-life risk factors and multimorbidity clusters at age 46-48.

N=7,951	Mental health	Arthritis	Diabetes	Asthma	Hypertension
	Relative risk (95%CI)				
Father's SES at birth[1]					
I – professional (reference)	-	-*	-	-	-*
II – managerial and technical	1.15 (0.89, 1.50)	0.86 (0.56, 1.36)	2.11 (0.83, 5.36)	1.31 (0.96, 1.80)	1.05 (0.75, 1.48)
III – skilled non-manual/manual	1.28 (1.01, 1.61)	1.29 (0.89, 1.86)	2.94 (1.22, 7.10)	1.16 (0.87, 1.54)	1.41 (1.05, 1.88)
IV – partly-skilled	1.47 (1.14, 1.89)	1.25 (0.83, 1.89)	3.38 (1.37, 8.35)	1.15 (0.83, 1.58)	1.66 (1.22, 2.27)
V – unskilled	1.54 (1.14, 2.10)	1.86 (1.19, 2.91)	3.29 (1.26, 8.56)	1.09 (0.73, 1.63)	1.52 (1.05, 2.20)
Birthweight[2]	0.94 (0.86, 1.03)	0.94 (0.81, 1.09)	0.69 (0.54, 0.87)*	0.84 (0.75, 0.95)	0.79 (0.71, 0.88)*
Cognitive ability (age 10)[3]	0.89 (0.84, 0.95)*	0.92 (0.83, 1.01)	0.92 (0.79, 1.08)	0.97 (0.90, 1.06)	0.93 (0.86, 1.00)
BMI (age 10)[4]	1.03 (1.00, 1.05)	1.03 (0.99, 1.07)	1.19 (1.13, 1.25)*	1.00 (0.97, 1.04)	1.10 (1.06, 1.13)*
Internalising problems (age 16)[5]	1.18 (1.13, 1.24)*	1.06 (0.97, 1.15)	0.97 (0.85, 1.12)	1.05 (0.98, 1.12)	1.02 (0.95, 1.09)
Externalising problems (age 16)[6]	1.01 (0.97, 1.06)	1.08 (1.01, 1.15)	1.07 (0.95, 1.20)	1.03 (0.96, 1.10)	1.02 (0.96, 1.08)

[1] Adjusted for gender.
[2] Adjusted for gender, father's social class at birth, mother ever smoked during pregnancy, mother breastfed, mother's height, mother's marital status at birth, mother being a teen at birth, household tenure (5-10), overcrowding (5), length of time absent from school due to illness (10), parental divorce (16), mother's mental health (10).

The following models included the above confounders and were additionally adjusted for:
[3] birthweight, BMI at age 10;
[4] birthweight, cognitive ability at age 10, externalising and internalising problems at age 16;
[5] birthweight, cognitive ability and BMI at age 10 and externalising problems at age 16;
[6] birthweight, cognitive ability and BMI at age 10 and internalising problems at age 16.

*significant at p-value (after the Bonferroni correction) = 0.003 (for father's SES at birth, it refers to all categories combined)

4.4.3 Cross-cohort comparisons

As shown in Table 4.10, the NCDS had 17.8% prevalence of multimorbidity at age 42-48 compared with 24.3% in BCS70 (RR=1.36, 1.28 to 1.45). Members of BCS70 had a higher lifetime prevalence of all included self-reported chronic conditions at age 42, except for cancer for which no cross-cohort difference was found. The BCS70 also had a higher point prevalence of obesity and diabetes and there was no difference between cohorts in the prevalence of hypertension at age 44-48.

The prevalence of individuals with high blood pressure was lower in the younger birth cohort (NCDS: 12.8% vs BCS70: 9.7%), whereas the proportion of the medicalised sample was higher (NCDS: 6.1% vs BCS70: 8.1%) (Figure 4.2; Panel A). The proportion of those with controlled hypertension (not having high blood pressure and taking medications) was higher in the younger birth cohort (NCDS: 23.9% vs BCS70: 35.9%), whereas the proportion of untreated (having high blood pressure and not taking medications) individuals was higher in the older birth cohort (NCDS: 67.5% vs BCS70: 52.4%). The proportion of uncontrolled hypertensive individuals (taking medications and still having high blood pressure) was also higher in the younger birth cohort (NCDS: 8.6% vs BCS70: 11.8%) (Figure 4.2; Panel A). Hypertension was also self-reported in BCS70: 10.3%.

For diabetes, the prevalence of those having high HbA1c (48 mmol/mol or higher; ≥6.5%) was higher in the younger birth cohort (NCDS: 2.5% vs BCS70: 3.5%) as well as of those taking medications (NCDS: 1.9% vs BCS70: 2.5%) (Figure 4.2; Panel B). The proportion of controlled diabetics was also higher in BCS70 (NCDS: 8.4% vs BCS70: 19.9%), while the proportions of uncontrolled diabetics was lower in BCS70 (NCDS: 61.3% vs BCS70: 35.8%) (Figure 4.2; Panel B). Whereas the proportion of

untreated diabetics was higher in BCS70 (NCDS: 30.7% vs BCS70: 44.3%). Diabetes was also self-reported in BCS70: 3.8%.

Table 4.10 Descriptive summary of the health variables and early-life exposures.

	NCDS (n=8,883)	BCS70 (n=7,951)	Relative difference
Outcomes (age)	%	%	RR (95%CI)
Multimorbidity (42-48)	17.8 (17.0, 18.6)	24.3 (23.2, 25.4)	1.36 (1.28, 1.45)
Obesity (44-48)	24.7 (23.8, 25.6)	29.1 (28.0, 30.2)	1.18 (1.12, 1.24)
Hypertension (44-48)	17.2 (16.4, 18.0)	16.0 (15.1, 17.0)	0.93 (0.86, 1.01)
Diabetes (44-48)	3.1 (2.7, 3.5)	5.9 (5.3, 6.5)	1.91 (1.62, 2.26)
Mental health case (42)	12.5 (11.8, 13.2)	17.0 (16.1, 17.9)	1.36 (1.26, 1.47)
Asthma/bronchitis (42)	18.4 (17.6, 19.3)	21.6 (21.6, 23.7)	1.23 (1.15, 1.31)
Migraine (42)	20.5 (19.6, 21.3)	26.8 (25.7, 28.0)	1.31 (1.23, 1.39)
Fits, convulsions or epilepsy (42)	2.5 (2.1, 2.8)	3.3 (2.9, 3.8)	1.35 (1.11, 1.63)
Cancer (42)	2.8 (2.5, 3.2)	2.8 (2.4, 3.3)	1.00 (0.82, 1.23)
	M (SD)	M (SD)	B (95%CI)
Multimorbidity (42-48)	1.02 (0.01)	1.23 (0.1)	0.22 (0.18, 0.25)
Multimorbidity (42-48; without obesity)	0.77 (0.01)	0.95 (0.1)	17.5 (0.14, 0.21)
BMI (44-48), $kg.m^2$	27.62 (0.06)	28.30 (0.08)	0.68 (0.48, 0.89)
Systolic blood pressure, mmHg (44-48)	127.64 (0.17)	125.39 (0.19)	-2.50 (-2.76, -1.74)
Diastolic blood pressure, mmHg (44-48)	79.72 (0.13)	77.73 (0.13)	-1.99 (-2.37, -1.61)
HbA1C, % (44-48)	5.29 (0.009)	5.59 (0.01)	0.26 (0.23, 0.29)
Risk factors (age)	M (SD)	M (SD)	B (95%CI)
Birthweight (0)	3.34 (0.01)	3.31 (0.01)	-0.03 (-0.04, -0.01)
BMI (10/11)	17.36 (0.03)	16.96 (0.03)	-0.40 (-0.48, -0.33)
Internalising problems (16)	0.89 (0.01)	0.92 (0.02)	0.04 (0.00, 0.08)
Externalising problems (16)	0.54 (0.01)	0.64 (0.16)	0.11 (0.07, 0.15)
	%	%	OR (95%CI)
SES at birth (0)			
I – professional	5.0 (4.5, 5.4)	6.1 (5.6, 6.6)	1.22 (1.07, 1.40)
II - managerial and technical	14.0 (13.3, 14.7)	13.8 (13.0, 14.6)	0.98 (0.90, 1.08)
III - skilled non-manual/manual	60.6 (59.6, 61.6)	60.8 (59.7, 61.9)	Reference
IV - partly-skilled	12.1 (11.4, 12.9)	13.7 (12.9, 14.5)	1.13 (1.02, 1.24)
V – unskilled	8.3 (7.7, 8.9)	5.6 (5.1, 6.2)	0.67 (0.59, 0.77)

NCDS = the 1958 National Child Development Study; BCS70 = the 1970 British Cohort Study; RR = risk ratio; BMI = body mass index; M = mean; SD = standard deviation.

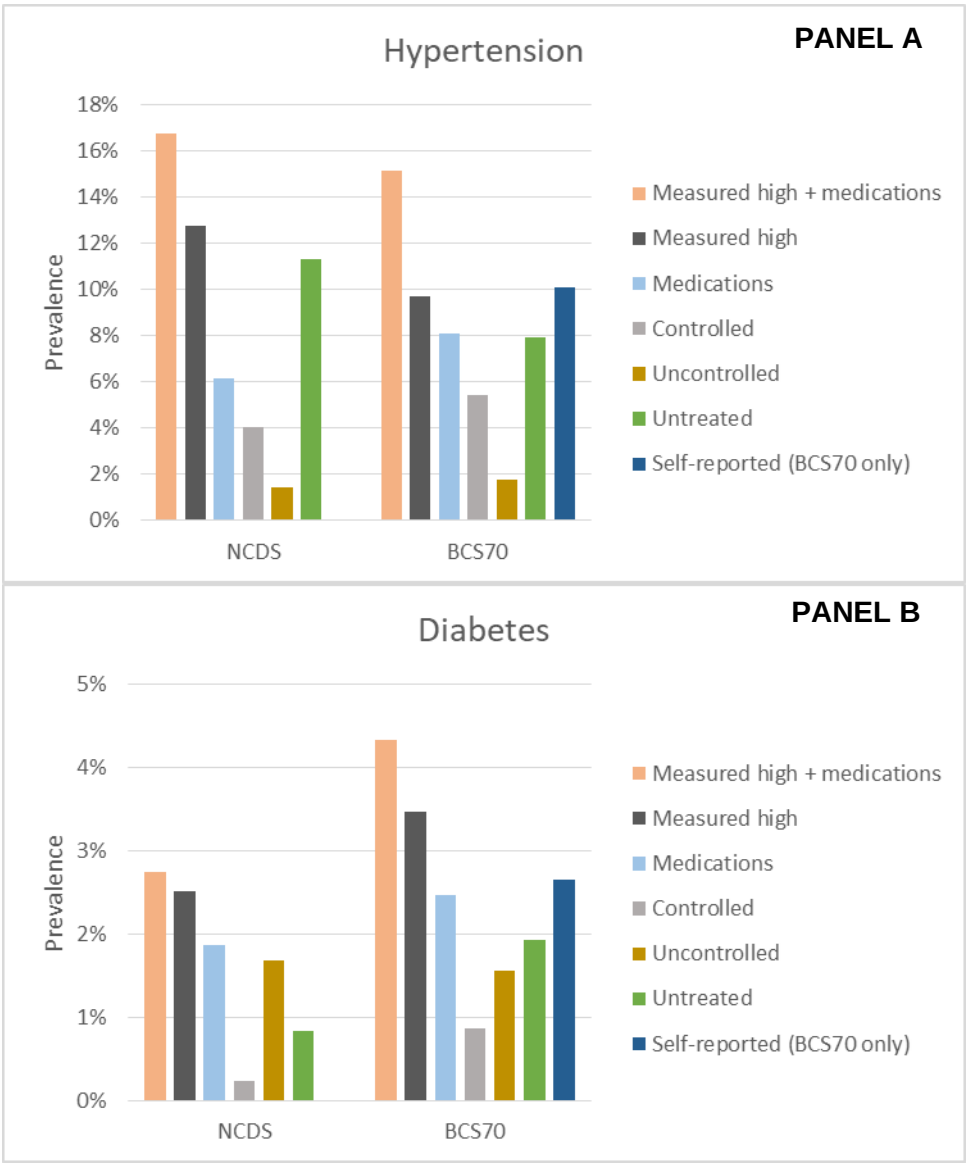


Figure 4.2 Prevalence of hypertension and diabetes at age 44-48 across NCDS and BCS70.

The associations between the exposures and multimorbidity were closely comparable across the BCS70 and NCDS (see Table 4.11 for results from the most adjusted models). I found no evidence for multiplicative effect modification of year-of-birth on any of the exposures. However, due to overall higher prevalence of multimorbidity in the BCS70, the absolute cohort-differences somewhat increased along with values of each exposure indicating higher vulnerability (e.g. higher number of internalising problems or lower cognitive score) (see Figure 4.9). For instance, among those with no internalising problems, probability of multimorbidity was higher in BCS70 than in NCDS by 5.7% (4.0, 7.4), whereas among those with four internalising problems this difference was 8.2% (3.5, 13.0). This increase was more substantial across values of BMI. For instance, at BMI equal 15, the BCS70 had 5.2% (3.5, 7.0) higher probability of multimorbidity than in the NCDS. Whereas at BMI equal 25, this difference was 12.9% (6.9, 19.0).

Table 4.11 The association between early-life exposures and multimorbidity at age 46-48 in the NCDS and BCS70.

	NCDS	BCS70
	RR (95%CI)	RR (95%CI)
Father's SES at birth[1]		
I – professional (reference)	-*	-
II – managerial and technical	1.36 (1.01, 1.81)	1.38 (1.06, 1.79)
III – skilled non-manual/manual	1.01 (0.77, 1.34)	1.01 (0.80, 1.29)
IV – partly-skilled	1.18 (0.92, 1.52)	1.18 (0.96, 1.46)
V – unskilled	1.42 (1.10, 1.87)	1.29 (1.02, 1.63)
Birthweight[2]	0.84 (0.77, 0.93)	0.87 (0.80, 0.94)
Cognitive ability (age 10)[3]	0.91 (0.85, 0.96)	0.93 (0.89, 0.99)
BMI (age 10)[4]	1.03 (1.01, 1.05)	1.05 (1.03, 1.08)
Internalising problems (age 16)[5]	1.11 (1.06, 1.16)	1.09 (1.05, 1.13)
Externalising problems (age 16)[6]	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)

Model 1: Adjusted for gender.
Model 2: Adjusted for gender as well as child and family confounders: father's social class at birth, birthweight —when it was not used as the exposure, mother ever smoked during pregnancy, mother breastfed, mother's height, mother's marital status at birth, mother being a teen at birth, household tenure (5-11), parental interest in child's education (10/11), overcrowding (5-11), length of time absent from school due to illness (10/11), parental divorce (16).
Model 3: Adjusted for variables from Model 2 and child characteristics that were used as exposures (as appropriate):
[1] N/A as all other additional variables in Model 3 are potentially on the causal pathway;
[2] Additionally adjusted for cognitive ability at age 10/11, externalising and internalising problems at age 16;
[3] Additionally adjusted for BMI at age 10/11;
[4] Additionally adjusted for cognitive ability and BMI at age 10/11, and externalising problems at age 16;
[5] Additionally adjusted for cognitive ability and BMI at age 10/11, and internalising problems at age 16.

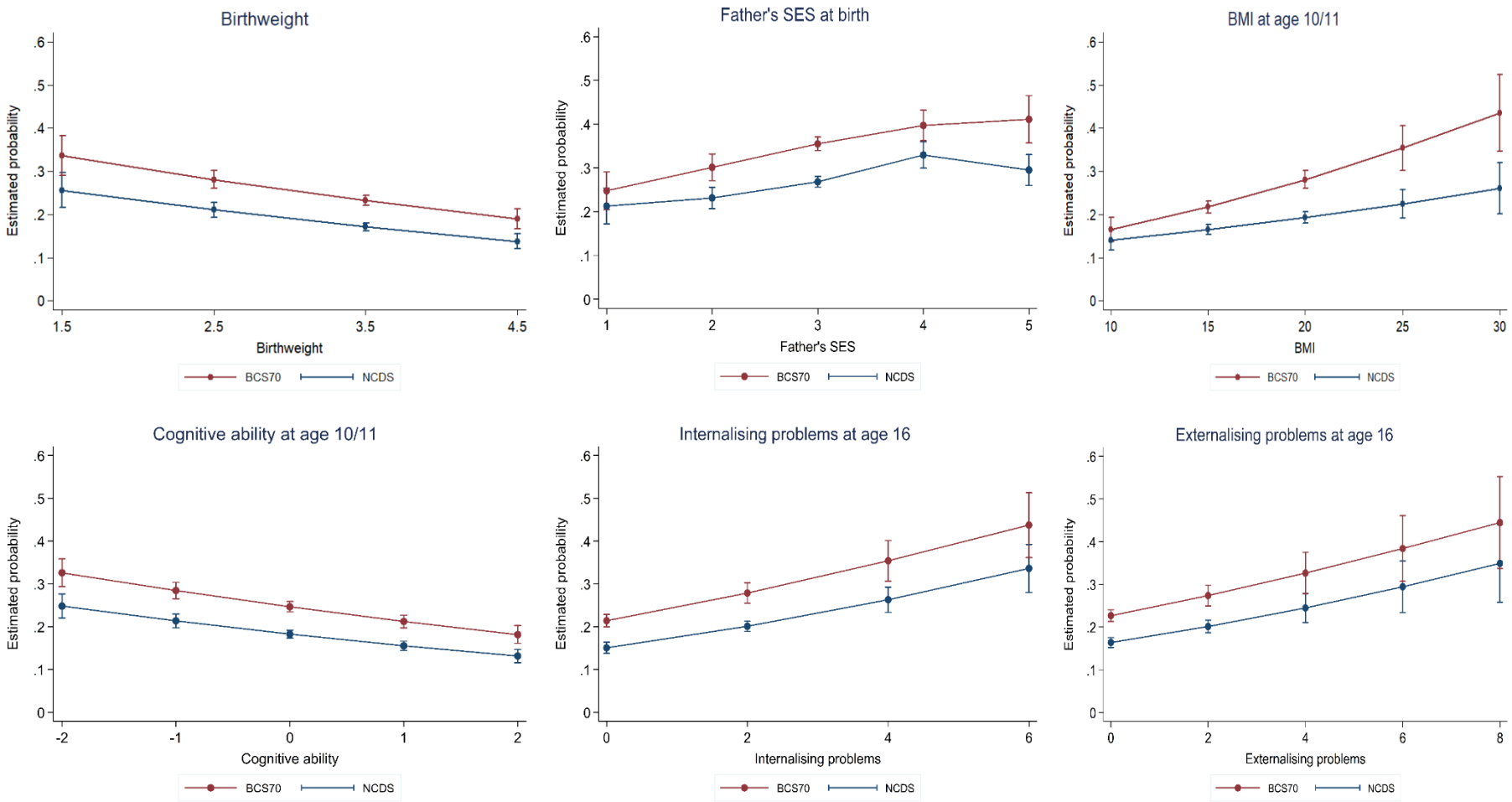


Figure 4.3 Birth-cohort-stratified predicted probability of multimorbidity across different values of early-life exposures in the most adjusted models.

4.5 Discussion

4.5.1 Summary of findings

The prevalence of multimorbidity was 33.8% at age 46-48—based on the data broadly representative for those born around 1970 in Great Britain. Lower birthweight, lower cognitive ability, higher BMI—both at age 10, more externalising and internalising problems at age 16 were found to be associated with higher mid-life multimorbidity after a rich set of confounders were controlled for. Also, those in less advantaged social classes at birth were at elevated risk of multimorbidity.

Higher BMI at 16 and lower birthweight were linked with diabetes and hypertension. Internalising problems and cognitive ability were found to be associated mainly with comorbidities including mental health problems. However, externalising problems were not predictive of any of the studied individual conditions or their clusters, despite being linked with the overall multimorbidity outcome. Finally, the association between father's SES and MH/hypertension as well as MH/arthritis was stronger in magnitude than for individual conditions.

I found that the prevalence of multimorbidity in mid-life was higher in BCS70 (24.3%) than in NCDS (17.8%)—based on an adapted outcome definition allowing for cross-cohorts comparison. The most substantial, relative, rise in prevalence was seen in diabetes and mental health problems. Members of BCS70 had a higher prevalence in all included conditions, except for cancer and hypertension, for which differences were not found.

There was no evidence for multiplicative effect modification of year-of-birth on any of the exposures. However, due to an overall higher prevalence of multimorbidity in the BCS70, the absolute cohort-differences somewhat increased along with values of

each exposure indicating higher vulnerability (e.g. a higher number of internalising problems or lower cognitive score). This additive interaction effect was particularly prominent for BMI, whereas for other exposures, the absolute differences were rather modest. However, they may amount to an important public health problem if the cross-cohort difference turns out to be a trend across successive birth cohorts.

4.5.2 Comparison with previous studies and interpretation

The prevalence of multimorbidity in this study was comparable with the most comprehensive estimate of multimorbidity in mid-life in the UK—which was 30.4% among over 1.7 million general practice patients aged 45-64 in 2007 (179). Consistently with findings of this study, previous evidence suggests that the prevalence of multimorbidity has increased over the past two decades internationally as well as in the UK (256-258).

Cross-cohort comparison indicated a higher prevalence in morbidity outcomes, such as objectively measured diabetes and obesity as well as self-reported asthma/bronchitis and epilepsy. Differences were not found in the lifetime prevalence of any cancer and objectively measured hypertension. Consistently with findings of this chapter, previous studies showed overall worse health outcomes in the BCS70 compared with NCDS, including psychological distress, self-reported health, long-standing illness (39, 215, 245). Hence, those born in 1970 appear to be generally more predisposed to suffer from poor health in comparison with individuals born in 1958. This may be due to 1958 cohort being part of the “Lucky Generation” of post-war baby boomers, who experienced greater social mobility and socioeconomic equality than the 1970 cohort (63). The 1970 cohort is part of the “Generation X”, characterised by unfavourable economic circumstances during their adulthood, such

as unemployment or elevated income inequality (63). As alluded to in section 2.4.2, the trends in most risk factors do not, however, show a consistent pattern in the last several decades: with some harmful exposures increasing over time and other decreasing. For instance, adolescent BMI was comparable across the birth cohorts (259), smoking prevalence declined, whereas alcohol consumption doubled between 1960 and 2002 in the UK (260). Participation in tertiary education, which tends to be positively associated with health (261), increased: e.g. proportion of those who stayed on beyond the compulsory school-leaving age of 16 years were 42% in 1979, rising to 52% in 1988 and 71% in 1999 (262).

Early-life BMI was found to be associated with multimorbidity, which is consistent with the previous literature on a range of adult morbidity outcomes as well as multimorbidity specifically (73, 200, 210, 221). The evidence on the association between BMI and diabetes and hypertension, found in this study, has been particularly consistent in observational studies (221) and in studies using Mendelian randomisation, in which genes are treated as instrumental variables (263). This may be due to an increased risk of dyslipidaemia and systemic inflammation due to obesity, which may constitute a common pathway to the development of both diabetes and cardiovascular conditions (264, 265).

Externalising and internalising problems have been found to be associated with adult morbidity (215, 223, 224); and with co-existing somatic and psychiatric symptoms in mid-life (213). However, it appears that the association between internalising problems and multimorbidity may be driven by their links with mental health problems included in the multimorbidity definition—the association vanishes when mental health morbidity is removed from the multimorbidity definition (results not shown).

Interestingly, externalising problems appear to increase the risk of overall multimorbidity to much larger extent than its major individual components. There are several potential mechanisms linking early-life mental health problems with adult multimorbidity. According to the allostatic stress model, exposure to chronic stressors may result in physiological dysregulation, which predisposes an individual to poor health (188). For instance, there is evidence on the association between children's depression and worse immune functioning (266). In addition, internalising and particularly externalising problems may have a more indirect effect on later multimorbidity, through their link with negative health behaviours, such as smoking and drinking (267-269).

The link between early-life cognitive ability and adult morbidity has been previously found (215, 222), yet there is no existing evidence on multimorbidity. I found evidence for a modest association, where an increase of one standard deviation in cognitive ability (around 15 points on a standard general intelligence test) was associated with 4% decrease in the probability of multimorbidity. There are several potential pathways linking early-life cognitive ability with adult multimorbidity, including better self-care, indirect link via health behaviours or shared pathways with education or socioeconomic position (270).

Father's social class at birth was associated with multimorbidity in this study, which is consistent with the extensive literature on adult morbidity (211, 217, 219, 271, 272) and multimorbidity specifically (173, 211). This research adds to this literature by showing a particularly strong association between father's SES and mental health problems clustered with hypertension or arthritis. Previous research found that the link between early-life socioeconomic circumstances is partially mediated by

cognitive ability, educational attainment and school type (211). Life course theory and related findings also suggest that early-life socioeconomic position increases the risk of other adverse exposures, such as negative health behaviours or unfavourable adult socioeconomic circumstances, which have a cumulative effect on health over the lifespan (273). For instance, a recent study based on the Panel Study of Income Dynamics found that children who experienced higher levels of early adversity were more likely to face adversities in their adulthood (274). Furthermore, those with both childhood and adulthood adversities had the highest risk of poor health, chronic conditions and psychological distress in adulthood (274). Likewise, a greater number of years in poverty was associated with increasingly dysregulated physiologic response, such as overnight cortisol and muted cardiovascular reactivity—potentially explaining how negative early-life experiences “get under the skin“ (275). However, research also found association between early-life socioeconomic circumstances and adult health, independently from adult socioeconomic position (274). This points out an important role of childhood and adolescence in further development, as emphasised by the sensitive or critical period life course models (50).

One study examined links between birthweight and multimorbidity finding no association (212), contrary to findings in this chapter. However, the effect size in this study is modest, with 10% decrease in risk corresponding to 1kg change in birthweight; or 1.6% avoided cases, assuming causality, if 20% with the lowest weight were “shifted” to the mean of other 80%. Overall, the evidence on the association between low birthweight and adult morbidity is somewhat inconsistent (214). It appears that birthweight may be an important exposure for diabetes and hypertension, as shown by this analysis and other observational studies (276, 277). However, the evidence suggests that only link with diabetes may be causal (276,

277). This may be due to prenatal growth stress leading to metabolic reprogramming beginning in utero (278, 279), according to the Barker hypothesis (43).

4.5.3 Strengths and limitations

To the best of my knowledge, this is the first study examining the association between emotional development, cognitive ability and multimorbidity. The main strength of this study is that it used a contemporary and representative sample of the mid-life population born in Britain and—contrary to the previous research (200, 210, 211, 213)—accounted for a rich set of confounders, particularly parental characteristics. There is always a risk of bias in the estimates based on observational studies, due to omitting potential confounders, for instance, genetic factors that may affect both early-life physical and emotional development and later health. As a sensitivity check, I estimated the E-value, which indicates the minimum strength of association that an unmeasured confounder would need to have with both the treatment and outcome to fully explain away a specific treatment–outcome association, after conditioning on the measured covariates (280). As shown in Appendix 2F, the association between each early-life exposure and multimorbidity at age 46-48, could be explained away by an unmeasured confounder that was associated with both the exposure and outcome by a risk ratio of 1.21-fold each, above and beyond the measured confounders. This value is stronger than the association between any measured exposure or confounder and the outcome in this study. Hence, these variables are strong candidates for potentially having a causal relationship with multimorbidity, which future research could explicitly examine.

Another limitation of this research is that it relies on self-reported health outcomes. However, I also included objectively measured diabetes and hypertension, which are

free from biases related to self-reporting. In addition, self-reports appear to be reliable measures at least in this study, as I found strong agreement between self-reported and objectively measured hypertension and diabetes (89% and 98% respectively; with fair—0.51—and good—0.74—Cohen's Kappa).

A following limitation, common to studies using prospective longitudinal data, is selective attrition and a large proportion of missing data. However, the estimates can be unbiased even with up to 90% missing data, provided that the imputation model is correctly specified and the data are Missing-at-Random (281). Hence, I used multiple imputation including a range of predictors of the probability of missing information in the outcome and the outcome itself—such as poorer general health—increasing the plausibility of the Missing-at-Random assumption. I obtained similar estimates of multimorbidity prevalence from analyses under different missing data generating mechanisms (MCAR vs MAR) and across imputations based on samples with varying missing data inclusion criteria, which provides evidence for robustness and generalisability of the findings (see Appendix 2E). I obtained a somewhat higher estimate of multimorbidity prevalence (35.9%, 34.9 to 37.0) based on the sample including all those who were alive and were not permanent emigrants from Britain by age 46-48, irrespectively if they participated in the data sweep at this age (n=15,821). This sample was the most generalisable to the population of mid-life individuals born around the same time. However, it was also most severely affected by attrition and non-response, which led to higher estimates as those with missing information were more likely to be of poor health (see Appendix 2D).

BCS70 was designed to be representative for cohorts born around the same, capturing nearly all births in a single week in 1970. Hence, the sample includes

nearly exclusively white, non-migrant population (155). The prevalence of multimorbidity may vary in the migrant population, for instance due to healthy migrant effect (385). A recent study showed that in 2019, 12% of the foreign-born population age 35-49 in the UK had a long-lasting limiting health problem, compared with 19%% among those born in the UK (282).

Finally, different measures of cognitive ability were used across the BCS70 and NCDS, which may not have ranked participants equivalently across the cohorts, potentially affecting cross-cohort comparisons in the unknown direction. However, the scores were reduced to a single component capturing general intelligence and standardised to reflect factorial equivalence between the two cohorts, as previously done in other studies (235).

4.5.4 Conclusions and implications

Multimorbidity affects over one-third of middle-aged individuals and its prevalence has increased in Britain. Due to increasing life expectancy in the last three decades, members of the younger birth cohort are likely to spend more time of their life with multimorbidity—a scenario known as the expansion of morbidity (see section 1.1). The greatest increase in prevalence was seen in mental health problems, obesity and diabetes. As multimorbidity increased in prevalence, there is a need for health policies and interventions that will act on multiple conditions simultaneously. Co-occurring mental and physical health conditions, such as diabetes or hypertension, appear to be particularly important comorbidity to target—not only due to their prevalence but also because of their detrimental link on overall functioning (205-207). Socioeconomic disadvantage, low birthweight, high BMI, low cognitive ability and mental health problems are all associated with mid-life chronic multimorbidity and

various clusters of conditions. Hence, reducing their impact or prevalence, through both health promotion and primary prevention, may improve various aspects of health.

Chapter 5: Mental health morbidity from early adulthood to early old age: Evidence from the 1946, 1958 and 1970 British birth cohorts

Chapter objectives:

- To investigate the age trajectory of mental health over time in three British birth cohorts (1946 – NSHD, 1958 – NCDS and 1970 – BCS70), including—to the best of my knowledge—the longest continuous follow up of this outcome within the same individuals from age 36 to 69.
- To examine cohort differences in mental health across three representative British birth cohorts: 1946 (NSHD), 1958 (NCDS) and 1970 (BCS70).

Key findings:

- Across three post-war British birth cohorts, there was an increase in mental health problems between early-adulthood and mid-life.
- This increase appeared to be steeper in relative terms in the NCDS and BCS70 than NSHD.
- In the NSHD, where additional data sweeps were available, mental health improved between mid-life and early old age.
- Participants of both NCDS and BCS70 also experienced elevated levels of mental health problems in their mid-20s.
- Participants of BCS70 had worse mental health than two other cohorts at overlapping ages (26-46)

5.1 Introduction

Common mental disorders (including depression and anxiety) are the leading cause of non-fatal disease burden, measured by years lived with disability, (283) and their prevalence has increased over the last three decades (284). Longitudinal studies can help us identify high-risk life periods—with modifiable risk factors—facilitating prevention and early detection of these disorders (52). Cross-cohort comparisons of distress profiles can also elucidate whether risk periods are stable or vary according to changing social and economic circumstances (63). For example, those born in the early-70s were exposed to economic and labour market turbulence as well as social changes, such as rising rates of divorce (63)—factors that have been linked to mental health morbidity (285).

5.1.1 Total vs direct effect of age

Before I discuss the evidence on age and cohort trends in common mental disorders and associated outcomes, I justify why in this study I investigate total, as opposed to direct, effects of age on mental health outcomes. This also determines the type of literature considered in this chapter. In the regression model, total effects represent the sum of direct effects of time variables and indirect effects through other variables. Whereas direct effects show effect of age (or period/cohort)—after adjustment for socioeconomic variables such as income, education or marital status. Whether reporting total or direct effects is of greater benefit sparked a debate in the literature, with prominent researchers sitting on either side of the argument.

Blanchflower and Oswald argued that looking at bivariate associations between exposure and outcome are generally unhelpful as they overestimate benefits of

acting on the exposure due to confounding factors of risk-factor – disease association that needs to be accounted for (286). Hence, age should be treated as a risk factor and its effects should be considered after taking into account potential confounders of age and mental health (286). The researchers used an analogy of the association between smoking and cancer. In this scenario, merely looking at bivariate association would be unhelpful, as the benefit of acting on smoking would be overestimated due to co-occurring risk factors among smokers, such as worse diet or lower income (286).

Glenn took a different stand, where he asserted that investigating unadjusted, total age effects, can reveal “what really has happened to people as they have grown older” (p. 483) and it is of “greater theoretical and practical importance than estimates of direct effects” (287) (p. 483). Glenn argued against controlling for variables such as marital status or socioeconomic position, as these cannot affect age hence they cannot be considered as confounders. They may, however, mediate the relationship between age and mental health outcomes and controlling for them may result in overadjustment bias (288). However, stratifying on certain variables that may act as proxies for age effects may be useful for descriptive and hypotheses-generating purposes (289). For instance, if mental health continuously worsens throughout the life course among those in a low but not in a high socioeconomic position, one could speculate this is related to disadvantage accumulated throughout the life course, which could be formally studied.

The smoking example given by Blanchflower and Oswald is a poor analogy (286). Smoking is a well-defined risk factor for lung cancer and the research is currently focused on understanding its mechanisms of action and “the medical benefit from

cutting back on cigarettes" as phrased by Blanchflower and Oswald (288) (p. 488). As we cannot "cut back" on age, we can only aim to reduce its impact by understanding proxy variables associated with ageing that can be intervened on. Indeed, after the evidence on trends is established, it would be of interest to better understand the mechanisms linking age and mental health. Potential mediators ought to be cautiously chosen using existing knowledge, while confounders of the relationship between those mediators and mental health should be considered using formal casual methods to estimate the mediated effects to understand potential benefits of an intervention (290). For instance, when studying income as a potential mediator of the relationship between age and mental health, factors such as cognitive ability, family structure or physical health, among other variables, should be accounted for.

There are only two variables that may confound the association between age and mental health—year-of-birth and calendar period (time of measurement of the outcome)—and they should be accounted for. However, they are perfectly collinear with age and cannot be simultaneously estimated (see section 1.2.2) (287). Nonetheless, studying cohort differences in age trajectories may improve generalisability of findings. If the age trends appear to be universal across birth cohorts (and different calendar years), potential causal explanations should be defined around age effects. Alternatively, if cohort differences are found, this may suggest that aetiological mechanisms may vary depending on social and economic context, associated with cohort effects (and possibly partially driven by period effects). For instance, higher levels of psychological distress were found in BCS70 than NCDS in early-adulthood (38, 291). This may be attributed to those born in 1970

being exposed to a disadvantage in their transition from education to work in the mid-1980s due to high unemployment among young people (292).

The debate about whether one should provide crude or adjusted estimates of trends has been focused around age effects (286, 287), however, the same arguments apply when studying cohort or period trends. All socioeconomic variables, which are commonly controlled for, such as socioeconomic status, education or marital status may mediate the relationship between year-of-birth (or calendar year) and mental health. Hence, they should be theoretically and methodologically formulated as mediators, as opposed to confounders. Such analysis was conducted by Ploubidis and colleagues, who used formal causal methods to examine the role of potential mediators in explaining differences in psychological distress at age 42 across 1958 and 1970 birth cohorts (38). Importantly, age should always be considered when studying cohort (or period) effects in order to ensure that changes over time are not purely due to ageing.

As I will argue in the following section, the trends in mental health are still poorly understood. Hence, they should be described using the best available evidence, before we study specific mechanisms explaining the relationship between time variables and mental health. Therefore, in the next section, I will consider key studies of the total effect of time variables on mental health.

5.1.2 Evidence before this study

As the systematic literature review in Chapter 2 focused mainly on period and cohort effects in physical health outcomes, I conducted a systematic search to identify key studies relevant for this chapter. I searched PubMed for studies investigating total effect of age and/or cohort time variables on outcomes related to common mental

disorders in high-income countries. The studies of interest were published between 1st January 2000 and 25th March 2019. Research published from 2000 onwards was considered, as Jorm and colleagues conducted a systematic review of studies published up to 2000. The search comprised a combination of terms related to mental health outcomes (depress*, anx*, common mental disord*, distress, mental health, mental illness) and secular trends (age effect*, period effect*, cohort effect*, age-period-cohort, secular trend*, life course trajector*, life course profile). In this study, I collectively refer to measures of diagnosed common mental disorders, their symptoms or general distress as mental health outcomes. I excluded studies with non-adults population (mean age under 18) and with time variables (year-of-birth and period) outside those included in this study (birth cohorts: 1946-1970 and period: 1972-2016). As explained in section 1.2.2, cross-sectional studies cannot disentangle age and cohort effects, as these variables are perfectly collinear—hence, they were also excluded. I identified 15 relevant studies, with abstracts published in English.

First, I outline evidence from repeated cross-sectional studies, which are designed to study period effects, but also allow for following the same birth cohorts over time (but not the same individuals)—therefore studying age and cohort effects simultaneously is possible by crating “pseudo cohorts”. Subsequently, I describe evidence based on longitudinal studies, as they have the advantage of following the same individuals over time, where each subject is his or her own control hence providing better estimates of the true ageing processes. However, when a single birth cohort is followed over time, age and period are perfectly collinear. Hence, using longitudinal studies with an accelerated design is necessary, where different birth cohorts are followed as they age. Such design can be achieved by combining multiple British birth cohorts, as it is done in this study and it allows for transcending period effects—

as each birth cohort experiences the same age at different calendar year. Nonetheless, as explained in section 1.2.2, even in accelerated longitudinal studies it is impossible to estimate age-period-cohort effects simultaneously and strict assumptions need to be made about one of the time variables. Following the approach of previous research (289, 293), I argue that period effects can be omitted as it is implausible that there would be any linear (or higher polynomial) period trend in mental health affecting all age groups simultaneously. There may be short-term events resulting in a decline in mental health of a large segment of the population, for instance, due to the 2008 economic crisis (294). Yet it is unlikely that they result in a continuous periodic trend affecting all ages. Cohort effects may provide a better explanation for changes in mental health over time due to changing social and socioeconomic circumstances affecting individuals as they age (295). In accelerated longitudinal studies, short-term fluctuations in mental health due to period effects will translate into age-specific cohort effects that can be discussed without a formal age-period-cohort analysis (295).

5.1.2.1 Age effects (age-by-cohort effects)

Jorm and colleagues conducted a systematic review of studies published before 2000 examining age effects in anxiety, depression or distress in the general population of high-income countries aged 30 or older. The review concluded that the most common trend across studies was an initial rise in mental health problems across age (up to age 45-55), followed by a drop—however, the patterns were somewhat inconsistent (296). One of the key strengths of the review was that it included studies using consistent methods of the outcome assessment throughout

age, for instance, the Present State Examination or General Health Questionnaire (296). However, most of the included studies were cross-sectional (296).

Probably the most well-known and cited study using repeated cross-sectional data was conducted by Blanchflower and Oswald (297). It found a U-shaped relationship between age and measures of wellbeing (e.g. happiness, life satisfaction), with the lowest point at around age 45, in 72 developed and developing countries. The analysis of the repeated cross-sections (pooled across 2004-2007) of the UK Labour Force Survey, showed an opposite, hill-shaped association between age and self-reported depression—picking at age 45 (297).

In a more recent study, Spiers and colleagues conducted a pseudo-cohort analysis of the British Adult Psychiatric Morbidity Survey conducted in 1993, 2000 and 2007, which used the Revised Clinical Interview Schedule (CIS-R)—a measure of common mental disorders (293). They found that the frequency of common mental disorders (CIS-R score 12 or above) peaked between ages 40 years and 50 years in men, but did not vary with age in women (293). When a more severe version of the outcome was considered (CIS-R score 18 or above), the frequency was at its highest after age 40 years in both genders (293).

The evidence from international repeated cross-sectional studies is largely consistent with the UK-based evidence. Keyes and colleagues conducted a comparative analysis of two large representative studies in Canada (1997-2010) and the USA (2000-2007), with distress being measured using the 6-Item Kessler Psychological Distress Scale (298). In both countries, psychological distress was highest in late adolescence and during the late 40s and early 50s (298). Likewise, Sunderland and others found increasing internalising psychopathology between age 30-39 and 40-49,

followed by a decrease from 50-59 to 60-69 (between 1997 and 2007) (299). Nonetheless, inconsistencies in age patterns occur across countries. For instance, three Danish population-based surveys of individuals aged 45 or older (in 1995-2001) showed little change during adulthood in depressive symptoms among those under 70 years old (300).

Longitudinal studies in the UK show somewhat inconsistent age patterns in mental health outcomes. The most common finding across the studies is an increase in mental health problems between early-adulthood and mid-life (289, 291, 301). However, there are some discrepancies in the evidence showing either a continuous increase from early-adulthood, or an initial decrease and subsequent increase (289, 291, 301). The greatest inconsistency in the evidence, however, is related to the apparent improvement in mental health between mid-life and older-age. The studies based on the British Household Panel Survey (1991-2008) found a peak in distress at around age 40, followed by a subsequent decline and rise again at older age (289, 291, 301). However, after controlling for birth cohort, mental health appeared to worsen throughout the life course, with a slowing decline in mid-life (289, 301). A study based on the English Longitudinal Study of Ageing showed declining rates of distress between age 50 and 60 regardless of birth cohort and subsequently increasing rates between age 65 and 90 (302). The initial decline in distress in the 50s was only seen in the war cohort in the USA, but not in the post-war cohort, in the US Health Retirement Study (302).

In other countries, Brault and colleagues showed increasing depressive symptoms throughout the life course among Belgians aged 25-74, followed annually from 1992 to 2002, with the steepest increases between age 25 and 50 as well as 65 and 74

(303). Likewise, a study in Sweden found a non-linearly increasing prevalence of anxiety by age among cohorts born between 1910 and 1989, with steeper increases in more recently born cohorts (304).

5.1.2.2 Cohort effects

Overall, the evidence rather consistently points towards worsening mental health across birth cohorts in the UK. The 1958 birth cohort (NCDS) had higher levels of psychological distress between age 23/26 and 42 than the 1970 birth cohort (BCS70) (38, 291). Bell found worsening mental health across 1984-1990 birth cohorts in the British Household Panel Survey, a large longitudinal household panel study (289). The 1970 birth cohort had higher levels of mental health problems than 1960 at overlapping ages (31-38) and 1960 had worse mental health than 1950 birth cohort (at age 41-48) in this dataset (289). Those born in 1957-63 also had worse mental health than 1943-9 at overlapping age in the National Psychiatric Morbidity Surveys in England (1993-2000), with 1971-77 having a higher prevalence of common mental disorders than the preceding cohorts (293). Increasing rates of mental health problems across birth cohorts were also found in Belgium (1918-27 – 1958-67) (303), Sweden (1910-7 – 1982-89), Canada (1940-3 – 1989-92) (298), USA (1948-50 – 1993-5) (298, 299), Australia (1940s vs 1970) (305).

5.1.3 Aims and hypotheses

This study aimed to investigate the age trajectory of mental health over time in three British birth cohorts (1946 – NSHD, 1958 – NCDS and 1970 – BCS70), including—to the best of my knowledge—the longest continuous follow up of this outcome within the same individuals from age 36 to 69. In addition, I examined cohort differences in

mental health across three representative British birth cohorts: 1946 (NSHD), 1958 (NCDS) and 1970 (BCS70). Combination of these three studies allowed for studying age and cohort effects in mental health among 28,362 participants, aged 23-69, over a period of 1981-2016.

A comparison across birth cohorts allows for greater generalisation of findings across post-WW2 generations and transcending period effects. This study expands on the previous analysis of age and cohort effects of NCDS and BCS70 (38, 291), by including additional waves of data (age 50 in NCDS and age 34 and 46 in BCS70) and by including NSHD—the oldest and longest-running birth cohort in the UK.

I hypothesise that (1) mental health morbidity will increase from early-adulthood and mid-life across all three birth cohorts; which is preceded by elevated distress in 20s (38, 291); (2) mental health morbidity will decline from mid-life into older age in NSHD; (3) mental health morbidity will increase across birth cohorts when age is accounted for.

5.2 Method

5.2.1 Study population and design

I excluded those who died, emigrated from Britain or without at least one valid measure of mental health between age 23 and 69, which resulted in the analytical longitudinal sample of: n=3,093 for NSHD, n=13,250 for NCDS and n=12,019 for BCS70 (Figure 5.1). The estimates of the prevalence of mental health caseness are also provided using cross-sectional sample attained at each data sweep, excluding those who died or emigrated (age 23-26: NCDS and BCS70; age 30: BCS70; age 33-36: all cohorts; age 42-43: all cohorts; age 50-53: NSHD and NCDS).

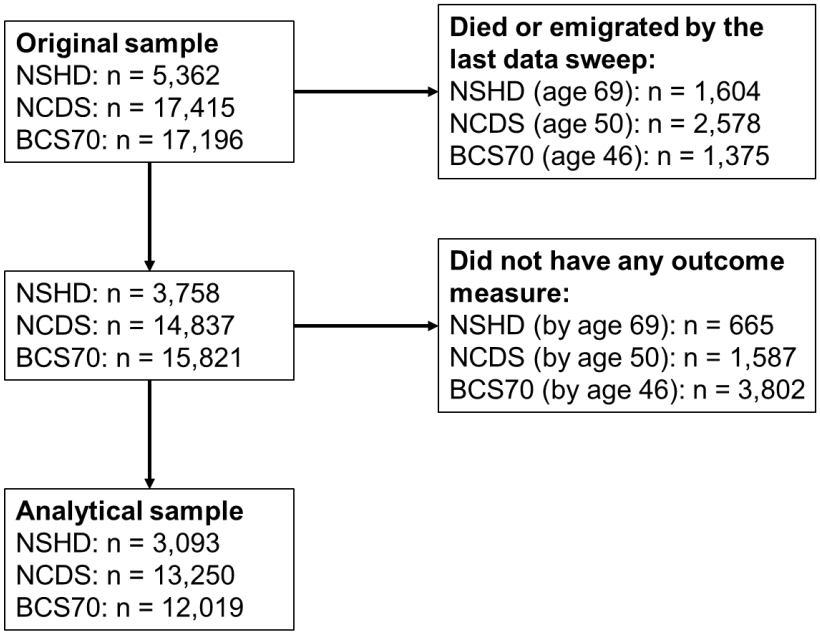


Figure 5.1 Flow diagram of the study sample.

5.2.2 Measures

The measures used in this study were not designed to diagnose any specific mental health condition, but rather capture symptoms related to common mental disorders, such as depression and anxiety. Both continuous and discrete versions of the variables were used. I derived a binary indicator of caseness, based on the validated thresholds (see Table 5.1), which helps to identify individuals who score high enough to be classed as a clinical case. It is a useful outcome from the public health perspective as it helps to estimate service needs. On the other hand, a problem with the categorical approach is the difficulty in defining empirically driven clear-cut thresholds distinguishing between the presence and absence of a disorder. For instance, those below cut-off thresholds of depression and anxiety disorders still tend to have a higher risk of functional impairment or premature mortality (306).

The NSHD included a range of mental health measures: a clinical interview for the frequency and severity of psychiatric symptoms in the preceding month at age 36 (the Present State Examination; PSE) (307); an interviewer-administered 18-item instrument derived from the PSE, focusing on symptoms of anxiety and depression during the preceding year at age 43 (the Psychiatric Symptom Frequency; PSF) (308) and a self-administered questionnaire assessing symptoms of anxiety and depression in the preceding four weeks at ages 53, 60-64 and 69 (the 28-item General Health Questionnaire; GHQ) (309). All measures were found to be psychometrically robust (see Table 5.1 for more details). Due to differences in the measures used within NSHD, the continuous version of the outcome was based on seven harmonised items, which captured the same symptoms (more details in section 5.2.3).

In NCDS and BCS70, at all ages, cohort members completed the Malaise Inventory (230), a measure of psychological distress level, or depression and anxiety symptoms. The longer version of the Malaise Inventory, including 24 “yes-no” questions was used at age 23, 33, 42 in NCDS and at age 26, 30 in BCS70. At age 34 and 46-48 within BCS70 and age 50 in NCDS, 9 of the 24 questions were asked (in the “yes-no” format). To aid comparability, only the shorter version was used in the current study, which correlated highly with the 24-item version (NCDS r = 0.91 at age 42 years and BCS70 r = 0.92 at age 30 years). The continuous outcome within NCDS and BCS70 was derived by summing up nine items of the Malaise Inventory at each data cross-section, with “yes” corresponding to 1 and “no” corresponding to 0. Hence, each participant who completed all nine items had a score ranging from 0 to 9 at each data sweep. Having four or more symptoms indicated being a case. The scalar invariance of the measure has been found within and across the NCDS and BCS70, as well as between genders (38, 310) (Appendix 3A). This implies that the symptoms captured by the items of the Malaise Inventory were interpreted equivalently by the participants, regardless of their age, cohort membership or measurement modes used at different ages. The Malaise Inventory has been found to have good psychometric properties (311) and has been used both in the general population and high-risk groups (312).

Table 5.1 Measures of mental health used across the cohorts; details.

Measure	Details	Caseness threshold	Psychometric (reliability/validity) and clinical properties
Present State Examination	A clinical examination, conducted by a nurse, assessing the frequency and severity of a range of psychiatric symptoms in the preceding month. Used at age 36 in NSHD.	5 or higher on the Index of Definition (307)	Tested in the general population: high agreement with the clinical diagnosis of common mental health disorders (≈90%); high concurrent validity with other measures of psychological distress (307). A diagnostic tool, hence information on specificity and sensitivity not provided.
Psychiatric Symptoms Frequency	18 items (based on the Present State Examination); 5-point scale (0 = never in the last year; 1 = up to 10 days in total, less than once a Month; 5 = every day in the last year); assessing on symptoms of anxiety and depression during the preceding year; administered by a nurse. Used at age 43 in NSHD.	23 or higher on the summed up score (308)	Tested in the general health care/general population (age ≈ 43); Cronbach's alpha = 0.88; all items identified a common factor; AUC against reports of contact with a doctor/use of prescribed medication for "nervous or emotional trouble or depression" (0.84 – 0.86) (308).
GHQ-28	28 items assessing symptoms of anxiety and depression in the preceding 4 weeks; a 1 to 4 point Likert scale and recoded into binary values; self-administered. Used at ages 50-69 at NSHD.	5 or higher endorsed symptoms (313)	Tested in the general health care (adults): Cronbach's alpha = 0.82 – 0.86 (313); all items identified 4 factors explaining 62% variance in psychological distress (309); AUC against diagnosed psychiatric morbidity (0.93) (313).
Malaise Inventory	A shorter 9-item version (as opposed the full 24 items version); binary ("yes-no") response scale; self-administered. Used across all ages in BCS70 and NCDS.	4 or higher on the summed up score	Tested in the general population (age 23-33); Cronbach's alpha = 0.70 – 0.80; all items identify a common factor; AUC against self-reported diagnosed psychiatric morbidity = 0.77 – 0.79) (238).

* Sensitivity (the proportion of cases who are correctly identified) and specificity (the proportion of non-cases correctly identified) expressed as area under the curve (AUC) (314).

5.2.3 Harmonisation of the continuous outcome

There were differences between the instruments within NSHD and between NSHD and the other two cohorts. Hence, it was necessary to select comparable items from each measure in order to produce valid comparisons within NSHD, as well as between NSHD and two other cohorts. To the best of my knowledge, this is the first attempt to correct for measurement error due to different measures of mental health in the British birth cohorts.

Candidate items for harmonisation were identified by three independent raters (psychologists all experienced in research and one in clinical practice). Initially, two raters scrutinised every available item within each measure administered in the cohorts and assigned each individual item a code reflecting its core content at the symptom level. In cases where the two raters disagreed, a third independent rater decided which item code (if either) was most appropriate (315). In this process, seven items were selected for the NSHD, which facilitated comparisons within the cohort. In addition, following the same process, four items were identified allowing for comparisons across the NSHD, NCDS and BCS70. Agreement between the raters was high (88%).

As a validity check, new binarised items were summed-up and correlated with the full, original scale scores. These correlations ranged from 0.78 (PSF) to 0.98 (Malaise), which demonstrated that the recoding process did not interfere unduly with the rank ordering of participants. To further test whether the two sets of harmonised items were comparable, their measurement equivalence within NSHD (7 items) and across all cohorts (4 items) was formally tested. Measurement equivalence or invariance, was tested using latent variable multigroup models that allow verifying the

degree to which items function equivalently and therefore if they can be reliably compared across groups (310, 316). The “groups” were defined by age within NSHD and by age and cohort across all three cohorts.

Scalar invariance was obtained for subscales consisting of the seven harmonised items within the NSHD (see Appendix 3B for model comparisons across different invariance levels). Thus, it be can concluded that the 7-item subset is highly comparable across ages within NSHD. With respect to the 4-item subset, partial scalar invariance was observed, thus it can be used for comparisons of mean-level scores (i.e. summed-up total) within and across cohorts (see Appendix 3C for model comparisons across different invariance levels) (317).

It was necessary to synchronise the response scales across the measures (see Table 5.2). As transforming the binary response of the Malaise Inventory was not possible, the other three measures were recoded to a binary format. Every item from the GHQ, PSF and PSE was recorded as either 0 (absence of symptom) or 1 (endorsement of symptom). The (0-0-1-1) scoring was used for the GHQ, with “worse/more than usual” or “much worse/more than usual” corresponding to an endorsement of a symptom. Symptoms within the PSE were considered as endorsed if present regardless of clinical severity. Finally, the endorsement of symptoms within the PSF was indicated by responding “quite often”, “often” or “always” to a question.

Table 5.2 Harmonised items across measures of psychological distress.

Symptom	**Present State Examination**	**Psychiatric Symptom Frequency Questionnaire**	**General Health Questionnaire**	**Malaise Inventory**
Low Mood	Do you keep reasonably cheerful or have you been very depressed or low spirited recently? (rate depressed mood)	Over the last year have you been in low spirits or felt miserable?	Have you recently been able to enjoy your normal day-to-day activities?	Do you often feel miserable or depressed?
Fatigue	Have you been exhausted and worn out during the day or evening even when you haven't been working very hard? (rate tiredness/exhaustion)	Over the last year have there been days when you tired out very easily?	Have you recently been feeling in need of a good tonic?	Do you feel tired most of the time?
Tension	Do you often feel on edge, keyed up, mentally tense or strained? (rate nervous tension)	Over the last year have you felt on edge, keyed up or mentally tense?	Have you recently felt constantly under strain?	Are you constantly keyed up and jittery?
Panic	Have you had times when you felt shaky or you heart pounded or you felt sweaty and you simply had to do something about it?	Over the last year have you been in situations when you felt shaky or sweaty or your heart pounded or you could not get your breath?	Have you recently been getting scared or panicky for no good reason?	Does your heart often race like mad?
Hopelessness	How do you see the future? (rate hopelessness)	Over the last year have you had the feeling that the future does not hold much for you?	Have you recently felt that life is entirely hopeless?	
Health anxiety	Do you tend to worry over your physical health? (rate hypochondriasis)	Over the last year have you been frightened or worried about becoming ill or about dying?	Have you recently felt that you are ill?	
Sleep problems	Have you had any trouble getting off to sleep in the last month? (rate delayed sleep)	Over the last year have you had trouble getting off to sleep?	Have you recently lost much sleep over worry?	
Response options	Symptom not present/ Symptom definitely present during past month, but of moderate clinical intensity/ Intense form of symptom present for more than 50% of past month	Never/ Occasionally/ Sometimes/ Quite often/ Very often/ Always	Not at all been feeling in need of a good tonic?)/ No more than usual/ Rather more than usual/ Much more than usual	No/Yes

*Additional items used for investigating age effects in mental health morbidity within the 1946 cohort (NSHD).
**Values provided for harmonised 4-items scale.

5.2.4 Missing data

The extent of missing data was greater in younger cohorts (Table 5.3); for instance, at age 42-43 the outcome data were missing in 12.2% of the eligible sample in NSHD, 20.8% in NCDS and 35.5% in BCS70 (Table 5.3). The multilevel models account for missing data using full maximum likelihood, which produces valid results under the Missing At Random (MAR) assumption (318). The MAR mechanism, which is largely untestable, implies that systematic differences between the missing values and the observed values can be explained by observed data (247). I re-ran the multilevel models after replacing missing data using multiple imputation (MI) with chained equations (20 imputations), obtaining consistent results. The multiple imputation (MI) also provides valid results under the MAR assumption (247). However, it allows for including variables in the estimation model, which are predictive of missingness in the outcome and/or related to the incomplete outcome itself—such as parental social class at birth, birthweight and mental health at age 15/16 (Table 5.3). The inclusion of these variables increases the plausibility of the outcome being MAR. The MI was also used to estimate, model-free, cross-sectional prevalence of cases within each cohort. A comparison of estimates based on different missing data strategies allows for testing robustness of the findings.

Table 5.3 Frequency and predictors of missing data in the outcome.

N (eligible sample)	**Age 33-34**		**Age 42**		**Age 50-53**	
	n (%)		n (%)		n (%)	
1946 (n=3,093)	376 (12.16)		376 (12.16)		520 (16.81)	
1958 (n=13,250)	2,854 (21.54)		2,751 (20.76)		4,129 (31.16)	
1970 (n=12,019)	3,287 (27.35)		4,270 (35.53)			
	Missing outcome	Outcome	Missing outcome	Outcome	Missing outcome	Outcome
Logistic regression estimates	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)	RR (95%CI)
Birth cohort (1946 – reference category)						
1958	1.76 (1.64, 1.88)	1.32 (1.17, 1.49)	1.61 (1.50, 1.72)	1.06 (0.97, 1.15)	1.77 (1.67, 1.87)	0.77 (0.72, 0.83)
1970	2.23 (2.08, 2.39)	2.70 (2.41, 3.02)	2.75 (2.58, 2.94)	1.48 (1.37, 1.61)		
Women (men – reference category)	0.83 (0.80, 0.87)	1.82 (1.68, 1.97)	0.85 (0.82, 0.89)	1.53 (1.44, 1.63)	0.96 (0.94, 0.98)	1.62 (1.51, 1.75)
Non-manual father's occupational class (manual – reference)	1.23 (1.16, 1.30)	1.24 (1.14, 1.36)	1.21 (1.16, 1.27)	1.28 (1.19, 1.38)	1.27 (1.19, 0.96)	1.07 (0.98, 1.16)
Mental health morbidity at age 15/16	1.17 (1.07, 1.28)	2.19 (1.95, 2.46)	1.15 (1.06, 1.25)	2.05 (1.86, 2.25)	1.04 (1.00, 1.09)	1.60 (1.42, 1.80)
Mental health morbidity at preceding age	1.28 (1.19, 1.38)	6.25 (5.72, 6.84)	1.62 (1.50, 1.74)	5.32 (5.00, 5.67)	1.26 (1.22, 1.31)	3.85 (3.58, 4.13)
Normal birthweight (low: <2500g – reference)	0.91 (0.83, 0.99)	0.80 (0.68, 0.93)	0.87 (0.81, 0.95)	0.85 (0.74, 0.97)	0.91 (0.87, 0.95)	0.82 (0.70, 0.96)

5.2.5 Age trajectories of mental health

I used the multilevel growth curve framework—with the logit models for a binary outcome and the Poisson models for continuous (count) outcomes. This framework allows for modelling data that are unbalanced in time as well as the inclusion of missing data (318). It also accounts for the hierarchical dependency of observations (level 1) within individuals (level 2)—with age becoming an observation-level variable (319). A similar modelling strategy was employed for both binary and continuous outcomes. Age polynomials were included as far as significant at $p<0.05$ (up to a cubic term) and they were retained in the model if this improved the model fit according to the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), with lower values indicating better fit. All-models were controlled for gender. The fixed part of all models included age, gender and the intercept. The random part of the model captured variance in the intercept. Random age slopes were not included as the models resulted in non-positive definite matrices, possibly due to highly unbalanced data (320), or very low variance in the random slopes. All models included weights to account for the social class-stratified sample of the NSHD, with participants from the NCDS and BCS70 being given the weighting value of one. All analyses were conducted using Stata 15 (321). The cohort- and-age-stratified estimates from the model, obtained with predictive margins, were compared to cross-sectional values that did not rely on the mathematical shape functions of the model.

In the analysis with a 4-items subset, age-by-cohort interaction was additionally tested in the fixed part of the model, at the significance level of $p<0.05$ and according to AIC and BIC. This formally examined if age profile in mental health outcomes was

universal across the birth cohorts. In addition, the main effects of birth cohorts were studied to test if younger birth cohorts had a higher level of mental health morbidity when age was accounted for. Finally, using comparable items across and within cohorts allowed for modelling the age trajectory of mental health pooled across all cohorts—resulting in a curve capturing growth based on observations from age 23 to 69.

5.2.6 Supplementary analysis - age distribution of individual symptoms

I also plotted cohort-stratified age profile of each symptom from the harmonised 4-items subset. This was a descriptive, model-free, analysis aiming to explore whether all symptoms followed a similar age distribution as the aggregated scales. In addition, the proportion of individuals with different counts of symptoms were plotted within each cohort (based on harmonised 7-items in NSHD and 9-items in NCDS/BCS70). This would help to explain potential discrepancies between the results obtained with the binary and continuous outcomes.

5.3 Results

5.3.1 Age distribution of mental health

Table 5.4 presents age distribution of mental health caseness, derived using the binary threshold. The MI (multiple imputation) column corresponds to cross-sectional estimates based on multiple imputation. The proportion of cases was highest in mid-life in all three cohorts (i.e. 19.1% at age 53 in NSHD, 15.2% at age 50 in NCDS, 19.9% at age 46 in BCS70) (Table 5.4). Across all ages, there was a higher proportion of cases in BCS70 than NCDS. A direct comparison with NSHD was not possible due to differences in the outcome measures—as explained in section 5.2.3.

Table 5.4 Age distribution of caseness (as a binary outcome) based on the multiple imputation and multilevel logit regression.

	NSHD		**NCDS**		**BCS70**	
	MI	**MLR**	**MI**	**MLR**	**MI**	**MLR**
	% (95%CI)	**%** (95%CI)	**%** (95%CI)	**%** (95%CI)	**%** (95%CI)	**%** (95%CI)
Age 23-26			9.6 (9.0, 10.1)	9.9 (9.3, 10.5)	16.0 (15.2, 16.8)	16.3 (15.5, 17.1)
Age 30					13.7 (13.1, 14.4)	14.8 (14.2, 15.4)
Age 33-36	6.0 (5.1, 6.9)	6.2 (5.4, 7.2)	7.9 (7.3, 8.4)	8.0 (7.5, 8.5)	16.1 (15.4, 16.9)	15.7 (15.1, 16.3)
Age 42-43	11.9 (10.7, 13.1)	12.5 (11.6, 13.5)	13.3 (12.6, 13.9)	13.7 (13.0, 14.4)	18.7 (17.9, 19.4)	19.7 (18.9, 20.5)
Age 46					19.9 (19.0, 20.1)	20.0 (19.2, 20.1)
Age 50-53	19.1 (17.6, 20.7)	19.5 (18.3, 20.7)	15.2 (14.3, 16.0)	15.8 (15.1, 16.6)		
Age 60-64	18.1 (16.5, 19.6)	19.5 (18.4, 20.6)				
Age 69	14.8 (13.3, 16.3)	15.2 (13.7, 16.8)				

MI = estimates based on multiple imputation; MLR = predicted probability from the multilevel logit regression.

5.3.2 Trajectory of mental health across adulthood (age effects)

The age trajectories of mental health, based on the model with the best fit, followed a quadratic shape in NSHD, cubic in NCDS as well as BCS70 (see Figure 5.3 – Panels A & B and Appendix 3D for details). There was an increase in the probability of caseness between early-adulthood and mid-life in all three cohorts. Predicted probability of being a case, obtained from the multilevel logit model, increased from 12.5% at age 36 to 19.5% at age 50-53 in NSHD; from 8.0% at age 33 to 13.7% at age 42 in NCDS; and from 15.7% at age 34 to 19.7% at age 42 in BCS70 (MLR column in Table 5.4). Both in the NCDS and BCS70, there was an initial drop in the probability of being a case between age 23-26 and 33-34. In NSHD, where the data were collected until an early old age, there was a drop in the probability of caseness from age 60-64 to 69 (19.5% vs 15.2%).

The best-fitted curves from the multilevel Poisson model, using a continuous version of the outcome, also had a quadratic shape in the NSHD and cubic in both the NCDS and BCS70 (see Figure 5.3 – Panels C & D and Appendix 3E for details). However, there were slight differences in the trajectories, compared with those obtained with the binary outcome. The curve in the NSHD was slightly flatter, where the increase in the mean number of mental health problems in mid-life was not as severe as the rise in the proportion of cases. In the NCDS, the predicted mean number of symptoms remained relatively stable between age 42 and 50 (1.65, 95%CI 1.61 to 1.69 vs 1.64, 95%CI 1.60 to 1.69), whereas the probability of being a case increased marginally in the same age range (13.7%, 95%CI 13.0 to 14.4 vs 15.8% 95%CI 15.1 to 16.6). In the BCS70, the mean number of symptoms declined between age 42 and 46 (2.04, 95%CI 1.99 to 2.09 vs 1.91, 95%CI 1.86 to 1.96) when the continuous outcome was

used, which was in contrast to stable probability of caseness (19.7% 95%CI 18.9 to 20.5 vs 20.0% 95%CI 19.2 to 20.1). Overall, women had higher levels of mental health problems across all birth cohorts when either version of the outcome was used (Appendices 3F and 3G).

Considering longitudinal changes in proportions of those with a different number of symptoms may help to understand the discrepancies between the binary and continuous outcomes. As presented by Figure 5.4, it appears that the initial increase in mental health problems in early-40s is driven by the declining proportion of those with no symptoms and an increase in the proportion of those with any number of symptoms. Hence, in this life stage, binary and continuous outcomes show similar results. Subsequently in mid-40s and early-50s, both the proportions of those with no symptoms and with four or more symptoms (or three or more in NSHD) increase. Whereas individuals who had between one and three (or one and two in NSHD) symptoms declined in proportion. This leads to a discrepancy in results between the binary and continuous outcomes, where the curves of a continuous outcome show a more positive trajectory.

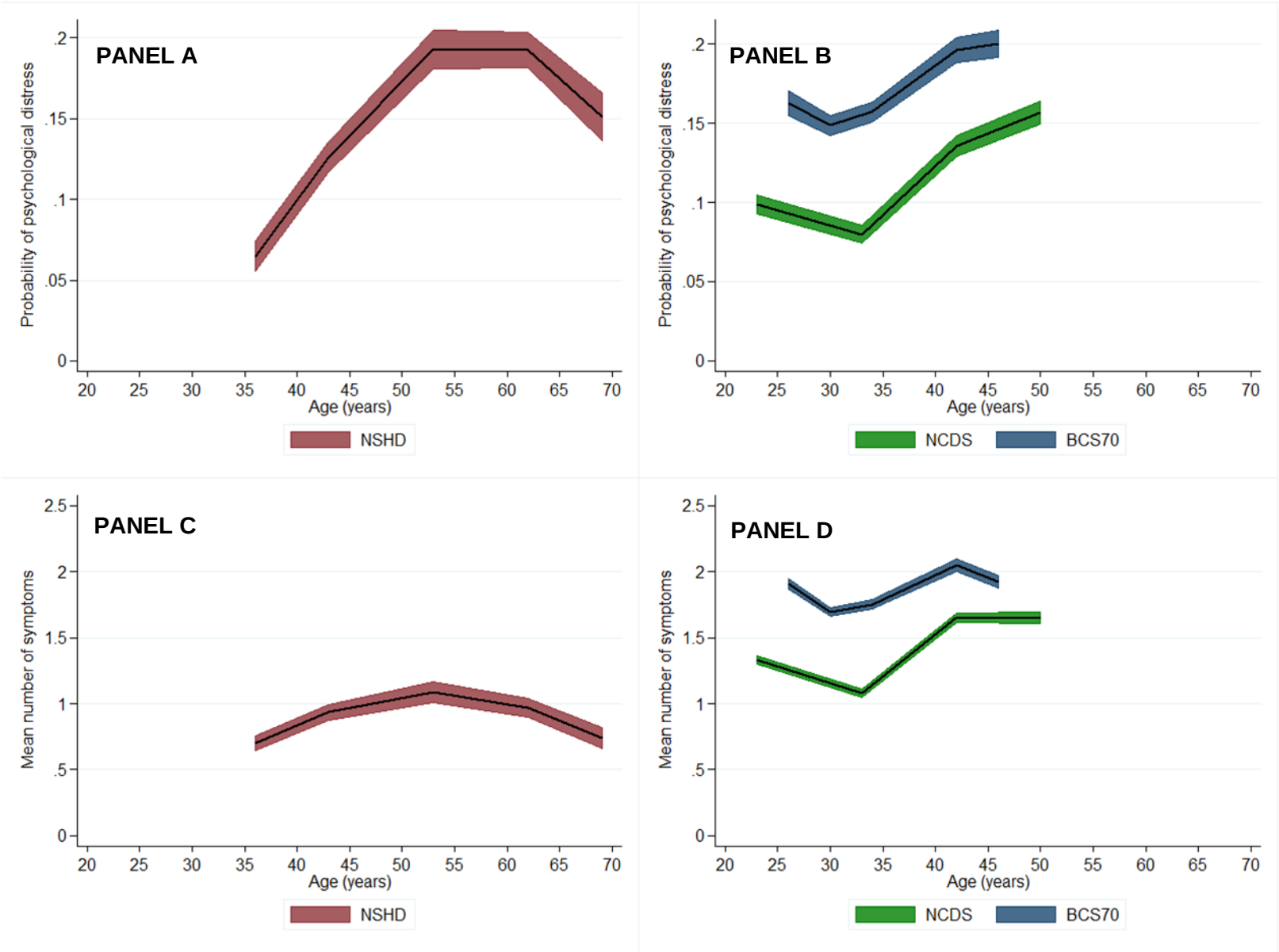


Figure 5.2 Cohort-stratified age trajectories in mental health – as a binary (Panels A and B) and continuous (Panels C and D) outcomes.

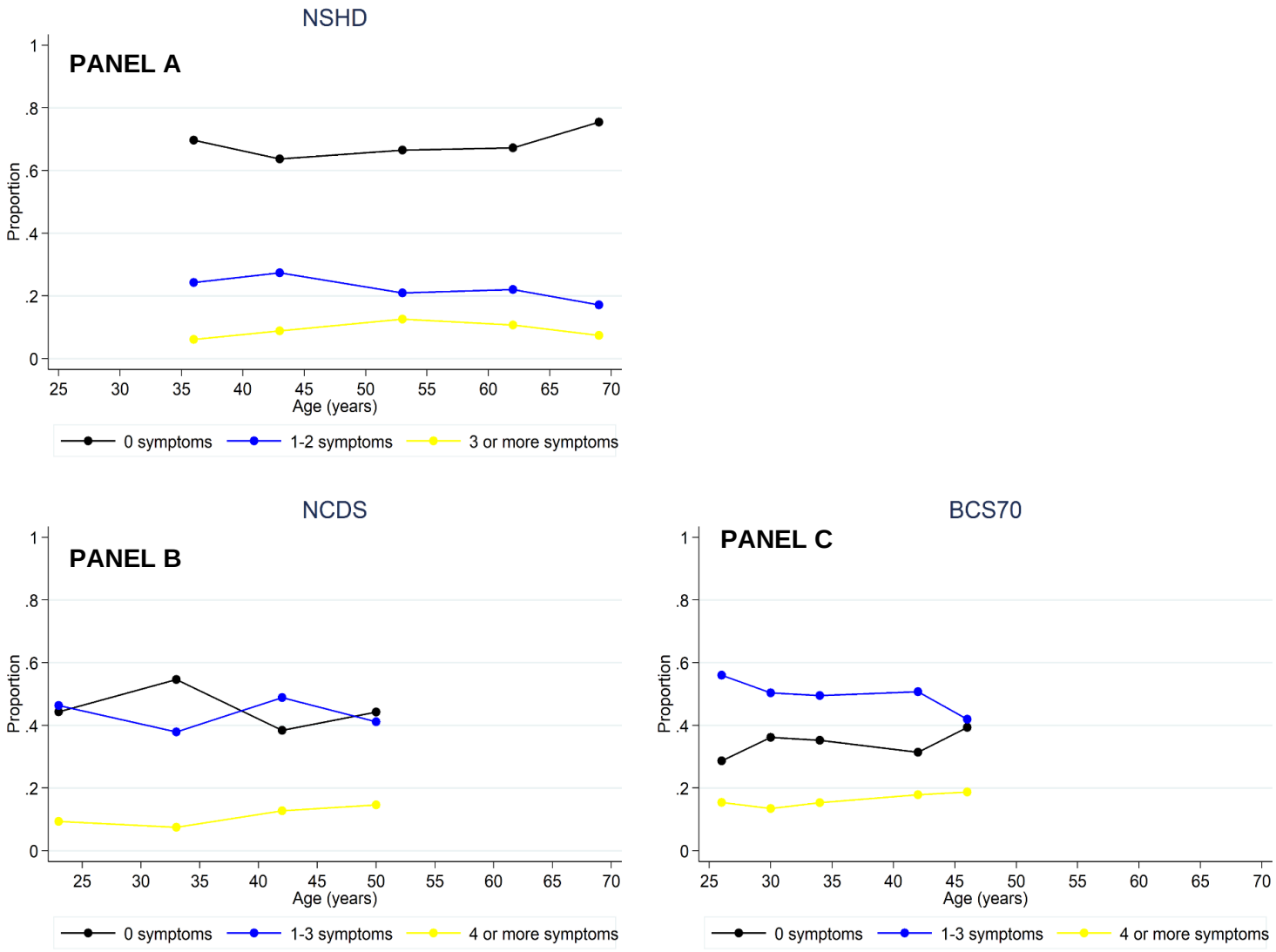


Figure 5.3 Cohort-stratified age distribution of participants with varying proportions of symptoms.

5.3.3 Age and cohort effects in mental health—based on the 4-items subset

Harmonisation of individual items allowed for direct comparisons across all three cohorts as well as for modelling the age trajectory based on observations from age 23 to 69 after pooling all measures across cohorts. Overall, the age trajectories within all cohorts were comparable to those obtained in the analysis using the binary and continuous versions of the outcome including seven (NSHD) or nine (NCDS/BCS70) items (Figure 5.5).

After pooling all measures across cohorts and keeping year-of-birth constant, the age trajectory followed a cubic shape (Figure 5.5), with mental health problems increasing from early-adulthood to mid-life and subsequently declining into older age. There was evidence for age-by-cohort interaction, indicated by significance of age*cohort terms ($p<0.05$) and improvement of the model according to AIC and BIC. This provided evidence for differences in age trajectories across cohorts. I further tested if the increase from early-adulthood (age 33-36) to mid-life (42-43) was uniform across the cohorts. There was evidence for a steeper increase in symptoms in NCDS (B = 0.51, 95%CI 0.48, 0.53) and BCS70 (B = 0.48, 95%CI 0.45, 0.50) compared with NSHD (B = 0.38, 95%CI 0.30, 0.46); no difference was found between NCDS and BCS70. Younger birth cohorts not only experienced a steeper increase in symptoms in mid-life, but also had overall higher levels of symptoms when age was accounted for (main effects of birth cohort, with NSHD as a reference: NCDS B = 0.24, 95%CI 0.17, 0.30; BCS70 B = 0.66, 95%CI 0.60, 0.72).

Considering all birth cohorts simultaneously also allowed for exploring potential period effects by plotting trajectories with calendar years on X-axis instead of age (Figure 5.6). The increase in mental health problems from early-adulthood to mid-life

occurred during 1990s in the NSHD and NCDS, which may suggest at least partial influence of period effects. However, a similar trajectory at the same life-phase was also observed for BCS70 from the year 2000, in which mental health problems started to decline in two other cohorts. This reinforces the conclusion that the increase between early-life and mid-life can be mostly attributed to age effects.

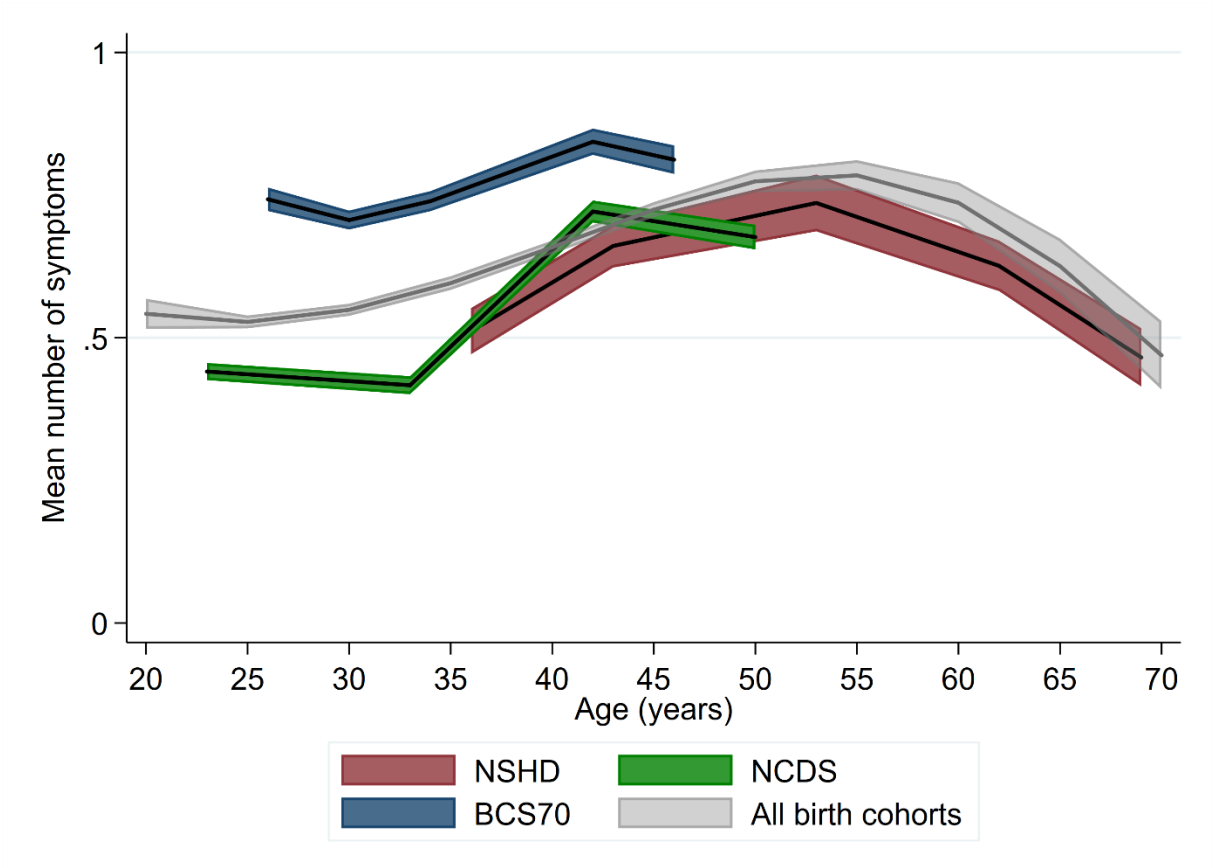


Figure 5.4 Age trajectory of mean number of symptoms—cohort-stratified and pooled across cohorts.

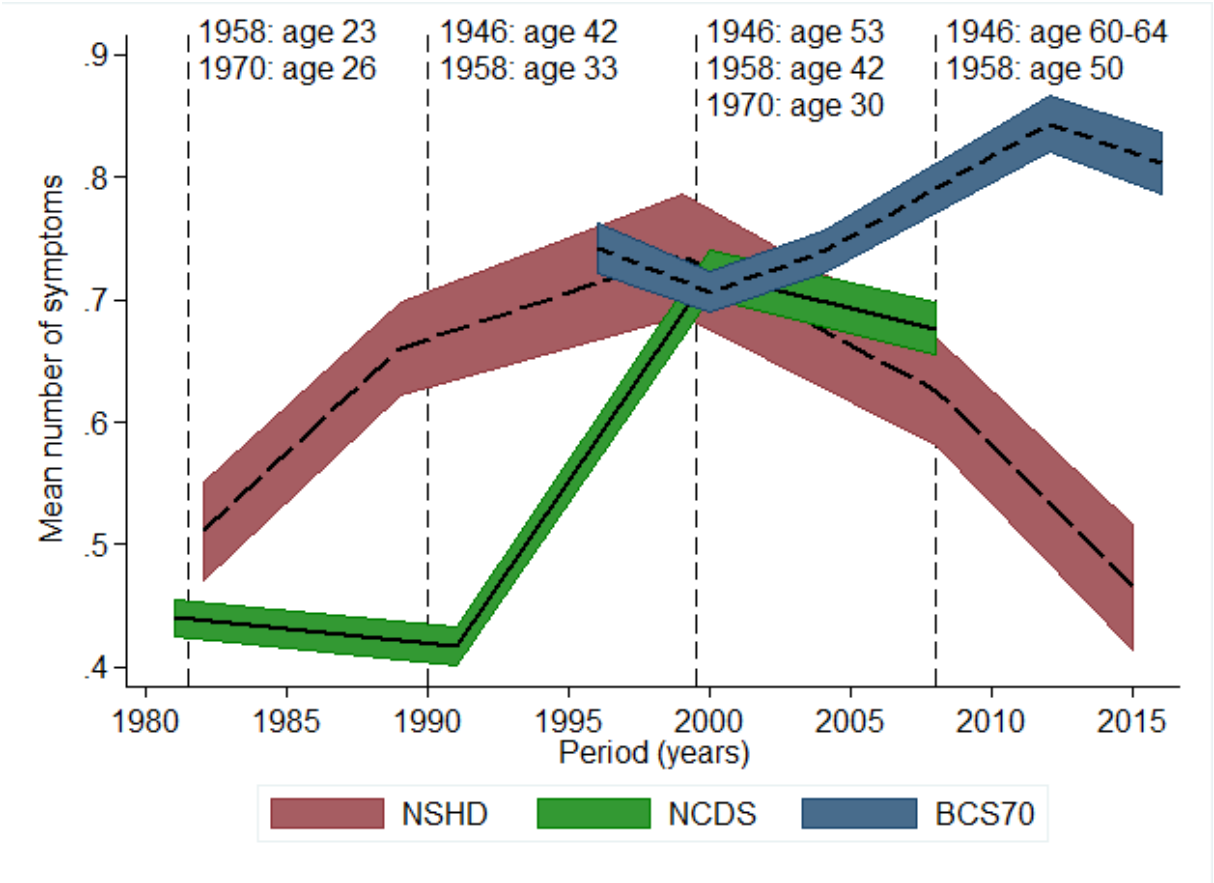


Figure 5.5 Cohort stratified age trajectory of mean number of symptoms—with calendar years on X-axis.

5.3.4 Age distribution of individual symptoms—exploratory analysis

Fatigue and low mood followed a very similar age trajectory as the main outcome measures in all three cohorts (Figure 5.7). Overall, these two symptoms were also the most prevalent. The age curve of the panic symptom, however, was much flatter in NCDS and BCS70 (Figure 5.7). Finally, tension appeared to marginally increase during the entire adulthood in NCDS and BCS70, whereas it peaked quite visibly at age 43 in NSHD and subsequently declined (Figure 5.7). Successively younger birth cohorts had an increasing prevalence of each symptom apart from tension, which was much higher in prevalence in NSHD than in two other cohorts.

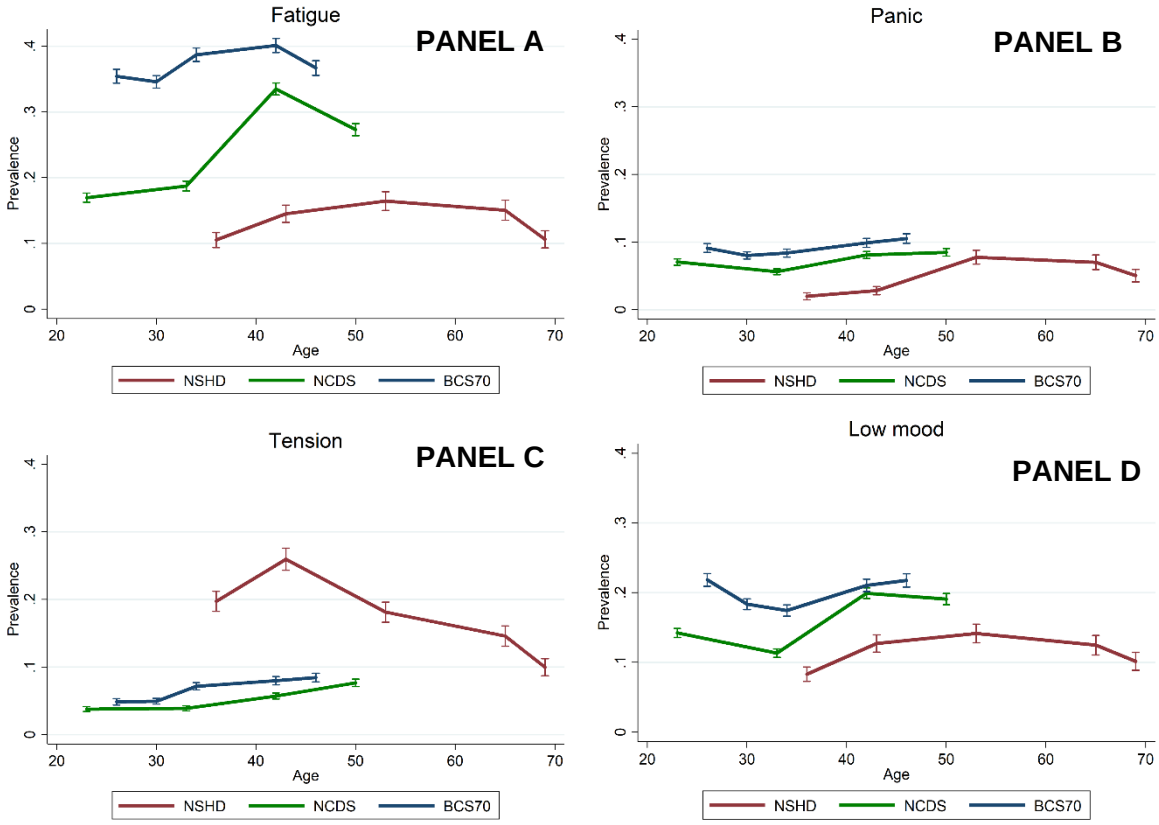


Figure 5.6 Cohort-stratified age distribution of individual symptoms.

5.4 Discussion

5.4.1 Summary of findings

Across three post-war British birth cohorts, there was a clear increase in mental health problems from early-adulthood to mid-life. This increase appears to be steeper in the NCDS (born in 1958) and BCS70 (born in 1970) than in the NSHD (born in 1946). In the NSHD, where additional data sweeps were available, mental health subsequently improved between mid-life and early old age. Participants of both NCDS and BCS70 also experienced elevated levels of mental health problems in their mid-20s. Overall, after controlling for cohort differences, the age trajectory of mental health followed an inverted U-shape in adulthood, with symptoms increasing from early- to mid-adulthood and subsequently declining. Finally, participants of the BCS70 had worse mental health than two other cohorts at overlapping ages (26-46).

5.4.2 Comparison with other studies

The most common pattern of the age distribution of mental health outcomes in the literature is an initial rise in mental health problems across age until around age 45-55, followed by a drop into older age (296). The most consistent finding is that mental health problems linearly increase between early-adulthood and mid-life (289, 291, 301, 322). However, in this study members of both the NCDS and BCS70 experienced worse mental health in mid-20s than in early-30s. Elevated levels of psychological distress across adulthood were also found among 20-24 year-olds in Canada and the USA born in 1970s-1980s, in repeated cross-sectional studies conducted between 1997-2008 (298).

The finding of elevated mental health problems in mid-20s has been rarely discussed in the literature in the UK. This may be due to modelling strategies masking this

effect, such as fitting polynomial age trajectories and pooling data across several birth cohorts to obtain a trajectory with a longer age range. For instance, worse mental health can be observed in the British Household Panel Survey at age between 15-24 and 25-34 in individual birth cohorts (born between 1960s and 1980s)—when age was treated as a categorical variable (301). However, when age trajectories within the birth cohorts were modelled as cubic polynomials, the apparent higher distress in early-20s was not observed anymore (289). A similar observation can be made in the British Adult Psychiatric Morbidity Survey, where mental health problems increased in mid-20s and subsequently declined in the cohorts born in 1964-1970 (among women only) and 1971-1977 (293). Nonetheless, when the age trajectory was pooled across different cohorts, it had an inverted U-shape (293).

This was also observed in this study—when age was modelled across individual birth cohorts, there was a clear spike in mental health problems in mid-20s in NCDS and BCS70. This was also reflected in descriptive analysis of the data. However, modelling age trajectory across all three birth cohorts resulted in the curve having an inverted U-shape—with a flattening tail in mid-20s where predicted values were slightly underestimated compared with the observed data. This highlights the strength of this study where the age effects were studied within the same individuals observed over an extended period of time, rather than relying on statistical methods pooling observations across multiple birth cohorts.

Further research is needed to understand the extent to which the elevated mental health problems is a cohort effect—applying mostly to those born in the 1960s and 1970s and to what extent this was an age effect—experienced also across younger

birth cohorts. In the UK, this research question can be tested with the Next Steps study (the generation born in 1989-90), the Avon Longitudinal Study of Parents and Children (born in 1991-1992) and in the near future, the Millennium Cohort Study (born 2000-2001).

Another inconsistency in the evidence is on the apparent improvement in mental health between mid-life and older age. Studies based on the British Household Panel Survey (1991-2008) found a peak in distress around age 40, followed by a decline and a subsequent rise at old age (289, 291, 301). However, again the results were somewhat inconsistent depending on the methodology used. When age was modelled as a cubic-shaped curve in this dataset, mental health appeared to worsen throughout the life course, with a slowing decline in mid-life (289). Whereas entering age as a categorical variable to the model, which did not impose any specific shape on the trajectory, resulted in a clear drop in mental health problems between age 45-54 and 65-74 (301). Noteworthy, in both studies, mental health started to deteriorate again after age 70 (289, 301). A study based on the English Longitudinal Study of Ageing showed declining rates of mental health problems between age 50 and 65 and subsequently increasing rates between age 65 and 90 (302). Hence, it is likely that the NSHD may also experience worsening mental health in the subsequent waves of data collection, which future research can investigate.

My analysis expands on previous studies that found higher levels of mental health problems from early-adulthood to mid-life among participants of BCS70 compared with NCDS (38, 291). In addition, this study contributes to the literature by adding a comparison with an older birth cohort—the NSHD—showing that their members experienced fewer mental health problems than NCDS and BCS70. This is

consistent with previous, cross-sectional, evidence on the increase in symptoms of common mental disorders (40-60-year-old) in cohorts born in 1950-56 compared with those born in 1943-9 (293). In line with the findings, a study based on the British Household Panel Survey (289) found that 1970 birth cohort had higher levels of mental health problems than 1960 at overlapping ages (31-38) and 1960 had worse mental health than 1950 birth cohort (at age 41-48) (289). Those born in 1957-63 also had worse mental health than 1943-9 at overlapping age in the National Psychiatric Morbidity Surveys in England (1993-200), with 1971-77 having a higher prevalence of common mental disorders than the preceding cohorts (293). Increasing rates of mental health problems across successively younger birth cohorts were also found in Belgium (born in 1918-27 – 1958-67) (303), Sweden (1910-7 – 1982-89), Canada (1940-3 – 1989-92) (298), USA (298, 299) (1948-50 – 1993-5), Australia (1940s vs 1970) (305).

5.4.3 Interpretation

Overall, there is little theory to draw on when explaining age profiles of psychological distress in adulthood (297). Here, I discuss factors potentially linked with mental health changes at different phases of adulthood.

Starting with the increase in poor mental health in mid-20s, it is most likely an age effect, due to relatively universal experiences at this age across different socioeconomic and historical contexts in high-income countries. It was found across different periods: in 1981 (in NCDS) and 1996 (in BCS70) in this study, as well as between 2000-2007 in the study conducted by Spiers and colleagues (293). In addition, this increase was also found across different birth cohorts ranging from the late 1950s to 1980s (289, 293, 301) and in different countries including the UK,

Canada and the USA (298). It has been argued that the age between 18 and 29 should be acknowledged as an important developmental period with major role shifts, as people leave their parental home and start developing their own home and family (323, 324). Cohort effects, however, still play a role in differences seen across birth cohorts in this life phase, such as higher distress among those born in 1970. As this birth cohort was likely to experience instability in tenancy and was particularly disadvantaged in their transition from education to work, as they entered the labour market in the mid-1980s during high unemployment among young people (292). This may have had lasting effects on psychological distress of this cohort throughout adulthood.

Processes underlying the observed increase in psychological distress from early-30s to mid-life are unclear. Mid-life tends to involve a “peak” in career, with middle-aged adults acquiring increasing responsibility as the “decision-makers” in society, which is accompanied by reduced leisure time (325). This is, for instance, reflected by elevated job-related stress in mid-life (326) and it may provide a partial explanation for rising fatigue as observed in this study. Mid-life individuals were found to experience declining quality and quantity of leisure time, as well as time with friends and family, which may translate into worse mental health (327). Middle-age is also often associated with changes to family structure, which may be linked with mental health, such as rising rates of divorce (328, 329). For instance, in this life phase, people are more likely to be parents and simultaneously care for ageing parents (330)

The reasons for the decline in psychological distress after mid-life are also speculative. Selective mortality is one of the candidate explanations, as those in

poorer mental health are at a greater risk of dying prematurely (331). However, consistent findings were obtained using cross-sectional samples (participants alive at each wave) and longitudinal samples (including those who were alive at all data waves). Moreover, assuming that the mortality rates in the three cohorts are representative of those observed in their target populations (332) and that absolute mortality rates have declined during the investigated period (1)—any effects of selective mortality due to mental health reflect a population selection process and are not sample-specific biases. Older individuals, particularly those in a more advantaged social class, may also experience improved mental health due to relief from major mid-life stressors, for instance, due to retirement or stabilisation in family life. Indeed, the perceived daily stress reduces in this life phase; however, this reduction was not found to be associated with whether one was in full-time employment or with marital status (333). It has also been suggested that older people shift from attainment-related goals, such as status or skills, towards those that help them maintain emotional stability—a phenomenon known as the socioemotional selectivity (334). For instance, older individuals may be more likely to invest in relationships and activities that are positive and rewarding whilst ceasing those that are not. This, in turn, helps them to confront stressors and adversity (334). It is also possible that mental health problems more specific to old age are not well-captured by conventional symptom scales, hence underestimating the frequency of distress (335). For instance, physical symptoms of distress, such as decreased energy, fatigue or difficulty with sleeping, may be normalised and explained through deteriorating health related to ageing rather than emotional state (336).

Higher levels of mental health problems were observed in successively younger birth cohorts, with the BCS70 being particularly affected compared with the NSHD and

NCDS. As these differences appeared to occur across all overlapping ages, this suggests that a cohort effect is the most plausible explanation for the findings. One potential explanation for rising mental health problems in younger birth cohorts is declining economic circumstances, which are strongly associated with mental health (337). The generation born in 1970 experienced economic and labour market transformation and increasing socioeconomic inequality, compared with those born in 1946 and 1958 (63).

Those born in 1970 were particularly disadvantaged in their transition from education to work, as they entered the labour market in mid-1980s during high unemployment among young people (63). This may partially explain why cross-cohort differences appear to already emerge in young adulthood. Unemployment was substantially higher (around 10%) when BCS70 respondents were turning 16 in the late eighties than when NCDS members turned 16 in 1974 (around 2.5%) (338). Due to contraction of the industries that tended to employ unqualified school-leavers, such as manufacturing, the transitions from education to labour market became increasingly unstable, nonlinear and unstructured, particularly for those of disadvantaged socioeconomic background (338). This may have also disproportionally affected men (63). Young people, overall, made up a smaller proportion of the potential labour market, that may have reduced their competitiveness (338). Furthermore, part-time, self-employment and short-term contracts became more common, potentially increasing occupational instability (338), which has been found to linked to distress (339).

Overall, it appears that those of disadvantaged background may have been disproportionally affected by changes in the socioeconomic circumstances leading to

a greater prevalence of mental health problems. However, certain changes such as rising social inequality may have affected wellbeing of individuals representing the entire socioeconomic spectrum. Members of more advantaged social groups may suffer from being negatively evaluated by the rest of the society, a phenomenon known as the ”social evaluative threats”, which was found to be linked with elevated stress-hormone (cortisol) in a meta-analysis of 2008 studies (340). This may also result in poorer social relationships, which are well-known risk factor for mental health and wellbeing (341). In addition, some argued that rising house prices have affected not only those on lower incomes, for instance relatively well-off members of middle class appear to work increasingly longer hours, borrow more, commute longer and save less in order to keep up with this increase—all of which may contribute to worsening mental health in the younger birth cohorts (342).

In addition to changing economic circumstances, members of the BCS70 experienced social and family-related transformations that may partially explain rising mental health problems compared with those born earlier. In particular, there has been an increase in divorce (63), step-families and lone parenthood (343)—all linked with greater mental health problems (344, 345). Still divorce or lone parenthood are still relatively rare, hence they are unlikely to fully explain the rise in mental health problems in the younger cohorts. However, these changes to family structure may indicate a trend in overall decline in stable family relationships and high marital quality, which are linked to mental health and potentially affect a large segment of the population (346).

5.4.4 Strengths and limitations

The main strength of this study is that it used three population-based prospective studies, including—to the best of my knowledge—the longest continuous follow up of psychological distress within the same individuals, from age 36 to 69. This in opposition to most of previous research that rely on statistical methods pooling observations from longitudinal or repeated cross-sectional surveys across multiple “pseudo” cohorts. Another strength is that the same measure of distress was used in two of the cohorts, which was found to be invariant longitudinally, across the cohorts and genders (38).

A key limitation is that different measures of psychological distress were used within the NSHD—this may specifically impair comparability at age 36-53—and between this cohort and the NCDS and BCS70. However, comparable items at the symptom level within and across cohorts were identified through a comprehensive and robust harmonisation process. This resulted in the harmonised subsets of items, which were found to be invariant within NSHD (7-items) and across the three cohorts (4-items). Hence, their means can be compared within and across cohorts without bias (317). In addition, differences in measures are unlikely to solely explain the major finding of this study—an increase in psychological distress from early-adulthood to mid-life, followed by a decline in an early old age. In the NCDS and BCS70, the same measure was used between age 23 and 50—the Malaise Inventory. Hence inferences regarding the age distribution of psychological distress within and across the NCDS vs BCS70 are robust. In the NSHD, an increasing trend in psychological distress between age 36 and 43 can be observed, which is based on two closely-related measures increasing the confidence in findings. The Psychiatric Symptoms

Frequency used at age 43 was developed based on the Present State Examination that was used at age 36 (308). Likewise, the observed decline in psychological distress between age 53 and 69 in the NSHD, cannot be attributed to differences in measures since the GHQ-28 was used at all three ages.

Another limitation of the study, as with most longitudinal research, is a considerable amount of missing information. This analysis relied on the missing-at-random (MAR) assumption that is not empirically verifiable (248). Not meeting this assumption may potentially lead to bias. However, the plausibility of the MAR assumption was maximised by including rich information on health and related variables available from birth in the imputation model. The information contributed by these auxiliary variables allows for predicting missing data with greater accuracy, minimising non-random variation in these values (347). In addition, obtaining consistent findings when using different missing data strategies—multiple imputation and full information maximum likelihood (348)—further increased the robustness of the analyses. A related limitation for generalisability of the findings for today's population is that the participants of the British birth cohorts are nearly exclusively white, not accounting for migration that has taken place over time in the UK (349). The health of migrants may vary from those of the participants, for instance, due to healthy migrant effect (350).

5.4.5 Conclusion

Across three post-war British cohorts, there was a clear increase in psychological distress from early-adulthood to mid-life. In the NSHD, where additional data sweeps were available, psychological distress diminished into early old age. There is a need for further research to understand processes underlying elevated psychological

distress at each life phase (early and mid-20s as well as 40s-50s) and for cross-cohort differences. The British birth cohorts, including those following younger participants, are well-suited for studying those mechanisms.

Chapter 6: Inequality in hospitalisation due to non-communicable diseases in Sweden: age-cohort analysis of the Uppsala Birth Cohort Multigenerational Study

Chapter objectives:

- To examine cohort differences in age trajectories of hospitalisation due to key non-communicable conditions and if these varied by paternal socioeconomic position.

Key findings:

- Successively younger birth cohorts had a higher prevalence of hospitalisation at overlapping ages, with inter-cohort differences emerging from early-adulthood and increasing with age in absolute terms.
- Those with medium and low parental socioeconomic position (vs high) had 13% and 20% higher odds of experiencing hospitalisation during the observation period—when age, year-of-birth and gender were accounted for.
- No progress was made in reducing the socioeconomic inequalities according to parental social class across cohorts born between 1915 and 1972.

6.1 Introduction

In Sweden or other Scandinavian countries, routinely collected, administrative health data are of high quality, are available over an extensive period of time (from the 1980s for most of the outcomes) and can be linked with other registries, for instance, related to education or social class. Hence, they can be used in a complementary manner with the population-based surveys that are particularly prominent in the UK. Triangulation of information from these diverse sources allows for attaining more reliable evidence on population health trends and in a wider range of morbidity outcomes (88), which was the key motivation for this study.

Life expectancy at birth has increased by six years in Sweden and eleven years across the members of the Organization for Economic Co-operation and Development (OECD) in the last five decades (2). Nonetheless, growing evidence suggests that this increase in the lifespan has not translated into longer periods of life free of morbidity (351, 352) (in the UK: Chapter 2). Due to population ageing, chronic morbidity is projected to rise further—presenting policymakers with a challenge related to future healthcare policy, allocation of resources (353) and predicting trends in the workforce (354). Those with lower socioeconomic status or living in poorer areas appear to suffer from higher rates of chronic conditions compared with their better-off counterparts (355-359). This is despite Sweden having been particularly determined to reduce the health gap between rich and poor, making it a central objective of public health and social policy agendas since the 1980s (360). An important step in the development of health policies and interventions is to produce high-quality evidence on how changing socioeconomic

and policy contexts have affected health over time and if these effects varied across socioeconomic groups.

Currently, the evidence on secular trends and the socioeconomic gap in morbidity in Sweden is mainly cross-sectional, limited to comparing age-standardised rates of individual conditions over time across all ages (361, 362) or in older age exclusively (56, 355, 359). These studies have shown worsening in various self-reported health domains in the last three decades—when ageing was accounted for—including mobility, psychological distress, disability, chronic morbidity as well as objectively-measured physical capacity, lung function, vision (56, 355, 359). As in other high-income countries, the speculative reason for greater rates of morbidity is an improved survival among the older population with non-communicable health problems (359, 363). However, contrary evidence also exists suggesting an increase in years free from disability and mobility problems from the early 1990s until the early 2010s in both elderly men and women (364).

Evidence consistently points towards a health gradient according to social class, education or income (355-359)—with the differences remaining stable over time in the last few decades (356-358, 365). However, the evidence on cohort differences in age trajectories of morbidity—to my best knowledge—is virtually absent in Sweden. There are a few studies, mainly conducted in Great Britain, which explored cohort trends in age trajectories of body mass index, blood pressure and frailty (40, 366, 367). Such studies allow for identifying life stages when the differences across cohorts start to emerge. In addition, life course studies conducted across different birth cohorts allow for disentangling age and cohort effects, which is not possible in cross-sectional research due to exact collinearity of age and year-of-birth.

None of the life course studies, however, examined trends in non-communicable diseases and hospitalisation. This chapter contributes to the literature by focusing on inpatient hospital admissions, which indicate direct demands on health services and are also closely associated with other health measures, such as self-reported health, all-cause mortality (368) and quality of life (369, 370). Inpatient care constitutes one-fourth of total health expenditure in Sweden, mainly due to cancer and heart diseases (371). A large proportion of inpatient admissions, for such conditions as asthma or diabetes, could be managed in primary care or community settings—which would reduce costs and improve the effectiveness of health care (371, 372). Hence, hospital admissions are a particularly useful outcome to monitor over time. Studying cohort effects in admissions helps to project future demands. Considering age at which cohort differences emerge is also important as health-care spending increases after age 50 and escalates after age 70 (373).

I also examined whether cohort differences in age trajectory of hospitalisation varied by parental socioeconomic position (SEP). Higher rates of hospital admission among disadvantaged socioeconomic groups have been found in Sweden (avoidable hospitalisation) (368), New Zealand (for general and psychiatric admissions) (374), Amsterdam (for psychiatric admissions) and for Norway (375), Australia (376), with trends being less clear in Canada (377), Italy (378) and the USA (379). None of the above studies used childhood socioeconomic indicators. Childhood socioeconomic circumstances are important health determinants as they are associated with adult chronic health, independently of adult SEP (380)—possibly due to accumulation of negative health effects over the life course (381). Using parental SEP also has a methodological advantage, as it is less likely than adult measures of SEP to suffer

from reverse causality (382). Currently, the evidence in Sweden is limited to adult socioeconomic indicators (355-359, 365). In addition, I explored gender effects in cohort and socioeconomic differences in hospitalisation.

I used the Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen) which is linked to the general population and health registers in Sweden, providing virtually complete information on medical diagnoses and family links. This allowed me to study secular trends in age trajectories of hospitalisation across two generations (over the period of 1989-2008)—among those born in 1915-1929 and their children born in 1938-1972, ranging in age from 19 to 91. Due to recent evidence on the increase of burden due to non-communicable morbidity (351, 352), I hypothesised rising rates of hospitalisation across cohorts. Those in lower socioeconomic position were hypothesised to have greater rates of hospitalisation (355-359), with the socioeconomic gradient remaining stable over time (356-358, 365).

6.1.1 Study population

I used data from the UBCoS Multigen (157, 158)—the cohort of 14,192 men and women born in the Uppsala University Hospital (Uppsala, Sweden) between 1915 and 1929 (G1) and their children (G2) identified through the Multi-Generational Register. Among the members of G1, 12,168 were living in Sweden in the late 1940s, hence they received unique personal identification numbers (159), which remain unchanged and allow for the linkage across national registers. The study was approved by the Regional Ethics board in Stockholm. G1 is nationally representative of Sweden in terms of infant mortality and fertility (160), with a marginally higher proportion of births to single mothers (161) and infants from urban areas (162). Figure 6.1 depicts the selection process of the study population. The sample was limited to G1's biological children born between 1938 and 1972—as there were too few individuals outside of this range. I excluded those who died or emigrated from Sweden before 1994, which was the end of the first 5-year-interval of the observation period (n=4,141) or those with missing gender information (n=24). Being a man as well as having medium or low SEP were predictive of being excluded at this stage (see Appendix 4A). The final sample in this study constituted 28,448 (28,238 in models with SEP variable).

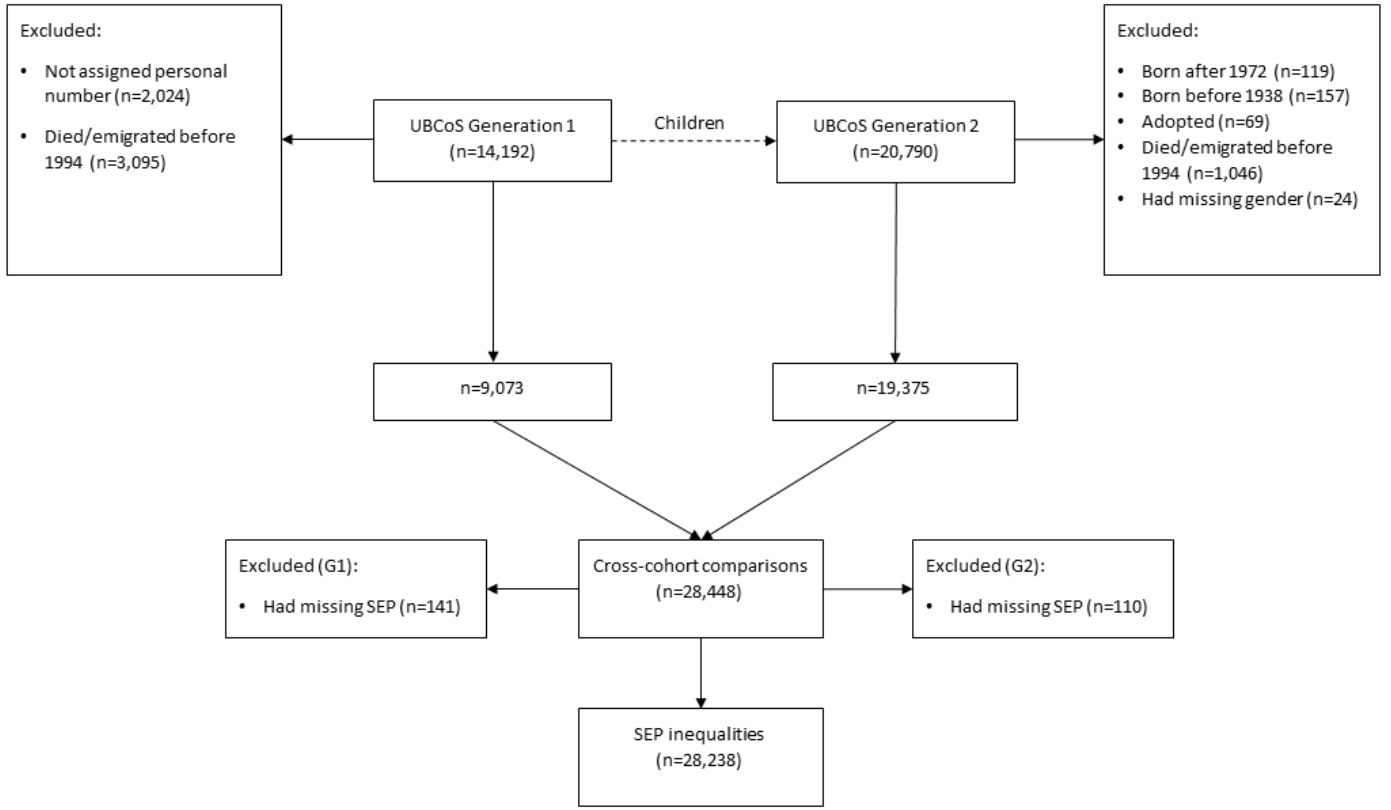


Figure 6.1 Flow chart of sample selection.

6.1.2 Measures

The outcome of interest was any hospitalisation due to a major non-communicable condition (see Table 6.1 for details) within four 5-year intervals (1989-1993, 1994-1998, 1999-2003, 2004-2008). These conditions were selected as they constitute the key contributors to the overall burden of morbidity (351), they are largely preventable and socially structured (383). The outcome was ascertained from the Swedish National Patient Register, which comprises complete coverage of all public and private inpatient care since 1987 (384). Cases were identified as individuals with a recorded primary or secondary diagnosis with the corresponding International Classification of Disease Ninth and Tenth Revisions (ICD-9/10) codes in the register (see Appendix 4B) (385). The exposures of interest were: age (19-91), year-of-birth (1915-1972), gender (man vs woman) and parental socioeconomic position (SEP). Parental SEP—categorised as “high”, “medium” and “low”—was derived from the fathers’ or mothers’ occupations. Information on occupations was retrieved from archived obstetric records, school records or Census 1930 for G1 and the Population and Housing Census 1960 for G2. The Swedish socioeconomic classification was assigned occupations to different categories of socioeconomic status (386). Table 6.1 describes each variable in more detail.

Table 6.1 Description of variables used in the analysis.

Outcome	
Hospitalisation due to chronic morbidity	A binary indicator (0 = Not hospitalised, 1 = Hospitalised) of any public and private inpatient hospitalisation, within four 5-year intervals (1989-1993, 1994-1998, 1999-2003, 2004-2008), due to: depression, asthma, cerebrovascular disease, chronic kidney diseases, cirrhosis, chronic obstructive pulmonary disease, dementia, diabetes, heart failure, cancer, hypertension, ischemic heart disease, migraine, Parkinson's disease, rheumatoid arthritis. Information on hospitalisation was ascertained from the Swedish National Patient Register, which includes complete information on the public and private inpatient care utilisation since 1987, using ICD-10 and equivalent ICD-9 codes (see Appendix 4B for details).
Exposures	
Age	A continuous variable ranging from 19 to 91. Age was derived by subtracting mid-year within each 5-year interval from year-of-birth (e.g. those born in 1962 would have age of 29 in the observation period of 1989-1993, 34 in 1994-1998, 39 in 1999-2003 and 44 in 2004-2008) (see Supplementary Figure 1 for graphical representation of the data).
Year-of-birth	A continuous variable ranging from 1915-1929 (G1) and 1938-1972 (G2). Year-of-birth was centered on its grand mean.
Gender	A binary indicator (0 = Man, 1 = Woman). Sample included 14,234 (50.04%) men and women 14,214 (49.96%).
Parental socioeconomic position	A categorical variable (0 = High, 1 = Medium, 2 = Low), was derived based on the approach used by Sidorchuk and colleagues (2018) (387): • Parental SEP for G1 was based on father's occupation, if available; otherwise on mother's occupation and categorised into (1) high: for higher/intermediate non-manuals, academic professionals; (2) medium: the self-employed, farmers and lower non-manuals; and (3) low: skilled/unskilled manuals. Data was retrieved from archived obstetric and school records and Census 1930. • Parental SEP for G2 was based separately on father's and mother's occupation and categorised as (1) high: higher/intermediate non-manuals, self-employed in academic professions; (2) medium: the self-employed in industry, trading, transport or service with employees, farmers with employees, lower non-manuals and persons at the military service; and (3) low: skilled/unskilled manuals, self-employed in industry, trading, transport or service without employees, farmers without employees, students, persons with unidentified occupation and others. The highest parental social class was defined by comparing maternal and paternal occupations. Data was obtained from the Population and Housing Census 1960. Sample included 9,616 (34.05%) people in high SEP, 6,453 (22.85%) in medium SEP and 12,169 (43.09%) in low SEP.

Table 6.1 (cont.) Description of variables used in the analysis.

Random (structural) variables	
Observation	103,262 observations (102,571 in models with SEP variable).
Individual	28,448 individuals (28,238 in models with SEP variable).
Family	16,203 families (16,027 in models with SEP variable); the variable was created by linking siblings within generation 2 with their parents (G1) and siblings across G1.

6.1.3 Analysis

Data were set up as an accelerated longitudinal study: with 1915-1929 (G1) and 1938-1972 (G2) birth cohorts, observed at 5-year periods (1989-1993, 1994-1998, 1999-2003, 2004-2008). In such set-up of registry-based data, we can observe cohort-specific age trajectories of hospitalisation over an overlapping 20-year study period (Appendix 4C). This allows for comparing the level and rate of change in hospitalisation at equivalent ages, but across individuals born at different points in time (see section 1.2.2 for more details). I used a multilevel growth curve framework in the analyses—with a logit link function due to the binary nature of the outcome.

This framework allows for modelling data that are unbalanced in time—where some individuals do not contribute information during the entire observation period, in this case, due to death or emigration (318). It also accounts for the hierarchical dependency of observations (level 1) within individuals (level 2)—with age becoming an observation-level variable (319). I extended this model by including family identifier as a third hierarchical level, in order to account for the dependency of individuals within the same families across two generations. This was due to 73% of the participants having at least one member of the family in the dataset. Hence, the models had three hierarchical levels: observations (n=103,262-102571; level 1) nested within individuals (n=28,448-28,238; level 2) nested within families (n=16,203-16,027; level 3)—included as random intercepts (see Appendix 4D). However, the variance due to family level was very low, as majority of the families had few members among the participants. For instance, out of all the families in the dataset, 74% had three or less members among the participants. The analyses including two hierarchical levels were largely consistent.

All exposure variables and their interactions were specified in the fixed part of the model. I did not explicitly modelled period effects, as the focus of the analyses was on differences in age trajectories due to year-of-birth. If periodical changes were at play, they would result in cohort differences in the age trajectory of hospitalisation as birth cohorts vary by age in any historical moment (see section 1.2.2). Hence, inter-cohort variations due to period effects are captured by age*year-of-birth interaction (388). All models were estimated using Markov chain Monte Carlo (MCMC) in MLwiN v3.03 (389) with the runmlwin command in Stata 15 (390).

6.1.3.1 Cohort differences in hospitalisation

I tested for inter-cohort differences in age trajectories of hospitalisation, by fitting a model including age and year-of-birth polynomials as far as significant up to a cubic term ($p<0.05$), alongside an age*year-of-birth interaction. Year-of-birth and age were centred at their grand mean to alleviate the interference of the nonessential multicollinearity (391). Subsequently, I examined if men or women experienced any inter-cohort differences in hospitalisation by adding gender variable and gender*year-of-birth interaction to the model.

6.1.4 Socioeconomic inequalities in the rate of hospitalisation

Subsequently, I examined any time and gender effects in socioeconomic inequalities in age trajectories of hospitalisation. I fitted a model including age and year-of-birth polynomials as far as significant up to a cubic term ($p<0.05$), alongside an age*year-of-birth interaction, gender and SEP variables as well as SEP*year-of-birth and SEP*age. SEP*year-of-birth, SEP*age interactions were tested one-by-one at the

significance level of $p<0.05$. Gender effects in socioeconomic inequalities were also examined by including gender*SEP interaction.

6.1.4.1 Supplemental analyses

The main effects of socioeconomic position on hospitalisation were additionally tested using parental income and education within G2 only, as these socioeconomic indicators were available for a small proportion of G1 members (see Supplementary Table 3 for details).

There were too few cases of hospitalisation to test inter-cohort differences in each individual condition or groups conditions. However, I tested inter-generation differences between parents (G1) and their children (G2) in age and gender adjusted models for overall hospitalisation. Likewise, inter-generation differences in socioeconomic inequalities in each individual condition or groups conditions were also tested—by including generation*SEP interaction.

6.2 Results

6.2.1 Burden of hospitalisation

There were 11,996 individuals who experienced at least one hospitalisation during the study period—amounting to 16,073 cases of hospitalisation. Figure 6.2 presents the proportion of hospitalisation due to each condition or group of conditions out of studied hospitalisation cases. When an individual was hospitalised due to more than one condition within a five-year period—this is referred to as repeated hospitalisation. The greatest proportion of cases were hospitalised due to repeated hospitalisation (25.4%). Other most common reasons for hospitalisation were ischemic heart disease (12.6%), cancer (12.4%) and hypertension (10.8%). Among those with low SEP—compared with high or medium—I found a greater proportion of the total burden of hospitalisation being due to repeated hospitalisation (absolute difference: 5.2%), dementia (1.1%), cerebrovascular disease (0.8%), heart failure (0.8%), chronic obstructive pulmonary disease (0.6%); and lower proportion due to cancer (2.0%), depression (1.8%), chronic kidney diseases (1.4%), schizophrenia (1.5%) and migraine (0.6%).

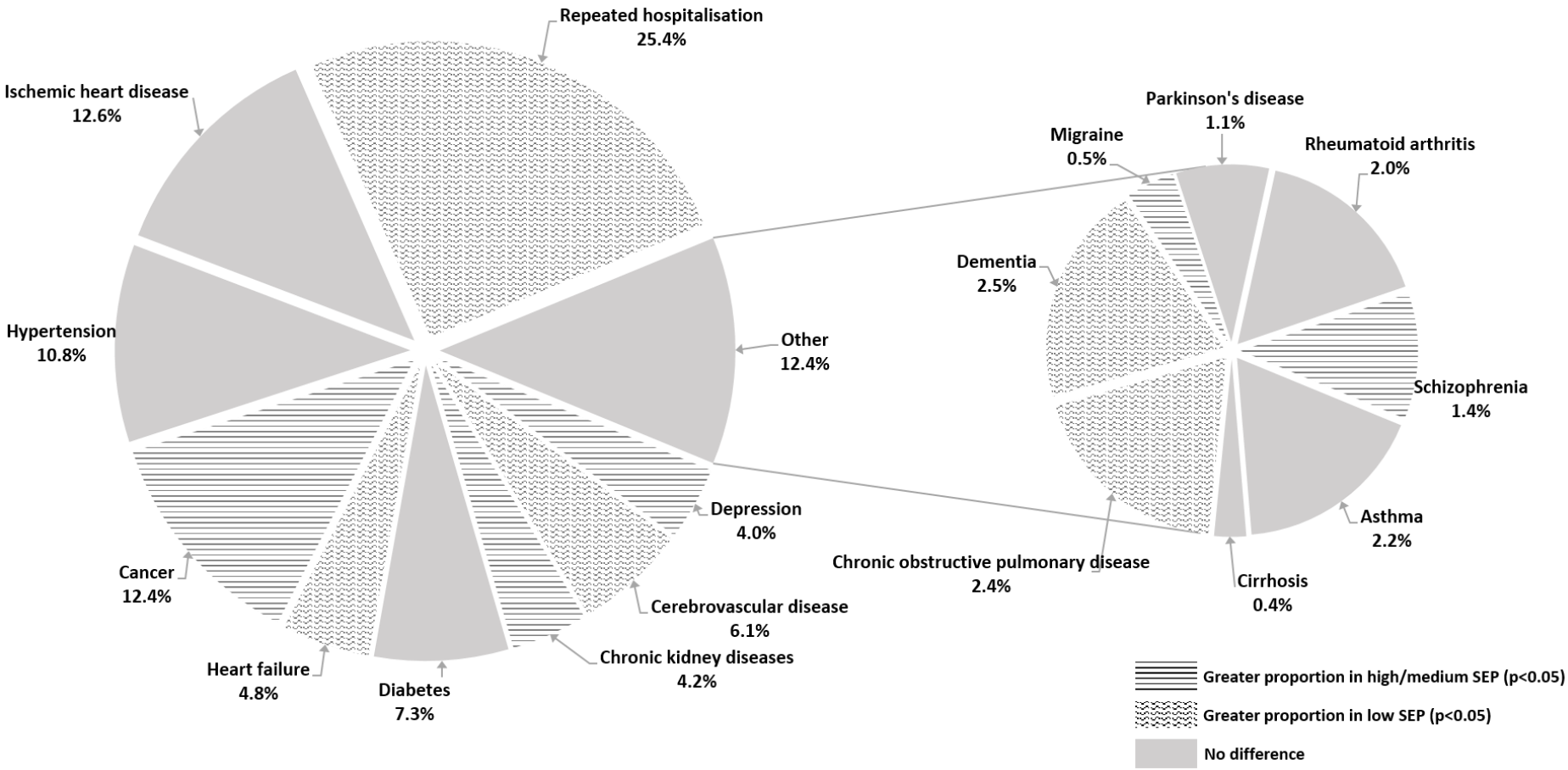


Figure 6.2 Proportion of total burden of hospitalisation due to specific conditions or group of conditions.
*Wavy lines indicate a greater proportion of total hospitalisation due to a given conditions among those with low SEP, whereas horizontal lines show a greater proportion among those in medium/high SEP (at $p<0.05$ according to chi square test).

6.2.2 Cohort differences in the rate of hospitalisation

As shown by Table 6.2 and Figure 6.3, younger cohorts had a higher prevalence of hospitalisation at overlapping ages, with inter-cohort differences emerging from early-adulthood and minimally decreasing with age in relative terms (age*YoB interaction: OR=0.9995, 95% CI 0.9993 to 0.9996), however increasing in absolute values. For instance, at age 40 predicted probability of hospitalisation increased across birth-cohorts—from 1.2% (born in 1948-52) to 2.0% (born in 1963-67), whereas at age 50 it was 2.9% for those born in 1938-42 compared with 4.6% among participants born in 1953-57. At older age, the absolute cohort differences were much larger—for instance at age 80 they increased from 33.7% to 39.0% between 1915-19 and 1925-29 birth-cohorts. Men appeared to have a higher probability of hospitalisation both in relative and absolute terms, with gender differences increasing slightly across cohorts when age was held constant (gender*YoB interaction: OR=1.01, 95% CI 1.01 to 1.02, p<0.001).

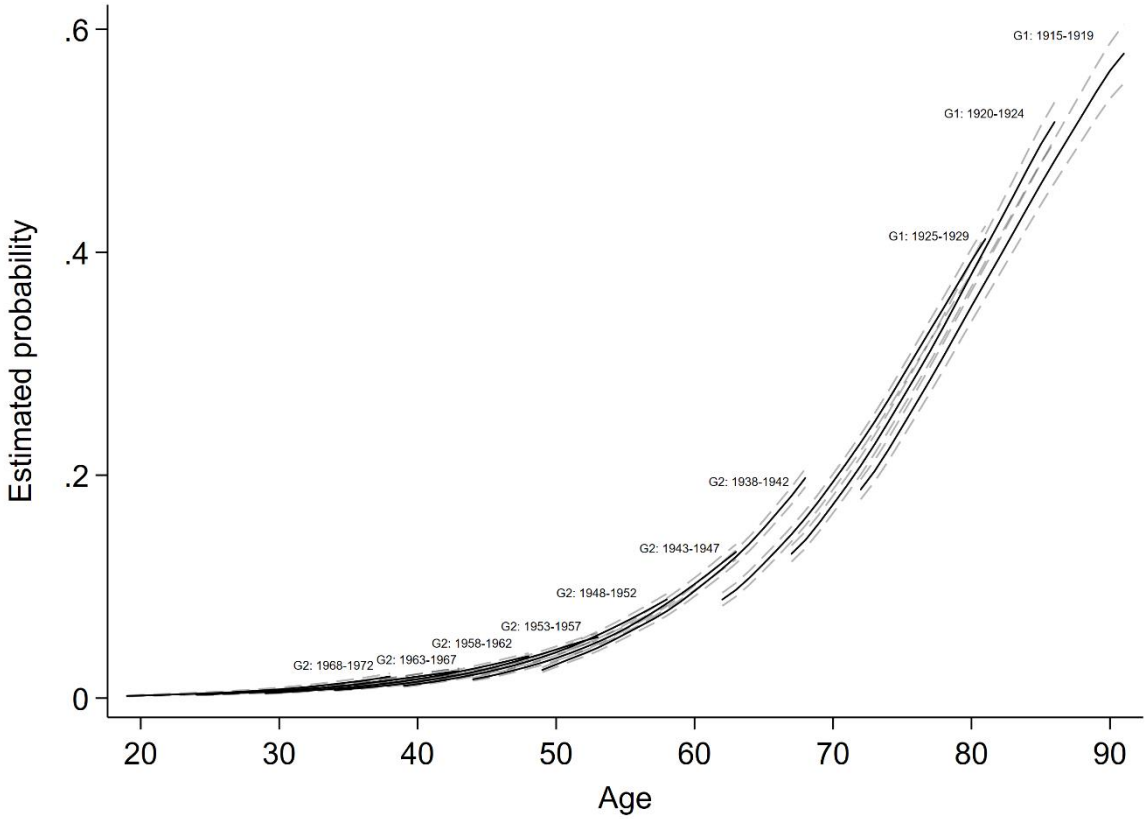


Figure 6.3 Birth-cohort-specific age-course trajectories of hospitalisation with 95% confidence intervals represented by dashed lines.

Table 6.2 Associations of age, year-of-birth with odds of hospitalisation, including gender modification effects – results from the multilevel logit models.

Exposure	Cohort differences	Cohort differences + gender inequalities
Fixed effects		
Intercept	0.04 (0.03, 0.04)	0.04 (0.04, 0.04)
Age	1.14 (1.14, 1.15)	1.14 (1.14, 1.15)
Year-of-birth (YoB)	1.04 (1.04, 1.05)	1.04 (1.03, 1.04)
Age*YoB	0.9995 (0.9993, 0.9997)	0.9995 (0.9993, 0.9996)
Woman		0.84 (0.79, 0.90)
Woman*YoB		1.01 (1.01, 1.02)
Random effects		
Level 2: individual (intercept)	2.20 (2.03, 2.36)	2.50 (2.36, 2.64)
Level 3: family (intercept)	0.30 (0.23, 0.40)	0.02 (0.01, 0.02)
Model fit		
DIC	56988.25	56948.60
Observations	103,262	103,262

6.2.3 Socioeconomic inequalities in the rate of hospitalisation

Those born to parents with medium and low SEP had respectively 13% and 20% higher odds of experiencing hospitalisation during the observation period—when age, year-of-birth and gender were accounted for. I found no evidence for a differential relative socioeconomic gap in hospitalisation across birth-cohorts, age or gender (see Table 6.3)—indicating similar age slopes across those variables. However, the absolute SEP differences in hospitalisation did increase across age—with rising overall prevalence (Figure 6.4). For instance, at age 40 those with low SEP had 1.6% probability of hospitalisation compared with 2.3% for high SEP, at age 60 this difference increased from 9.9% to 11.1% and at age 80 from 32.2% to 37.0%.

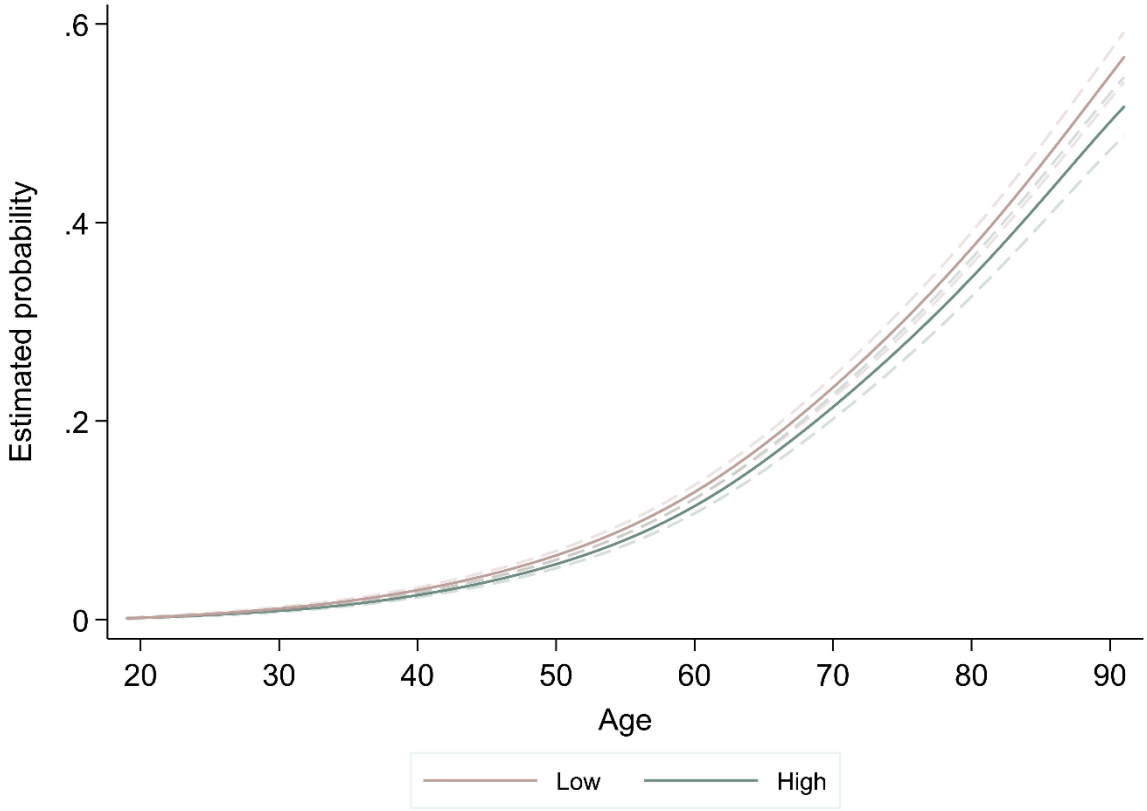


Figure 6.4 Year-of-birth adjusted age trajectories of hospitalisation stratified by high vs low SEP.

Table 6.3 Socioeconomic inequalities in hospitalisation, including cohort, age and gender effects – results from the multilevel logit models.

Exposure	Socioeconomic inequalities	Socioeconomic inequalities + cohort effects	Socioeconomic inequalities + age effects	Socioeconomic inequalities + gender effects
Fixed effects				
Intercept	0.04 (0.03, 0.04)	0.04 (0.03, 0.04)	0.04 (0.03, 0.04)	0.04 (0.03, 0.04)
Age	1.14 (1.13, 1.15)	1.14 (1.14, 1.15)	1.14 (1.14, 1.15)	1.14 (1.14, 1.15)
Year-of-birth (YoB)	1.04 (1.04, 1.05)	1.04 (1.04, 1.05)	1.04 (1.04, 1.05)	1.04 (1.04, 1.05)
Age*YoB	0.9995 (0.9994, 0.9997)	0.9995 (0.9993, 0.9997)	0.9995 (0.9993, 0.9997)	0.9995 (0.9993, 0.9997)
Woman	0.77 (0.72, 0.82)	0.77 (0.72, 0.82)	0.77 (0.72, 0.82)	0.82 (0.73, 0.92)
Woman*YoB				
Parental SEP (high – reference)				
Medium	1.14 (1.05, 1.24)	1.12 (1.01, 1.23)	1.13 (1.01, 1.25)	1.24 (1.09, 1.43)
Low	1.21 (1.12, 1.31)	1.21 (1.10, 1.32)	1.23 (1.13, 1.35)	1.25 (1.12, 1.39)
Medium*YoB		1.003 (0.996, 1.010)		
Low*YoB		1.005 (0.999, 1.012)		
Medium*age			1.00 (0.99, 1.01)	
Low*age			1.00 (0.99, 1.00)	
Medium*woman				0.93 (0.79, 1.08)
Low*woman				0.82 (0.68, 0.99)
Random effects				
Level 2: individual (intercept)	2.47 (2.31, 2.63)	2.32 (2.10, 2.52)	2.14 (1.93, 2.34)	2.13 (1.97, 2.30)
Level 3: family (intercept)	0.0003 (0.0001, 0.0004)	0.14 (0.07, 0.26)	0.35 (0.27, 0.43)	0.35 (0.26, 0.45)
Model fit				
DIC	56508.20	56494.46	56450.29	56469.48
Observations	102,571	102,571	102,571	102,571

6.2.4 Supplemental analyses

Socioeconomic inequalities in hospitalisation were also found due to parental education and parental income for generation 2 (see Appendix 4E for more details).

Children (G2) had higher odds of repeated hospitalisation and hospitalisation due to depression, COPD, cancer, hypertension, migraine and rheumatoid arthritis (see Appendix 4F for the estimates) than their parents. Whereas they experienced lower odds of asthma, diabetes and ischemic heart disease. No inter-generation differences were found in dementia, cerebrovascular disease, chronic kidney disease and heart failure.

Overall, there was a trend of greater inequality in most conditions among children (G2) compared to their parents (G1). However, generation*SEP interaction did not reach significance ($p<0.05$) for any of the individual conditions apart from diabetes ($p=0.03$), possibly due to overall low numbers of hospitalisation. Likewise, confidence intervals around the estimates of social inequality tended to overlap across generations as they were relatively wide (see Appendix 4G). Most substantial relative inter-generation differences in SEP inequality were found for: depression (G1: OR=0.86, 95%CI 0.56 to 1.31 vs G2: OR=1.25, 95%CI 0.98 to 1.58), asthma (G1: OR=1.16, 95%CI 0.72 to 1.73 vs G2: OR=1.41, 95%CI 0.96 to 2.08), cerebrovascular disease (G1: OR=0.98, 95%CI 0.81 to 1.19 vs G2: OR=1.39, 95%CI 1.02 to 1.90), diabetes (G1: OR=1.03, 95%CI 0.76 to 1.39 vs G2: OR=1.74, 95%CI 1.28 to 2.38) (see Appendix 4G).

6.3 Discussion

6.3.1 Summary of findings

Using the first (born 1915-1929) and second-generation (1938-1972) of the Uppsala Birth Cohort Multigenerational Study, I examined cohort differences in age trajectories of hospitalisation due to major non-communicable conditions and if these varied by parental socioeconomic position. In addition, I explored gender effects in cohort and socioeconomic differences in hospitalisation. As hypothesised, younger birth cohorts had a higher prevalence of hospitalisation at overlapping ages—with inter-cohort differences increasing with age in absolute terms. Consistent with the hypothesis, those born to parents with medium and low socioeconomic position had higher odds of experiencing hospitalisation during the observation period—with the socioeconomic gradient remaining stable across cohorts. I found no evidence for varying socioeconomic differences in hospitalisation across age or gender in relative terms. However, due to the overall increase in the probability of hospitalisation with age—the absolute difference between those in low and high SEP increased as participants got older.

6.3.2 Comparison with other studies

In line with previous findings from Sweden as well as other high-income countries, I found an increasing burden of chronic morbidity between 1989 and 2008, when ageing was accounted for (56, 351, 352, 355, 359, 361, 362). The findings of this chapter are consistent with a study conducted in the Netherlands, investigating trends in primary care visits due to major chronic conditions, which showed an increase in visits by nearly 6% between 2004 and 2011 (392).

As in this study, the evidence consistently shows that those in lower socioeconomic position—defined according to social class, education or income—had worse health (355-359) and were more likely to be admitted to a hospitable across most high-income countries (368, 374-376). As found by previous studies as well as this research, the social gradient has remained stable, in relative terms, from the 1990s to 2000s in Sweden (356-358, 365). This study is the first one to compare trajectories in hospitalisation due to major non-communicable conditions across such a long-range of birth-cohorts (1915-1929; 1938-1972) and age (19-91), which helps to disentangle age and cohort effects in this outcome. This contributes to the literature by showing that inter-cohort differences as well as a socioeconomic gradient in health can be already observed in early adulthood and started to emerge among cohorts born as early as the beginning of the 20th century. Previous longitudinal evidence in Sweden was limited to older population (56, 355, 359), whereas most life course studies come from the UK—showing higher rates of frailty and risk factors for morbidity, such as BMI and blood pressure, in younger cohorts (40, 366, 367).

6.3.3 Interpretation

An increase in hospitalisation across younger birth cohorts may be due to a rising burden of non-communicable morbidity. If the burden of non-communicable morbidity among people of the same age but born at later time, is increasing—this leads to extending their lifespan with morbidity. This provides support for the scenario known as expansion of morbidity (393). However, the relationship between morbidity and hospitalisation is complex and potential reasons for an increase in hospitalisation may be related to both changes in the prevalence of morbidity and healthcare utilisation over time.

If increasing hospitalisation is driven by rising morbidity, there are several complementary explanations for worsening health in younger birth-cohorts. The trends in non-communicable conditions could be explained by changes over time in risk factors. However, these trends are inconsistent, with certain risk factors decreasing since the 1990s—e.g. hypertension (394), smoking (395), or alcohol consumption (396) and others increasing—e.g. fat intake (397), cholesterol (397) and obesity (397). Another hypothesis is that more effective disease management appears to have led to improved survival with previously fatal diseases (106, 122, 398). Hence, declining mortality due to major non-communicable conditions associated with ageing, such as cancer or coronary heart disease—results in a greater number of people and extended lifespan with those disorders (399, 400). Improved management of non-communicable conditions may have also led to the conditions being less disabling over time. For instance, one study found an increase in years free from disability and mobility problems from the early 1990s until the early 2010s in both elderly men and women in Sweden (364).

It is also likely that increases in diagnosed and treated conditions are due to more accessible healthcare services, combined with greater health awareness and propensity to seek health—which are associated with rising education over time (397). However, a greater inclination to seek help or report health problems still indicate a growing demand on health services and should be considered as a public health problem as opposed to an artefact in the data on secular trends.

The rising trend in hospitalisation may not be universal across all major non-communicable conditions. Age-cohort investigation of trends in each health condition was not feasible in this study due to hospitalisation being a relatively rare outcome.

However, I compared the prevalence of hospitalisation between parents (born in 1915-1929) and their children (1938-1972) accounting for age differences. I found that the younger generation had a greater prevalence of hospitalisation due to such conditions as depression, COPD, hypertension and migraine. These conditions are typically managed in ambulatory care and hospitalisation is considered to be potentially avoidable (401). On the contrary, hospitalisation due to asthma and diabetes did decrease over time indicating an improvement in patient management and access to primary care, despite some evidence for their rising prevalence (402, 403).

I found a greater prevalence of hospitalisation due to non-communicable conditions among those born to parents of a disadvantaged social class. This may be due to overall worse health among those in disadvantaged social circumstances (355-359). It is also likely that individuals with a lower social class are at a higher risk of clustering and accumulating risk factors for morbidity—such as poor diet, smoking, physical inactivity or engaging in risky behaviours (404). However, a higher prevalence of morbidity does not need to directly translate into higher demands for healthcare services (405). Factors such as healthcare-seeking, communication skills, health literacy and practices may all play an important role in inequalities in hospitalisation. It would be beneficial to further understand to what extent these contextual factors and an actual health need explain higher rates of hospitalisation in more disadvantaged groups.

I found that no progress was made in reducing the socioeconomic inequalities in hospitalisation due to non-communicable conditions from 1989 to 2008. This is despite Sweden having been particularly determined to reduce the health gap

between rich and poor, making it a central objective of public health and social policy agendas since the 1980s (360). However, this study was focused on childhood SEP, not considering adult SEP. It is feasible that some participants may have experienced upward or downward mobility in their adulthood, hence overestimating or underestimating the inequality in hospitalisation. Social policies in Sweden are considered to be particularly protective for those suffering poor health, as individuals do not easily lose their job when facing morbidity (406). This, at least, should be effective in preventing downward mobility. Overall, generous social benefits, for instance, due to unemployment or childcare may be supportive of upwards mobility (407-409)—particularly among those in lower socioeconomic position—potentially leading to less health inequality. In addition, it appears that the association in Sweden between upward mobility and good health is stronger than between downward mobility and poor health (410, 411). For instance, men's all-cause mortality—as well as due to physical diseases, health related behaviour and suicide—was found to be inversely linked with upward mobility but rarely with downward mobility (410). If this was also true for hospitalisation, one would expect a diminished health gap when considering adult SEP indicators. This is something that future research could explore, however deriving a consistent adult SEP variable was not feasible in the dataset used in this study as the age of participants varied from age 19 to 91.

Furthermore, there was an indication of greater inequality among a younger generation compared to their parents in several conditions, due to which hospitalisation could be avoided. This includes depression, asthma, diabetes or heart failure. It is important to understand the reasons for this increase in inequity in healthcare utilisation to facilitate devising more effective policies and interventions.

Stronger association between childhood SEP and hospitalisation in the second generation compared with the first may also be explained, to some extent, by the fact that SEP and hospitalisation were measured closer in time for the second generation. For instance, previous research has shown that the most recently measured SEP—with the smallest time gap before the incidence of morbidity or mortality—tends to have the strongest association with these outcomes (412).

6.3.4 Strengths and limitations

The main strength of the current study is the use of register databases, which enable analysis with virtually no missing data for other reasons than emigration or death. In addition, the data are free from response biases, such as recall or social desirability bias, which are present in self-reported outcomes. Moreover, the registries allow for setting up the data as an accelerated longitudinal study—which is a gold standard for studying age and cohort effects (see section 1.2.2). Nonetheless, there is no guarantee that cohort effects are not partially attributable to period effects. Period effects could be manifested by an overall trend in the population to have a greater propensity to report health problems, for instance, due to rising health awareness and expectations. This, however, would still translate into higher rates of hospitalisation in younger birth cohorts at the same age—captured by age-cohort analysis (see section 1.2.2). Another limitation of the study is that the data were available only until 2008, hence studying the trends during the last decade was not possible.

6.3.5 Conclusion

Younger birth cohorts had a higher prevalence of hospitalisation at overlapping ages, with inter-cohort differences increasing with age in absolute terms due to overall

rising probability of hospitalisation. Those born to parents with medium and low socioeconomic position had higher odds of experiencing hospitalisation during the observation period—with no evidence of reductions in the socioeconomic gradient across cohorts. The findings emphasise the need for policies and interventions reducing morbidity burden due to key non-communicable conditions, particularly among those of low socioeconomic position.

Chapter 7: Discussion

In this thesis, I systematically reviewed the evidence on secular trends in key chronic conditions, disability and self-assessed general health among adults in the United Kingdom and conducted three empirical studies using the British birth cohorts and the Uppsala Birth Cohort Multigenerational Study. In this section, I first summarise the main findings of each study (Chapters 2, 4-6). Subsequently, I provide a critical evaluation of methodological issues. This is followed by recommendations for future research, policy and practice implications as well as conclusion.

Chapter 2 comprises a systematic review of evidence on secular trends in main chronic conditions (accounted for at least 1% of disability-adjusted years of life), disability and self-assessed general health among adults in the United Kingdom between 1946 and 2017, as reported in primary/secondary care databases and population-based surveys. The focus of the review was on (1) trends in age-standardised or age-specific prevalence of major non-communicable diseases, disability and self-reported general health; (2) trends in health expectancy. Studying trends in a wide range of morbidity outcomes was in contrast with previous systematic reviews, which investigated trends focused on only disability-related measures (34, 35).

There was no evidence on improvement in the age-standardised or age-specific prevalence of any of the studied major chronic conditions over the last few decades, apart from Alzheimer's disease. Both increasing or stable prevalence rates with simultaneous rising life expectancy support the expansion of morbidity theory, meaning that people are expected to spend a greater number of years with chronic

condition(s). The evidence on trends in disability, expressed as prevalence or health expectancy, was more inconsistent, with slight support for the expansion of morbidity among those aged 65 or over.

As shown by the systematic review, most research on secular trends in morbidity is focused on the older population or across entire age-standardised populations. Hence, it was not possible to determine the age at which morbidity differences start to emerge across different birth cohorts. This emphasised the need for more research using longitudinal data across multiple birth cohorts, which allows for comparing trajectories in health outcomes at overlapping ages across groups of individuals born at different time.

Chapter 4 includes analyses of prospective longitudinal birth cohort studies, with the main objectives: (1) to estimate the prevalence of multimorbidity in mid-life (age 46-48) in the British cohort born in 1970 (BCS70); (2) to examine the association between early-life characteristics and mid-life multimorbidity in BCS70; (3) to compare the estimates of multimorbidity, as well as its components and the magnitude of associations across two cohorts, born 12-years apart (1958 vs 1970): the NCDS and the BCS70. This study serves as the first investigation of trends in multimorbidity, with likely nationally representative (see Chapter 3) samples of the mid-life population in the UK, contributing to the limited evidence (256-258).

The prevalence of multimorbidity was alarmingly high in mid-life (33.8% at age 46-48) in BCS70, with those in lower social classes at birth being disproportionally affected. The prevalence also appeared to increase over time—among those born in 1970 compared with 1958. Multiple early-life exposures including social class at birth, birthweight, BMI (at age 10), cognitive ability (at age 10), internalising and

externalising problems (at age 16) were associated with mid-life multimorbidity (at age 46-48); with the association between BMI as well as externalising problems and multimorbidity being particularly strong. I did not find any changes over time in the magnitude of the association between early-life exposures and multimorbidity in relative terms, indicating that other factors, perhaps in early adulthood account for the observed increase in multimorbidity. However, due to overall higher prevalence of multimorbidity in the BCS70, the absolute cohort-differences somewhat increased along with values of each exposure indicating higher vulnerability (e.g. higher number of internalising problems or lower cognitive score). This additive interaction effect was particularly prominent for BMI, whereas for other exposures, the absolute differences were rather modest. However, they still may amount to an important public health problem if the cross-cohort difference turns out to be a trend across successive birth cohorts.

Previous studies showed overall worse health outcomes in BCS70 compared with NCDS, including psychological distress, self-reported health, long-standing illness (39, 215, 245). My research contributed to these findings by showing a higher prevalence in other outcomes, such as objectively measured diabetes and obesity as well as self-reported asthma/bronchitis and epilepsy. Differences were not found in lifetime prevalence of any cancer and objectively measured hypertension, which also points towards expansion of morbidity.

Chapter 5 reports on the study that investigated the age trajectory of psychological distress over time in three British birth cohorts (1946 - NSHD, 1958 - NCDS and 1970 – BCS70), including—to the best of my knowledge—the longest continuous follow up of this outcome within the same individuals from age 36 to 69. I also examined cohort

differences in mental health across three representative British birth cohorts: the 1946 (NSHD), 1958 (NCDS) and 1970 (BCS70).

The combination of these three studies allowed for studying age and cohort effects in mental health among 28,362 participants, aged 23-69, over a period of 1981-2016. A comparison across cohorts allowed me to test cohort differences, enabled greater generalisation of the findings across post-WW2 generations and helped to transcend period effects. This study expanded on the previous analysis of age and cohort effects of NCDS and BCS70 (38, 291), by including additional waves of data (age 50 in NCDS and age 34 and 46 in BCS70) as well as by including NSHD—the oldest and longest-running birth cohort in the UK.

Across three post-war British cohorts, there was a clear increase in mental health problems between early-adulthood and mid-life. This increase appeared to be steeper in the NCDS and BCS70 than NSHD. In the NSHD, where additional data sweeps were available, mental health improved into early old age. Participants of both NCDS and BCS70 also experienced elevated levels of mental health problems in their mid-20s. Progressively younger birth cohorts had worse mental health across adulthood, providing evidence for the theory of expansion of morbidity.

Chapter 6 encompasses a prospective longitudinal study, using two generations of the Uppsala Birth Cohort Multigenerational Study conducted in Sweden, which aimed to examine cohort differences in age trajectories of hospitalisation due to key non-communicable conditions and if these varied by paternal socioeconomic position. Sweden is known to have high quality administrative data allowing for studying trends in hospitalisation as a quasi-objective health indicator.

The study found that successively younger birth cohorts had a higher prevalence of hospitalisation at overlapping ages, with inter-cohort differences emerging from early-adulthood and increasing with age in absolute terms. For instance, at age 40 the predicted probability of hospitalisation increased across birth-cohorts—from 1.2% (born in 1948-52) to 2.0% (born in 1963-67), whereas at age 50 it was 3.0% for those born in 1938-42 compared with 4.6% among participants born in 1953-57.

Those with medium and low parental socioeconomic position (vs high) had 13% and 20% higher odds of experiencing hospitalisation during the observation period—when age, year-of-birth and gender were accounted for. Hence, no progress was made in reducing the socioeconomic inequalities across cohorts born between 1915 and 1972.

7.1 Evaluation of data and methods

In this section, I provide an overview of some challenges related to the data and methods used in the thesis and discuss resulting limitations. More specific limitations of each individual study were described in corresponding chapters.

7.1.1 Generalisability

All four data sources—NSHD, NCDS, BCS70 and Multigen UBCoS—are considered to be broadly representative for the population of the same age as participants of the studies (149, 153, 155, 157, 158). The British birth cohorts included everyone who was born within one week in a given year (1946, 1958, 1970), hence they were deemed to be representative for those birth cohorts at the time of recruitment (149, 153, 155). The UBCoS comes from the Uppsala region in Sweden. There is considerably little published work on the external validity of the UBCoS in the context of the general population, particularly among the younger generations. Generation 1 within the UBCoS has been found to be nationally representative of Sweden in terms of infant mortality and fertility (160), with a higher proportion of births to single mothers (161) and infants from urban areas (162).

The main limitation for generalisability of all four studies for today's population is that they do not account for migration that has taken place over time in the UK (349) or Sweden (413). Hence, their participants are nearly exclusively white. The empirical studies in this thesis were largely focused on the cohort effects in morbidity, which may differ compared with those at play among the migrant population, for instance, due to healthy migrant effect (350). However, the evidence from this thesis is discussed in the context of repeated cross-sectional studies, which overcome this limitation as they provide snapshots of the entire population over time.

Another potential limitation is the lack of permanently institutionalised population in the sample of most reviewed studies (Chapter 2) as well as in the samples used in the empirical studies (Chapters 4-6). The changes in the prevalence of institutionalisation over time may lead to under-/overestimation of prevalence of morbidity. A few studies that took that into account did not, however, find any difference in estimates—due to the overall low proportion of the institutionalised population (<5%) (126, 130). The potential bias is expected to be particularly low in Chapters 4 and 5—as participants of these studies were young compared with the typically institutionalised population (414).

Finally, non-response and attrition are a threat to the representativeness of the British birth cohorts. As shown previously (415) and found in the thesis (Chapters 4 and 5), processes leading to missing data are highly selective—with those in poorer health and lower socioeconomic position being more likely to have missing information. However, as explained in the following section, I took advantage of statistical methods to model missing data, thus increasing generalisability of findings.

7.1.2 Missing data

As discussed in Chapters 4 and 5: the NSHD, NCDS and BCS70 had missing data due to attrition and non-response. This issue was particularly problematic for BCS70, partially due to a large loss of sample at age 16 when fieldwork was interrupted by teachers' strike (416). Using composite variables, such as multimorbidity, which requires complete data on multiple variables, further increases the amount of missing information. Statistical techniques employed in Chapters 4-6, such as maximum likelihood estimation and multiple imputation were used to maximise power and reduce potential bias. Nonetheless, these techniques rely on certain assumptions,

which are discussed in more detail below. The study in Chapter 6 had very little missing information, hence the discussion of missing data is focused on Chapters 4 and 5.

The first assumption is that the data are Missing-at-Random (MAR), which implies that systematic differences between the missing values and the observed values can be explained by observed data (247). This assumption is largely untestable, hence there is no guarantee that the data are not, in fact, missing Not-at-Random, potentially leading to biased estimates. MAR is a particularly strong assumption in health-related research, as those participants with missing data do tend to be of poorer health prior to attrition or non-response (see sections 4.2.3.1 and 5.2.4). For instance, if the most disadvantaged and of poor health participants tend to be at greater risk of dropping out, this would lead to underestimation of morbidity. This can be seen in Chapter 4 when complete cases are used to estimate multimorbidity. The strength of the British birth cohorts is that they include rich information on health and socioeconomic variables, whose inclusion in the imputation model increases the plausibility of the MAR assumption. These variables may be used as auxiliary to the main analysis, allowing for predicting missing data with greater accuracy, which leads to minimising non-random variation in predicted values (347).

The second key assumption is that the imputation models are correctly specified (281). Simulation studies show that the estimates can be unbiased even with up to 90% missing data if this assumption is met and data are MAR (281). In line with the recommendations, the imputation models in this thesis included all of the variables from the analyses, ensuring that the relationship between the variables of interest

was preserved (246). Additionally, the models were enriched with the aforementioned auxiliary variables.

The missing data were imputed using multiple imputation by chained equations (MICE), due to non-monotone pattern of missing values and due to its ability to accommodate various types of variables in the imputation model, including continuous and categorical ones. This approach uses a series of univariate conditional imputation models to impute missing data (417). Continuous variables were imputed using predictive mean matching and categorical ones using logistic regressions. Predictive mean matching approach provides robust estimates if the normality assumption is in question (418), as for instance with mental health outcomes that tend to be positively skewed (419), or when associations are non-linear (418). In Chapter 4, similar results were obtained under varying missing data scenarios and in Chapter 5 when using multiple imputation and full information maximum likelihood, hence increasing the confidence in the robustness of the estimates.

7.1.3 Measurement error in health

A variety of morbidity outcomes were used in this thesis, which may have different implications on understanding secular trends. Trends based on self-reported measures were examined in Chapters 2 and 4-6. Increases in this type of outcomes may likely be due to changing definition of health, which has become increasingly oriented towards wellbeing rather than the mere absence of disease (420). Hence, younger cohorts may have higher expectations about their health (108). In addition, rising education might have translated into better health awareness, leading to a greater willingness to report health problems (421). This may be particularly true for

mental health outcomes, as there has been great effort to reduce mental health stigma, yet there is little evidence if stigma has indeed lessened (422).

It is also likely that more effective screening has contributed to the rising rates of conditions. For instance, there have been some concerns that asthma may be currently overdiagnosed in primary care, after years of underdiagnosis (139, 423). Also, the quality of recording tends to improve over time, particularly after adopting new computer systems, which may lead to higher estimates (140). Moreover, rising rates of morbidity may be partially caused by programmes incentivising accurate maintenance of registers of patients with diseases such as asthma or diabetes (e.g. the New General Medical Services Contract (141)). However, studies that limited their analysis to services with highly accurate data—as a sensitivity check—tended to find similar trends—for instance in diabetes (115).

The morbidity outcome used in Chapter 6 may to some extent be free from the above biases. As it is a proxy of more severe morbidity, one would expect that it would be less affected by screening programmes or greater willingness to report health problems, which may be expected to be more relevant for less severe and more common conditions such as asthma or diabetes. Also, as the analysis in Chapter 6 was limited to years with high-quality data (1989-2008), improvements in data collection over time should have little impact on the trends. However, the relationship between morbidity and hospitalisation is complex and potential reasons for an increase in hospitalisation may be related to both changes in the prevalence of morbidity and healthcare utilisation over time. Observer-measured morbidity outcomes were also used in Chapter 4: BMI, blood pressure and HbA1c. These variables are not affected by self-report biases and may provide “true” estimate of

morbidity and its secular trends—as long as they are measured in a consistent manner over time, as it was the case in Chapter 4.

There is little evidence that the described challenges related to the measurement of health indeed affect secular trends. Moreover, most health problems, particularly related to mental health are considered to be underdiagnosed (424). As shown in Chapter 4, this also may be true for diabetes and hypertension as a large proportion of untreated individuals remains. Hence, the increase in morbidity over time, even if partially driven by greater willingness to report health problems, may just reflect diminishing underestimation of health problems over time—hence representing the morbidity burden with increasing accuracy. Furthermore, the evidence suggests that at least interpretation of questions related to mental health has not been affected by self-report biases over time (38, 310). As long as rising trends in self-reported outcomes reflect increasing demands on public services, they should be treated as a real public health problem—regardless if this is due to a greater propensity to report health problems, as opposed to “true” (latent) underlying health.

7.1.4 Age-period-cohort effects

Most studies included in the systematic review (Chapter 2) investigated age-adjusted (mainly by standardisation) or age-specific period effects in morbidity. The vast majority of included publications used routinely collected data, or repeated cross-sectional studies. The evidence based on longitudinal data was limited to a few studies using the ELSA and BHPS (35, 95, 96, 125). This provided motivation for Chapters 4-6, in which I combined longitudinal data across multiple birth cohorts in a fashion of accelerated longitudinal design—a gold standard in studying age-period-

cohort effects. The advantages of different study designs were discussed in more detail in section 1.2.2.

In this thesis, I examined age-specific cohort effects in the prevalence of multimorbidity and in the magnitude of the association between early-life characteristics and multimorbidity (Chapter 4). Cohort effects were studied by a simple regression analysis with year-of-birth (or cohort membership) treated as the exposure and multimorbidity as the outcome. The advantage of this analysis is that it is unfeasible that there are any confounders of this association, that is, anything which may simultaneously cause year-of-birth and multimorbidity. The cohort effects in the association between early-life characteristics and multimorbidity were studied by including an interaction with year-of-birth as a modifier of the association.

In Chapter 5, I studied age and cohort effects in mental health, by stratifying age trajectories of the outcome across birth cohorts. As explained in section 1.2.2, this allowed to improve the generalisability of the findings. For instance, I found that mental health universally worsened between early-adulthood and mid-life. In order to examine if these trajectories differed across birth cohorts, I included age-by-year-of-birth interaction term. This analysis helped to examine cohort effects occurring at different ages—which further revealed that mental health problems increased to a greater extent between early and mid-adulthood in NCDS/BCS70 compared with NSHD. In addition, I examined overall differences in mental health across birth cohorts with age-adjusted multilevel regressions, where year-of-birth was treated as the exposure and mental health as the outcome. Overall higher levels of mental health problems were found in successively younger birth cohorts, when age-differences in birth cohorts were accounted for.

Period effects were not formally tested in this analysis, however, their potential implications were discussed. I used a simple strategy to facilitate this discussion, where cohort-stratified trajectories were plotted with age being replaced by calendar years on the X-axis (Figure 5.5 in section 5.3.3). As the increase in mental health morbidity from early-adulthood to mid-life was observed universally across all three Birth cohorts—occurring at different calendar years—it can be considered an age-effect. I used a multilevel framework with measurement occasions (age) treated as clustered within individuals throughout the study. This allows for accounting for the interdependence of the measurement points due to being observed within the same individuals, hence providing more accurate estimates of standard error (319).

In Chapter 6, I used a similar approach—where age and cohort effects in hospitalisation were modelled using a multilevel framework. However, the data had three hierarchical levels to account for: clustering of measurement points (level 1) within individuals (level 2), who in turn, were clustered within families (level 3; as the data included parents and their children). The data were set up in a form of accelerated longitudinal study: with 1915-1929 (parents) and 1938-1972 (children) birth cohorts, observed at 5-year-interval periods (1989-1993, 1994-1998, 1999-2003, 2004-2008). In such a set-up of registry-based data, we can observe cohort-specific age trajectories of hospitalisation over overlapping 20-year study period. In addition, I investigated age and cohort effects in inequality in hospitalisation, defined according to the father's social class at birth. There was no evidence for a differential relative socioeconomic gap in hospitalisation across birth cohorts or age. One limitation of the data is that by pooling age (and birth cohorts) groups within 5-year intervals we assume a uniform effect across those ages (and birth cohorts). However, this pragmatic approach had to be implemented due to the sparsity of the data.

Period effects were not explicitly tested in this analysis and there is no guarantee that cohort effects are not partially attributable to period effects. Period effects could be manifested by a greater propensity in the population to report health problems, for instance, due to rising health awareness and expectations. This, however, would still translate into higher rates of hospitalisation in younger cohorts at the same age—captured by age-cohort analysis.

7.2 Recommendations for future research

The need to further investigate secular trends

Population ageing leads to rising societal costs and demands on healthcare. In order to better anticipate these demands and allocate resources more effectively, evidence is needed to understand the mechanisms that underlie secular trends in various health outcomes. The most poorly understood trends are in disability, as the research is highly inconsistent and limited to the older population (see Chapter 2). Disability can occur at any time in life and research on disability at all ages is needed (143). For instance, 44 million people aged 15-64 (14.0 % of that age group) reported a basic activity difficulty in 2011 among the EU-28 countries (143). I was unable to investigate trends in disability across the British birth cohorts, due to a lack of comparable measures. However, consistent measures exist within other datasets, such as the English Longitudinal Study of Ageing (ELSA) or the Understanding Society, which, allows for studying trends in the younger population. In addition, further research would benefit from studying trends in cause-specific disability leading to more precise practice and policy implications.

The evidence is lacking in trends of risk factors and morbidity outcomes in early-adulthood. These trends can be better understood by comparing more recent birth cohorts, including the Millennium Cohort Study (born in 2000-01), the Next Steps (born in 1989-90) or the Avon Longitudinal Study of Parents and Children (born 1991-92). These studies have been increasingly used for cross-cohorts comparisons, for instance, to investigate trends in mental health (201), obesity (37) or various negative health behaviours (425-427).

Using registries allows for studying trends in the onset of disease, which would further help to understand whether members of younger birth cohorts are more likely to develop specific morbid conditions at an earlier age. In Sweden or other Scandinavian countries, registry data have nationwide coverage, they are of particularly high quality and are available over an extensive period of time (from 1980s for most of the outcomes) (428). Hence, these datasets can be used in complementary manner to the population health surveys that are particularly prominent in the UK—as this thesis aimed to do.

In addition, secular trends in morbidity across various segments of population should be studied more extensively—for instance depending on geographic area, urbanity or ethnic group. This was not the focus of this thesis, however it can be done with the British birth cohorts, which include information on the aforementioned variables. This would help to recognise if there are any groups at increasingly disproportional risk of morbidity, in comparison with the general population and if targeted policies are needed to address the specific needs of these populations.

The need to explain secular trends

An important next step in research on population health change is to explain secular trends in morbidity, in the context of declining mortality. As it was observed in Chapters 2, 4 and 5, there appears to be the greatest increase in types of non-communicable morbidity, which can be relatively well-managed and do not directly lead to mortality. For instance, prevalence of asthma, diabetes, depression is on the rise. Whereas diseases that are of much higher risk for mortality appear to be stable (e.g. cancer, hypertension) or declining (e.g. Alzheimer's disease). Hence, one could hypothesise that risk factors that have stronger links with morbidity rather mortality

may be increasing in prevalence or they may become gradually more strongly linked with morbidity. For instance, in Chapter 4 we saw that those born in 1970 experienced marginally more mental health problems in their youth and on average lower birthweight—both linked with a range of adult morbidities. Furthermore, although BMI was comparable across both birth cohorts, there was some evidence that the link between BMI and multimorbidity has slightly strengthened over time (73). Likewise, emotional problems in childhood appear to be more strongly associated with future mental health problems (201). Similar studies could be conducted using mortality as an outcome, for instance by combining multiple British birth cohorts, which would elucidate whether there any changes over time in the magnitude of association between important risk factors for mortality (e.g. hypertension) and mortality. As in Chapter 4, this could be done by using year-of-birth (or cohort membership) as a moderator of the association between a given risk factor and mortality.Another approach to explaining secular trends in morbidity, is by studying mediating mechanisms linking year-of-birth and morbidity. Such factors may include changes across birth cohorts in education, health behaviours, socioeconomic circumstances (e.g. see section 5.4.3 for discussion of these factors in the context of mental health). Such analysis can be conducted combining the British birth cohorts used in this study or taking advantage of other previously mentioned studies, including the ELSA or Understanding Society. Most studies tried to explain those trends by adjusting for potential mediators in a regression analysis, including them alongside confounders as controls in the model, without providing explicit estimates of the effect that they explain (289, 297). Another disadvantage of these studies is lack of consideration of potential bias due to intermediate confounder or mediator-outcome confounding (218). For instance, conduct problems measured in early-life

may mediate the association between year-of-birth and a range of morbidity outcomes whilst confounding the relationship between adult socioeconomic status and those outcomes. Future research would benefit from using formal mediation methods, in a causal framework, which would produce estimates of indirect effects of potential mediators and allow for testing potential bias due to mediator-outcome confounder (429). For instance, Ploubidis and colleagues examined the extent to which differences in psychological distress between NCDS and BCS70 can be explained by early-life conditions using mediation analysis with g-computation (38). The study found that higher levels of distress in the BCS70 than in NCDS at age 42 may be partially attributed to breastfeeding and behavioural adjustment at age 16 years (38).

Future research may also examine whether rising secular trends in morbidity are not merely due to differences in reporting. For instance, it has been repeatedly suggested that people are progressively more likely to report health problems due to rising health awareness and expectations (108). This hypothesis can be tested by studying measurement invariance across different birth cohorts, as it has been done for mental health outcomes (310). If indeed, a scalar invariance was found, as it was the case with the mental health measures used in this thesis (Chapter 5), this would indicate that participants who have the same value on the latent construct have equal values on the items used to measure the construct. This would imply that the latent mean of morbidity could be compared across different birth cohorts.

A somewhat indirect test of the aforementioned hypothesis would be to examine the change in the magnitude of associations between morbidity (as an exposure) and other wellbeing-related, societal and economic outcomes. These outcomes could be

selected to reflect overall functioning of an individual in various life domains: disability, life-satisfaction, wellbeing, human capital, absenteeism or social participation to name a few. As in the dynamic equilibrium theory, if a higher level of morbidity was purely due to a greater willingness to report health problems or earlier detection via screening programmes, one would expect a diminishing association between morbidity and other outcomes over time. If morbidity is equally (or more) detrimental for one's functioning, while its prevalence is increasing, this would indicate an increasing burden for the society. Such studies have been conducted, one showing that mental health problems have become more strongly associated with negative social, educational and mental health outcomes over a 40-year period (201). Another study found a marginal reduction of the impact of multimorbidity on primary care visits and functional capacity, but not on hospital admissions and quality of life in ten European countries between 2006-07 and 2015 (430). Similar research could be conducted using the British birth cohorts, where a range of comparable social, economic and wellbeing measures are available.

7.3 Policy and practice implications

This thesis shows that there is a clear increase in the prevalence of non-communicable, mostly chronic conditions (e.g. diabetes, asthma) as well as mental health problems, with some conditions indicating stable prevalence (e.g. cancer, hypertension). Due to increasing life expectancy, only reduced morbidity in younger birth cohorts can be considered as a truly positive scenario. Any other outcome would translate into more years spent with morbidity during the lifetime and an increasing number of individuals experiencing morbidity in the population. Even if the dynamic equilibrium scenario would turn out to be true, the demands on healthcare

system would still increase as a greater number of individuals would require health services. Moreover, younger birth cohorts appear to experience higher rates of multimorbidity already in mid-life and are hospitalised at an increasingly younger age. This supports the assumption that the onset of morbidity happens at an earlier age in younger birth cohorts. If the differences in mid-life morbidity found in Chapter 4, indicate a more long-term cohort effect, rather than being limited to these specific birth cohorts (born around 1958 vs 1970), the current young adults would be expected to have even higher rates of morbidity when they reach mid-life and potentially older age. There is some evidence suggesting that, indeed, we may expect a gradual increase risk in morbidity, for instance due to drastically rising BMI in childhood in more recently born cohorts (e.g. in 2000 compared with 1990) (37).

This emphasises the need for more preventative efforts, rather than merely focusing on treatment. Acting in early-life may be particularly effective for preventing a range of morbidity outcomes in adulthood, as that is when life course trajectories of adverse exposures tend to emerge—predisposing to adult morbidity (181, 182). As higher rates have been observed across a range of morbidity outcomes, it is necessary to act on wider health determinants, likely to generally predispose to poor health. Such determinants were studied in Chapter 4, which found that BMI and externalising problems have particularly strong links with mid-life multimorbidity. Their impact on adult morbidity may be reduced by either lowering prevalence of those characteristics, or by reducing their harmful consequences.

This can be done either by directly acting on those characteristics or on potential mechanisms linking them with future morbidity (as discussed in Chapter 4). For instance, it may be more feasible to devise health interventions and policies aiming at

reducing childhood obesity, rather than its impact on morbidity. These may include educating about and promoting a healthy diet and exercise at schools (431, 432), or higher taxation of sugary products (433), however the evidence on effective interventions is lacking. For mental health problems, a combination of interventions can be implemented—both shifting their distribution and promoting equal opportunities for those predisposed to suffer from poor mental health. Schools may be particularly suitable environment for such interventions, as they already comprise structures for wellbeing promotion and prevention of mental health problems (197, 434). However, the evidence on effective interventions, particularly for externalising problems, is still limited (434).

Externalising problems appear to be linked with unhealthy behaviours (435), possibly leading to an accumulation of risks across the lifespan that are related to a range of morbidity outcomes (55). An effective approach may address modifiable risk factors that mediate the relationship between early-life externalising problems and later health—including alcohol consumption, smoking, sedentary lifestyle and diet (55). Specific recommendations for tackling these problems have been developed. For instance, the National Institute for Health and Care Excellence emphasised the need to recognise problematic consumption of alcohol early and act both at the population level (e.g. by reducing marketing of harmful substances) and the individual level (e.g. cognitive-behavioural skills training) (436).

Childhood adverse socioeconomic circumstances appear to be directly linked to adult morbidity, through sensitive or critical periods and they increase the risk of experiencing multiple risk factors accumulating over the life course (437), leading to a socioeconomic gradient in health (as found in Chapters 4 and 6). People of manual

social class or low education lagged behind more advantaged groups in their improvement in life expectancy and to even a greater extent, in health expectancy—disproportionally extending their time lived with morbidity between the 1990s and 2000s in the UK (128, 129). These inequalities were seen in studies included in Chapter 2—both at the national level (Scotland having worse outcomes than England) and regional level (Northern England having a greater burden of morbidity than Southern England) (119, 122, 123). Regional variability appeared to be larger in mortality than morbidity (398). Overall, this emphasises the need for health policies and interventions targeted at particularly vulnerable groups, in order to close the health gap between rich and poor. In addition, these efforts ought to be more focused on morbidity prevention, where the largest inequalities appear to exist (106, 122, 398). Wide-reaching structural changes, rather than approaches focused on individuals, will likely have a greater impact on improving health of the most vulnerable populations (438). For example, adversities across the life course can be reduced by providing families with young children with affordable quality childcare, investing in neighbourhood safety and social capital, increasing minimum wage (438). Despite the priority of policy-makers in Europe to reduce health inequalities, they have generally widened from the 1980s to the late 2000s (365) and have been persistent in the last decade (439). This emphasises the difficulty in creating effective policies. In Sweden, where the efforts to reduce health gap have been particularly intensive since the 1980s, the inequalities have remained largely stable between the 1990s and late 2000s as shown in Chapter 6 and previous research (365). This is despite wide-ranging policy programmes, which focused on several areas including nurturing social capital, improving conditions at work, stimulating health-promoting life habits and developing a satisfactory infrastructure for health (440). Policymakers

employed specific strategies aimed to address factors such as social cohesion and housing segregation, children's education opportunities and reduction of smoking and alcohol consumption (440), which overall appear to be largely ineffective. A positive aspect of Swedish policies is their focus on employment protection and promotion of participation in the labour market among citizens with chronic illness (440). These policies appeared to be effective in protecting vulnerable individuals from unemployment during the recession of the 1990s (441) and the more recent financial crisis of 2008 (210). One criticism of these policies is that they had a limited evidence-base, largely because such evidence was not available and were mainly founded around consultations with experts (440), which may partially explain their overall modest impact.

Findings of this thesis may also contribute to the discussion about policies surrounding rising retirement age. The common argument for the increase in retirement age is rising life expectancy, leading to ageing of the population and increasing proportion of economically inactive individuals (442). For instance, in 2042, there will be 367 pensioners per 1,000 people of working age, 67 more than in 2016) (442). Hence, in the UK state pension age is increasing from 65 to 66 in 2020 and will reach 67 in 2028 (442). However, as it has been seen in this thesis, rising life expectancy does not necessarily translate into healthier life. The findings of this thesis suggest the opposite, the population health appears to be worsening, with the onset of various non-communicable morbidities potentially having an earlier on-set—for instance in multimorbidity (Chapter 4), mental health problems (Chapter 5) and inpatient hospitalisation (Chapter 6). If younger birth cohorts are of worse health, it is unlikely that they have the capacity to work longer. In addition, there are striking differences between those living in favourable socioeconomic conditions, compared

to those who do not (e.g. Chapter 6). For instance, analysis of healthy working life expectancy indicated a strong north-south divide and it appears that these geographical health gaps may be widening (127, 443, 444). The socioeconomic health gap exists not only in morbidity, but also in mortality. For example, a 65-year-old man in Harrow is expected to live additional 20.9 years, six years more than his equivalent in Glasgow (445).

Hence, seeking to lengthen working life may turn out to be ineffective in the face of the changing labour market. Instead the focus of the policies may be placed on enabling those who want to work and are unable to do so, particularly as around half of workers leave the workforce before the eligible age for pension (445). For instance, it was observed in Chapter 5 that mental health problems appear to peak in mid-life. Mental health has been the leading cause of sickness absence and long-term incapacity (446). Therefore, potential policies and interventions may focus on designing workplaces supportive for mental health, for instance by reducing job strain and increasing job control and on improving working conditions and opportunities for those affected by mental health problems (447). However, there appears to be a gap in recommendations for mid-life mental ill health, for example reflected in the Royal College of General Practitioners Mental Health Toolkit (448). It also implies the need for increased public awareness of mental health in midlife.

7.4 Conclusion

The key finding of this thesis is that we have observed expansion of morbidity in the last four decades in the United Kingdom: due to key chronic conditions (Chapters 2 and 4), including their multimorbid combinations in mid-life (Chapter 4) and mental health outcomes (Chapter 5). Likewise, the expansion of morbidity in hospitalisation

due to major non-communicable conditions was observed in Sweden from the early 1980s to 2000s (Chapter 6). In both countries, expansion of morbidity is not limited to the older populations, as younger birth cohorts appear to be at elevated risk of morbidity already in their mid-life. Early-life characteristics, including social class, birthweight, BMI and cognitive and emotional development (as found in Chapter 4), appear to be associated with a range of morbidity outcomes in adulthood, hence they may serve as foundations for preventative efforts.

Chapter 8: Thesis publications and presentations

Gondek, D., Bann, D., Ning, N., Grundy, E. & Ploubidis, G. B. (2019). Post-war (1946-2017) population health change in the UK: A systematic review. PLoS ONE 14(7):e0218991

Gondek, D., Bann, D., Patalay, P., Goodman, A., Richards, M. & Ploubidis, G. B. (under review). Psychological distress from adolescence to early old age: Evidence from the 1946, 1958 and 1970 British birth cohorts.

Gondek, D., Ploubidis, G. B., Hossin, M. Z., Gao, M., Bann, D. & Koupil, I. (under review). Inequality in hospitalization due to non-communicable diseases in Sweden: age-cohort analysis of the Uppsala Birth Cohort Multigenerational Study.

Gondek, D., Bann, D., Brown, M., Hamer, M., Sullivan, A. & Ploubidis, G. B. (under review). Prevalence and early-life determinants of mid-life multimorbidity: evidence from the 1970 British birth cohort.

Gondek, D. (2018). Post-war (1946-2017) population health change in the UK: A systematic review. Presented at the SLLS International Conference: Qualitative and Quantitative Longitudinal Research on Social Change, Milan, Italy.

Gondek, D. (2018). Psychological distress over the life course: Evidence from the 1946, 1958 and 1970 birth cohorts. Presented at the 60 years of our lives: A scientific conference celebrating the National Child Development Study at 60, London, England.

Appendices

Appendix 1A Trends in incidence of chronic conditions.

Coronary heart disease

There is some evidence that age-specific, adjusted or standardised incidence rates of coronary heart disease, have been decreasing since the mid-1960s (91, 96, 140, 398, 449, 450), particularly due to reduced rates of myocardial infarction (140, 398, 449), thus future declines in prevalence are likely. However, it is unlikely that these reductions in the incidence are large enough to compensate for declining cause-specific mortality (91).

Stroke

The incidence of stroke has been continuously decreasing from the early-1980s, mainly among those aged under 75 (109, 451-455). However, this has coincided with even greater improving survival hence leading to increased prevalence (91).

Colorectal/breast cancer

There was no clear trend in incidence of colorectal cancer between 1970 and 2007 (456-460). The evidence consistently suggested an increase of breast cancer across all ages between 1971 to 2007, with a simultaneous decline in mortality, (459, 461) thus leading to higher prevalence rates (457, 459-464).

Asthma

The incidence was found to decrease between 2001 and 2005 (2001: 6.9, 95%CI 6.8–7.0; 2005: 5.2, 95%CI 5.1 to 5.3 per 1000 patient-years, p<0.001) (122).

Alzheimer's and other dementias

Due to decreasing incidence rates, declines in dementia prevalence are projected to continue (125). Nonetheless, there is some evidence from a large study based on data from a public register in Wales that the incidence has been rising among patients who are 75 years and older (465).

Osteoarthritis

One study, based on the Consultations in Primary Care Archive including 11 general practices in North Staffordshire reported an increase in incidence of osteoarthritis between 2003 and 2010 from 0.3 to 2.0/1000 persons among those aged 35-44 (87).

Lung cancer

The incidence rates of lung cancer have been stable over this period with increases seen among women and decreases among men, whilst mortality rates have been declining (124, 140). Incidence peaked among men in the late 1970s and has been declining ever since, whereas among women a steady increase has been found (92, 457-459, 462, 463, 466-468).

Diabetes

The increase in prevalence of diabetes has been driven by rising incidence (64, 110, 111, 469-471) and decrease in mortality (110).

Appendix 1B Risk of bias assessment tool.

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: In the comment section briefly justify your answer and explain if anything was done to assess the impact of a potential bias (e.g. by using sensitivity analyses) and mitigate its consequences (e.g. using sampling weights to increase representativeness).

Different sources of bias may apply to different study designs, for instance attrition will apply to population-based surveys, whereas ascertainment bias will be relevant for the studies based on routinely collected data.

Selection

1) Representativeness of the sample for the UK population (to consider: selection bias, attrition, inclusion of institutionalised population)

a) Representative of the population

b) Somewhat representative of the population

c) No description (there is not enough information to make the judgement)

Note. Representativeness of the study population is considered in the context of the population of the UK, rather than the community which the sample was drawn from as in the original tool. Nonetheless, if the study includes participants of a certain gender or age, the representativeness is assessed in the context of that gender or age. A study still can be considered as representative if institutionalised population is not included, however this should be noted in the comment section.

Justify your answer:

*2) Demonstration that outcome of interest was not present at the start of the study (not applicable in studies estimating lifetime prevalence)

a) Yes

b) No

Justify your answer:

*This item only applies to studies on incidence.

Outcome

1) Assessment of outcome

a) Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (x-rays, medical records, etc.)

b) Record linkage (e.g. identified through ICD codes on database records)

c) Self-report (i.e. no reference to original medical records or x-rays to confirm the outcome)

d) No description

Provide a brief description, consider any potential sources of bias:

Comparability of trends

1) Studies used the same methodology to assess outcome (consider method of collecting data and definition of outcome; answer “no” if either of these were different and provide explanation)

a) Yes

b) No

c) No description

Justify your answer:

Note. Select “Yes” if diagnostic criteria for a given condition changed at the national level over the study period, however it is unclear if this had a direct impact on the data of interest and make a note of it at the second criterion within comparability of trends.

2) Any other potential biases reducing comparability of the trends (consider: ascertainment bias, e.g. introduction of screening programmes or more effective methods of assessment; changing screening criteria; changing demographics of the population; for instance due to migration, which was not accounted for)?

a) Low risk

b) Moderate risk

c) High risk

d) No description

Justify your answer

Note. Consider if the potential impact of the bias was tested (e.g. sensitivity analysis) or mitigated. Select “No description” if the author does not provide any information on any other potential biases (not related to previous criteria) and the study design is not described in enough detail to make the judgement.

Appendix 1C Summary of data source evaluation.

As summarised in Appendices 1C and 1D, most commonly used primary/secondary care databases (the Health Improvement Network, n=4; the General Practice Research Database, n=4; QRESEARCH, n=2) were large, continuously updated and representative for the United Kingdom (472-474). These data sources also appeared to have a low risk of bias due to outcome assessment as they all passed through regular rigorous validity and reliability checks, thus the risk of bias due to outcome assessment was low (472-474).

Other, considerably smaller or less-established, primary care databases tended to have limited representativeness of the UK population. This includes the Continuous Morbidity Recording project run by the Primary Care Clinical Informatics-Research Unit (PCCIU-R) (106) and the Diabetes Audit and Research in Tayside (110) (based in Scotland and not representative for the UK population), the Doctors' Independent Network (DIN) (115) (estimates in the included study based only on a subset of family practices), Hospital diabetes register in the Poole area (UK) (94) (unlikely to be representative for the general population). Also, there was no detailed information about how the outcome was assessed in the Quality and Outcomes Framework (119), Poole hospital diabetes register (94) and the Cardiff/the Vale of Glamorgan routine hospital and mortality data (116).

It is unclear to what extent the methodology used to record and identify cases in primary/secondary care databases and other routinely collected data was consistent over time, as detailed information was rarely available. Nonetheless, there were

certain issues that might have had an impact on the estimates of trends. For instance, the Health Improvement Network (THIN) database started recording patients information prospectively from 2002 (474), however a few studies based their estimates on information from earlier periods reaching 1996 (64, 105, 111) when the records were retrieved from other systems. Those might have differed in their quality and use of clinical codes. Davies and colleagues (105), however, found little change in the use of different Read codes of coronary heart disease over the period 1996–2002 in their sensitivity analysis. Other studies did not conduct such analysis (64, 111), but performed a detailed search of records or only used data meeting the quality assurance standards. There were also changes in the coding system within GPRD, from ICD-8 to READ in 1998 (121) and the impact of this change on trends is unclear.

The main UK representative population-based surveys used for estimating trends in prevalence and health expectancy were the Health Surveys for England and Scotland (HSE/S) (n=8), the General Household Survey/General Lifestyle Survey (GHS/GLS) (n=10). Other surveys, tended to be limited to older population (the Medical Research Council Cognitive Function and Ageing Study; the British Regional Heart Study; the English Longitudinal Study of Ageing), or were only representative for small regions rather than the general population (general practices in Gloucestershire; general practices in Leicestershire; the Arthritis Research Campaign). Nonetheless, representativeness of the population in those studies was counterbalanced by stability in the population that increased confidence in the comparability of trends over time (92, 102, 133). Importantly, only three databases

included institutionalised population (MRC CFAS study, UK census and study based on information from general practices in Gloucestershire).

As summarised in Appendix 1D, the outcome in most surveys was self-reported, through self-administered questionnaire, which are prone to a recall or desirability bias (475). In one study, physician-reported survey was used (National Morbidity Survey) (91) and in two studies self-reports were validated with medical records to address these biases (BRHS) (95, 96). Nonetheless, the data collection procedures in key surveys (GHS/GLS; HSE/S; MRC CFA) tended to be standardised, with extensive training for interviewers and reliability checks, thus they were considered as having low risk of bias due to outcome assessment.

The methodology of the studies was rarely identical over time, however in most cases the changes did not appear to introduce any serious biases. For instance, there were changes to the sampling strategy in HSE/S; GHS/GLS; MRC CFAS; Arthritis Research Campaign, which however did not compromise the representativeness of the sample.

Appendix 1D The assessment of the risk of bias in primary/secondary care databases and other routinely collected data.

Database (n studies)	Country	Representativeness of the UK population	Assessment of outcome	Risk of bias due to assessment of outcome	Any changes to the methodology over time
THIN (n=4)[64, 105, 111, 124]	UK	Representative (primary care)	Record linkage	Low	Consistent from 2002; while prospective data collection for THIN started in 2002, the database includes practice data from the date a practice became computerised, which for some of the THIN practices dates back as far as 1987.
GPRD (n=4)[109, 120, 121, 136]	UK	Representative (primary and secondary care)	Record linkage	Low	Change of coding system from ICD-8 to READ
QRESEARCH (n=2)[122, 123]	England	Representative (primary care)	Record linkage	Low	No information
QOF (n=1)[119]	UK	Representative (primary care)	Record linkage	No information	No information
CMR (n=1)[106]	Scotland	Representative (primary care; unrepresentative of people from very deprived areas)	Record linkage	Low	No information
DIN (n=1)[115]	England/ Wales	Representative of age-gender population structure (primary care; northern population slightly under-represented)	Record linkage	Low	No information
DARTS (n=1)[110]	Scotland	Representative of the community population (Tayside, Scotland), but unclear to what extent representative for the UK (primary care)	Record linkage	Low	No information
Hospital diabetes register (n=1)[94]	England	Representative of the community population (Poole, England), but unclear to what extent representative for the UK	Record linkage	No information	No information

Appendix 1D (cont.) The assessment of the risk of bias in primary/secondary care databases and other routinely collected data.

Routine hospital and mortality data (n=1)[116]	Wales	Somewhat representative (mainly urban area)	Record linkage	No information	Differences in case identification (in 1996, patients were identified from a data derived from a primary care audit and a data set created using record linkage on mainly hospital-based sources; in 2004, the audit data were not available, but HbA1c data from general practice and data from a podiatry clinic were available)

Note. THIN = Health Improvement Network; ICD-8 = International Statistical Classification of Diseases and Related Health Problems 8th Revision; GPRD = General Practice Research Database; QOF = Quality and Outcomes Framework; CMR = Continuous morbidity recording project; DIN = Doctors' Independent Network; DARTS = Diabetes Audit and Research in Tayside.

Appendix 1E The assessment of the risk of bias in population-based surveys.

Database (n studies)	**Country**	**Design**	**Representativeness of UK population**	**Assessment of outcome**	**Risk of bias due to assessment of outcome**	**Any changes to the methodology over time**
GHS/GLS (n=10)[97-101, 107, 114, 119, 127, 128, 138]	UK	Repeated cross-sectional (GHS)/ prospective longitudinal (GLS)	Representative (no institutionalised population)	Self-reported (CAPI; face-to-face interview)	Low (highly standardised procedures; extensive training for interviewers)	Change of the design from in 2005, from a cross-sectional to a longitudinal format
Health Surveys for England and Scotland (n=8)[91, 104, 113, 114, 118, 119, 134, 137]	England/ Scotland	Repeated cross-sectional	Representative (no institutionalised population)	Self-reported (CAPI; face-to-face interview)	Low (highly standardised procedures; extensive training for interviewers; reliability checks)	Highly consistent methodology; nonresponse weighting has been incorporated into the weighting strategy
MRC CFAS I & II (n=3)[108, 126, 132]	England/ Wales	Repeated cross-sectional	Somewhat representative of age 65+ (rural area in East England, mainly white, healthier; includes institutionalised population)	Self-reported (face-to-face interview)	Low (highly standardised procedures; extensive training for interviewers; reliability checks)	Highly consistent methodology; stable diagnostic criteria (algorithmic approach to diagnosis; CFAS I was a two-stage study whereas CFAS II was one-stage, not accounting for the uncertainty introduced in multistage processes leads to overoptimistic confidence intervals)

Appendix 1E (cont.) The assessment of the risk of bias in population-based surveys.

Database (n studies)	Country	Design	Representativeness of UK population	Assessment of outcome	Risk of bias due to assessment of outcome	Any changes to the methodology over time
BRHS (n=2)[95, 96]	UK	Prospective longitudinal	Somewhat representative of middle-age men (socioeconomically and geographically representative; mainly white; lack of inner city populations and towns with high mobility)	Self-reported (self-completed questionnaire) and medical records	Low (high agreement between self-report and medical records, but medical records not available for entire period of study)	Somewhat consistent methodology; the wording of questions and coding schemes were the same for each questionnaire; higher attrition among less healthy participants, simple sensitivity analyses suggested that these differences were unlikely to have a significant impact on the estimated prevalence trends; questionnaires were self-completed, with the exception of the questionnaires in 1979 (administered) and 1999 (assistance offered)
UK Population census (n=2)[129, 131]	UK	Repeated cross-sectional	Representative (includes institutionalised population)	Self-reported (self-completed questionnaire)	No information	Disability questions varied somewhat between 1991 and 2001 (a Brass relational model used to account for that)
General practice in Leicestershire (n=2)[102, 103]	England	Repeated cross-sectional	Somewhat representative of aged 75+ (representative for the Leicestershire population; similar age, gender and social class distribution to England and Wales; includes institutionalised population)	Self-reported (self-completed questionnaire)	Low (standardised procedures; training for interviewers)	Consistent methodology; stable population over time
National Morbidity Survey (n=1)[91]	England/ Wales	Repeated cross-sectional	Representative sample of GPs	Reported by GPs (self-completed form)	No information	No information

Appendix 1E (cont.) The assessment of the risk of bias in population-based surveys.

Database (n studies)	Country	Design	Representativeness of UK population	Assessment of outcome	Risk of bias due to assessment of outcome	Any changes to the methodology over time
ELSA (n=2)[35, 125]	England/ Wales	Prospective longitudinal	Representative (survey weights used; sample refreshments; no institutionalised population)	Cognitive assessment (face-to-face interview)	Low (highly standardised procedures; extensive training for interviewers; reliability checks)	Consistent operational case definition based on standardised assessments of cognition and function was applied (more consistent than clinical assessments amenable to change in diagnostic criteria)
BHPS (n=1)[112]	UK	Prospective longitudinal	Representative (no institutionalised population)	Self-reported (face-to-face interviews)	No information	No information
Family Resource Survey (n=1)[130]	UK	Repeated cross-sectional	Representative (no institutionalised population)	Self-reported (face-to-face interviews)	Low (highly standardised procedures; extensive training for interviewers)	No information
Arthritis Research Campaign (n=1)[92]	England	Repeated cross-sectional	Somewhat representative (limited to the northwest region)	Self-reported (face-to-face interviews and self-administered questionnaire)	No information	Different modes of data collection (study 1: face to face interview vs study 2: self-administered questionnaire); different definitions for identifying pain syndromes over time, however the bias judged to be minimal by authors
Randomly selected from lists of GPs (n=1)[93]	UK	Repeated cross-sectional	No information	Self-reported (self-administered questionnaire)	No information	Consistent sampling methods and response rates

Appendix 1E (cont.) The assessment of the risk of bias in population-based surveys.

Database (n studies)	**Country**	**Design**	**Representativeness of UK population**	**Assessment of outcome**	**Risk of bias due to assessment of outcome**	**Any changes to the methodology over time**
General practices in Gloucestershire (n=1)[133]	England	Repeated cross-sectional	Somewhat representative of aged 75+ (representative age and gender structure; only Gloucestershire, England; mainly rural towns; mainly white population; more affluent; includes institutionalised population)	Self-reported (self-administered questionnaire)	No information	Consistent methodology; stable population; institutionalised population only representative in the second survey
Annual Population Survey (n=1)[138]	UK	Repeated cross-sectional	Representative (no institutionalised population)	Self-reported (face-to-face interviews)	No information	Used in comparison with GHS/GLS, no information on consistency of the methodology

Note. GHS/GLS = General Household Survey/General Lifestyle Survey; CAPI = Computer-assisted personal interviewing; MRC CFAS = Medical Research Council Cognitive Function and Ageing Studies; BRHS = British Regional Heart Study; UK = United Kingdom; GP = General Practitioner; ELSA = English Longitudinal Study of Ageing; BHPS = British Household Panel Survey.

Appendix 2A Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Belbasis et al. (2016) (214)	Umbrella review of systematic reviews and meta-analyses (n=39)	- Highly suggestive evidence: Lower birthweight->All types of leukaemia, overweight or obese (16+)	Importance of gestational age emphasised.
Birnie et al. (2016) (272)	Meta-analysis (n=19)	- Low childhood SEP (vs high)-Grip strength (18+): -0.13 standard deviations (95% CI: -0.06, -0.21) - Low childhood SEP (vs high)->Chair rise time (18+): 6% (4%, 8%) higher - Low childhood SEP (vs high)->Inability to balance for 5s (18+): OR=1.26 (1.02, 1.55)	Age.
Booth et al. (2013) (210)	Clinical Practice Research Datalink (2005-2011)	- Obese category I (30+)->Multimorbidity (30+): OR=2.04 (1.98 to 2.11)	Age; gender; socioeconomic deprivation; smoking.
Buchanan et al. (2002) (223)	Great Britain; NCDS (born 1958)	Men: - Internalizing problems (7)->Psychological distress (33): OR=1.0 (0.57–1.90) - Externalizing problems (7)->Psychological distress (33): OR=1.9 (1.11–3.30) Women: - Internalizing problems (7)->Psychological distress (33): OR=1.2 (0.86–1.81) - Externalizing problems (7)->Psychological distress (33): OR=1.7 (1.03–2.70)	Gender and parental socioeconomic status when the child was born; parental mental health (7); structure of the parental background; social disadvantage; experience of care (7); family involvement with the police/probation service (7); agency referral for difficulties at school (7); social services involvement and domestic tension (7); outings with mother (7); father reads to child (7); child's good numeric and creative skills (7).

Appendix 2A (cont.) Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Cooper & Power (2008) (216)	Great Britain; NCDS (born 1958)	Men: - Lower birthweight->Higher total cholesterol (44-45): B=0.01 (−0.02 to 0.05) - Lower birthweight->Higher LDL-cholesterol (44-45): B=0.03 (−0.01 to 0.06) - Lower birthweight->Higher HDL-cholesterol (44-45): B=0.02 (0.01 to 0.03) - Lower Birthweight->Higher triglycerides (44-45): B=−0.04 (−0.06 to −0.02) Women: - Lower birthweight->Lower total cholesterol (44-45): B=−0.07 (−0.10 to −0.03) - Lower birthweight->Lower LDL-cholesterol (44-45): B=−0.03 (−0.06 to −0.002) - Lower birthweight->Higher HDL-cholesterol (44-45): B=0.01 (−0.005 to 0.02) - Lower birthweight->Lower triglycerides (44-45): B=−0.05 (−0.07 to −0.03)	Gestational age; smoking status; alcohol use; physical activity levels; indicators of lifetime socioeconomic position; menopausal status; height, BMI.
Galobardes et al. (2006) (219)	Systematic review (n=40)	- Childhood SEP->Higher risk of cardiovascular disease and coronary heart disease	Association tended to remain after adjusting for adult SEP.

Appendix 2A (cont.) Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Hardy et al. (2003) (217)	Great Britain; NSHD (born 1946)	- Birthweight (kg)->Systolic blood pressure (36): B=-1.86 mm Hg (-2.90 to -0.82; p<0.01) - Birthweight (kg)->Systolic blood pressure (43): B=-2.09 mm Hg (-3.20 to -0.98; p=0.0002) - Birthweight (kg)->Systolic blood pressure (53): B=-2.57 mm Hg (-4.00 to -1.14; p=0.0005) - Birthweight (kg)->Diastolic blood pressure (36): B=-0.28 mm Hg (-1.13 to 0.58; p=0.5) - Birthweight (kg)->Diastolic blood pressure (43): B=-0.48 mm Hg (-1.35 to 0.39; p=0.5) - Birthweight (kg)->Diastolic blood pressure (53): B=-0.48 mm Hg (-1.35 to 0.39; p=0.5) - Childhood manual social class (vs non-manual) (4)->Systolic blood pressure (36): B=2.09 mm Hg (0.99 to 3.19; p=0.0002) - Childhood manual social class (vs non-manual) (4)->Systolic blood pressure (43): B=2.50 mm Hg (1.33 to 3.68; p<0.0001) - Childhood manual social class (vs non-manual) (4)->Systolic blood pressure (53): B=3.91 mm Hg (2.40 to 5.43; p<0.0001) - Childhood manual social class (vs non-manual) (4)->Diastolic blood pressure (36): B=1.10 mm Hg (0.20 to 2.00; p=0.02) - Childhood manual social class (vs non-manual) (4)->Diastolic blood pressure (43): B=1.69 mm Hg (-0.79 to 2.59; p=0.0002) - Childhood manual social class (vs non-manual) (4)->Diastolic blood pressure (53): B=1.93 mm Hg (-1.02 to 2.85; p<0.0001) - Birthweight (kg)->Systolic blood pressure (36-53): B=-0.4 mm Hg (-1.3 to 0.5; p=0.3) per 10-year increase in age - Childhood manual social class (vs non-manual) (4)->Systolic blood pressure (36-53): B=1.0 mm Hg (0.01 to 0.19; p=0.03) per 10-year increase in age	Age; gender; birthweight; childhood social class.

Appendix 2A (cont.) Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Hardy et al. (2006) (46)	Finland UK, Faroe Islands; European Birth-Lifecourse-Studies (born 1927-1966)	Men: - Lower birthweight->Higher systolic blood pressure (31-62): B=0.4 (-4.8 to 5.5) to B=-2.1 (-3.8, -0.4) Women: - Lower birthweight->Higher systolic blood pressure (31-62): B=-1.6 (-4.0 to 0.9) to B=-2.1 (-3.0 to -0.1)	Mother's age, height and education; birth order; current BMI and height.
Henderson et al. (2009) (224)	Scotland; The Aberdeen Children of the 1950s	- Often appears miserable or unhappy (6-12)->Permanently sick or disabled (46-51): OR=3.81 (1.01 to 14.4)	Year of birth, gender, IQ and father's social class (6-12).
Henderson et al. (2012) (222)	Great Britain; NSHD (born 1946)/NCDS (born 1958)/BCS70 (born 1970)	- NSHD: Higher cognitive ability (10/11)->Long-term sickness (53): OR=0.70 (0.56 to 0.86) - NCDS: Higher cognitive ability (10/11)->Long-term sickness (42): OR=0.69 (0.61 to 0.77) - BCS70: Higher cognitive ability (10/11)->Long-term sickness (34): OR=0.80 (0.66 to 0.97)	Gender and parental social class.

Appendix 2A (cont.) Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Humphreys et al. (2018) (212)	England; Hertfordshire Cohort Study/ Clinical Outcomes Study	- Lower birthweight->Multimorbidity (64–68): unadjusted OR=1.29 (0.58, 2.89) - Higher no. of childhood illnesses->Multimorbidity (64–68): adjusted OR=1.15 (1.06, 1.25)	Diphtheria immunised; no. of childhood illnesses; paternal social class; maternal age at birth; breastfeeding; birthweight; growth in the 1st year; age; gender; adult BMI; adult physical activity; adult smoking and alcohol consumption.
Johnston et al. (2019) (211)	Aberdeen Children of the 1950s (ACONF) cohort (Scotland)	- SES associated with multimorbidity both in adjusted and unadjusted models ($p<0.001$), however after adjustment association between individual categories has attenuated (e.g.): Unskilled vs skilled manual social class at birth->Multimorbidity (mean age: 48): unadjusted OR=1.43 (1.06, 1.93); adjusted OR=1.20 (0.91, 1.70)	Educational attainment, gender, cognition at age 7 and school type.

Appendix 2A (cont.) Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Lebenbaum et al. (2018) (200)	Canada; National Population Health Survey (1996-7); Canadian Community Health Surveys (2012–13)	- Class II/III obesity (mean=45-47) ->Multimorbidity (mean=45-47): OR= 3.91 (3.06, 4.99) - Class I obesity (mean=45-47) ->Multimorbidity (mean=45-47): OR=2.30 (1.94, 2.74) Changes over time (1996–7 vs 2012-3): - Class II/III obesity (mean=45-47) ->Multimorbidity (mean=45-47): OR=1.48 (1.13, 1.95) - Class I obesity (mean=45-47) ->Multimorbidity (mean=45-47): OR=1.38 (1.14, 1.68)	Age, gender, marital status, immigrant status, home ownership, rural residence, education, income quintile, smoking status, alcohol consumption.
Li et al. (2015) (73)	Great Britain; NSHD (born 1946)/NCDS (born 1958)	Men: Associated only in NCDS: - NCDS: BMI (7-16)->SBP (43-45): r=0.21 (0.17 to 0.24) - NSHD: BMI (7-16)->SBP (43-45): r=0.04 (-0.03 to 0.12) Women: Stronger association in NCDS than NSHD: - NCDS: BMI (7-16)->SBP (43-45): r=0.19 (0.12 to 0.26) - NSHD: BMI (7-16)->SBP (43-45): r=0.11 (0.02 to 0.21)	Blood pressure device; medication; age at examination.

Appendix 2A (cont.) Key characteristics of main relevant studies.

Reference	Country; Study (period)	Exposure (age)->Outcome (age): strength of the association (SE/95%CI)	Adjusted confounders (age)
Mensah & Hobcraft (2007) (215)	Great Britain; NCDS (born 1958)/BCS70 (born 1970)	- Low birthweight (<=2.5kg)->Fair/poor general health (30/33): 1.16 (0.99 to 1.36) - Low birthweight (<=2.5kg)->Long-standing illness (30/33): 1.18 (0.96 to 1.46) - More behaviour problems (5-16)->Fair/poor general health (30/33): 1.40 (1.18 to 1.66) - More behaviour problems (5-16)->Long-standing illness (30/33): 1.29 (1.03 to 1.62) - Lower academic test scores (5-16)->Fair/poor general health (30/33): 1.48 (1.25 to 1.75) - 1.89 (1.64 to 2.18) - Lower academic test scores (5-16)->Long-standing illness (30/33): 1.30 (1.12 to 1.52)	Socioeconomic deprivation, family housing tenure, family disruption, parental interest, academic test scores, cohort gender; other predictors as appropriate.
Neeleman et al. (2002) (213)	Great Britain; NSHD (born 1946)	- Negative affect (13)->Somatic symptom count (43): B=0.090 (0.036, 0.144) - Negative affect (13)->Psychiatric symptom score (43): B=0.130 (0.090, 0.170) - Anxiety (15)->Somatic symptom count (43): B (boys)=0.110 (0.051, 0.169); B (girls)=0.044 (-0.018, 0.106) - Anxiety (15)->Psychiatric symptom score (43): B=0.066 (0.023, 0.109) - Aggression (13)->Somatic symptom count (43): B=0.052 (0.013, 0.093) - Aggression (13)->Psychiatric symptom count (43): B=0.046 (0.006, 0.086)	Gender.
Park et al. (2012) (221)	Systematic review (n=39)	- BMI/obesity (2-19)->Type 2 diabetes: OR ranged 1.22-2.04 - BMI/obesity (2-19)->Hypertension: OR ranged 1.35-3.75 - BMI/obesity (2-19)->Coronary heart disease: OR ranged 1.53-5.43	A range of confounders adjusted in individual studies.
Singh-Manoux et al. (2005) (220)	England; Whitehall II (born 1930-1950)	- Low childhood socioeconomic position (<16)->Coronary heart disease (47-69): RR=1.95 (1.36, 2.81) - Low childhood socioeconomic position (<16)->Physical component score (47-69): RR=1.30 (0.98, 1.74) - Low childhood socioeconomic position (<16)->Mental component score (47-69): RR=1.69 (1.26, 2.26) - Low childhood socioeconomic position (<16)->General Health Questionnaire (47-69): RR=1.52 (1.14, 2.03) - Low childhood socioeconomic position (<16)->Self-rated health (47-69): RR=1.69 (1.17, 2.44)	Age; cognitive ability (47-69).

Appendix 2B The health questions in NCDS and BCS70 at age 42 – used for deriving self-reported outcomes for cross-cohort comparisons.

Health condition	Study	Wording	Response	Methodology
Asthma / bronchitis	NCDS	Have you ever been told that you had asthma / bronchitis?	Yes/ No	CAPI (face-to-face)
	BCS70	Since [^date of last interview / month four years prior to interview310] has [^CM Name] had any of the health problems listed on this card? Please include any health problems that had already started before that date. (Asthma or wheezy bronchitis) + Age 38: Please look at show card C and tell me whether you are currently suffering from any of the following health conditions. (Asthma or wheezy bronchitis) + Age 34 (also includes age 30): See above.		Age 42: CAPI (face-to-face) Age 38: telephone survey Age 34: CAPI (face-to-face) Age 30: CAPI (face-to-face)
Migraine/ severe headache	NCDS	Have you ever been told that you had migraine or severe headaches associated with vomiting or dizziness?	Yes/ No	CAPI (face-to-face)
	BCS70	Since [^date of last interview / month four years prior to interview310] has [^CM Name] had any of the health problems listed on this card? Please include any health problems that had already started before that date. (Migraine) + Age 38: Please look at show card C and tell me whether you are currently suffering from any of the following health conditions. (Migraine) + Age 34 (also includes age 30): See above.		Age 42: CAPI (face-to-face) Age 38: telephone survey Age 34: CAPI (face-to-face) Age 30: CAPI (face-to-face)
Fits, convulsions or epilepsy	NCDS	Have you ever had or been told you had fits, convulsions or epilepsy?	Yes/ No	CAPI (face-to-face)
	BCS70	Since [^date of last interview / month four years prior to interview310] has [^CM Name] had any of the health problems listed on this card? Please include any health problems that had already started before that date. (Convulsion, fit, epileptic seizure) + Age 38: Please look at show card C and tell me whether you are currently suffering from any of the following health conditions. (Convulsion, fit, epileptic seizure) + Age 34 (also includes age 30): See above.		Age 42: CAPI (face-to-face) Age 38: telephone survey Age 34: CAPI (face-to-face) Age 30: CAPI (face-to-face)
Cancer	NCDS	Have you ever had or been told you had cancer?	Yes/ No	CAPI (face-to-face)
	BCS70	Since [^date of last interview / month four years prior to interview310] has [^CM Name] had any of the health problems listed on this card? Please include any health problems that had already started before that date. (Cancer or Leukaemia) + Age 38: Please look at show card C and tell me whether you are currently suffering from any of the following health conditions. (Cancer or Leukaemia) + Age 34 (also includes age 30): See above.		Age 42: CAPI (face-to-face) Age 38: telephone survey Age 34: CAPI (face-to-face) Age 30: CAPI (face-to-face)

Appendix 2C Description of covariates.

Variable	Type of variable	Age	Description
Year-of-birth	Confounder/moderator /exposures	0	A binary variable (1958 vs 1970) – recorded at birth.
Gender	Confounder/moderator	0	A binary variable (men vs women) – recorded at birth; if information was missing it was completed with records from age 10/11 and 42.
Gestational age	Confounder	0	Gestational age measured in days since the start of last menstrual period was recorded at birth and converted into completed weeks and used as a continuous variable.
Smoking during pregnancy	Confounder	0	All variables are self-reported by the mother at birth, except for number of children in household (at five years old). Unmarried is only based on marital status and includes cohabitation.
Mothers' height	Confounder	0	
Mother's unmarried at birth	Confounder	0	
Parental divorce	Confounder	0-16	In NCDS and BCS70, a number of variables which collected information on change of circumstances since previous sweep and whether parental divorce was the cause were collated across multiple sweeps in childhood and were used to create the divorce variables. In both NCDS and BCS70, study members were also asked in adulthood whether their parents divorced and what age they divorced; if study members said that their parents divorced by the time they were 16 years old.
Mother's mental health (BCS70 only)	Confounder	10	When the study members were age 10, their mothers were asked a series of questions which measured their own malaise using a 24-item Malaise inventory (230). The 24 items were scored from 0 to 100 with 0 reflecting seldom or never and 100 most of the time. The 24 items were added together to create a continuous scale from 1 to 2154, with a higher score reflecting higher levels of depression.

Appendix 2C (cont.). Description of covariates.

Variable	Type of variable	Age	Description
Tenure*	Confounder	5-11	This variable captures whether the study member was in rented or owned accommodation in early childhood and at age 10/11. This variable does not distinguish between accommodation rented privately and rented from the council.
Overcrowding*	Confounder	5-11	Whether the study member experienced overcrowding in childhood, which is measured as the number of persons per room. The measure is a median score of overcrowding collected at different points between birth and age 11 in the NCDS, but in the BCS70 overcrowding was only collected at 5 years of age. For any cases in NCDS which were missing data from one or more sweeps, the measure was derived using the sweeps where data was available.
Teen mother*	Confounder	0	Using the age of the mother when the study member was born. All those mothers under the age of 20 were identified as a teen mother.
Breastfeeding*	Confounder	5-7	Details on whether the study member was breastfed. The details were given by the mother.
Parental interest in child's education*	Confounder	10/11	Parental interest in schooling was reported by the child's teacher at age 11 for the NCDS and at age 10 for the BCS70 (high interest vs moderate interest vs low interest). The interest of the parent who was most interested in their child's education was used in NCDS and BCS70. If either parent in NCDS or BCS70 had missing data, then the response of the parent which had data was used.
Length of time absent from school due to illness*	Confounder	10/11	Parents were asked how long the study member had been away from school due to ill health in the past 12 months.

* The variable were harmonised across cohorts as part of CLOSER work package 2 (476).

Appendix 2D Frequency and predictors of missing data in the outcome and the outcome itself.

N=7,951	Prevalence of missing data n (%)	Predictors of missing data in multimorbidity RR (CI95%)	Predictors of multimorbidity RR (CI95%)
Multimorbidity at age 46-48	3,793 (47.7)	-	-
Being a man	0 (0)	1.00 (0.95, 1.05)	1.25 (1.14, 1.37)
Breastfed (never breastfed – reference)	1,172 (14.7)	0.93 (0.88, 0.98)	0.93 (0.84, 1.03)
Mother smoked during pregnancy (never smoked – reference)	44 (0.6)	1.06 (1.01, 1.11)	1.25 (1.14, 1.37)
Mother's birth marital status (non-married – reference)	8 (0.1)	0.92 (0.83, 1.01)	0.81 (0.67, 0.97)
Mother's height	64 (0.8)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)
Mother's age at birth	46 (0.6)	1.00 (0.99, 1.00)	0.99 (0.98, 1.00)
Birthweight	2 (0.03)	0.88 (0.84, 0.92)	0.91 (0.83, 1.00)
Father's manual occupational class at birth (non-manual – reference)	546 (6.9)	1.16 (1.09, 1.23)	1.09 (0.97, 1.24)
BMI at age 10/11	1,935 (24.3)	1.03 (1.01, 1.04)	1.03 (1.01, 1.06)
Cognitive ability problems at age 10/11	1,751 (22.0)	0.86 (0.84, 0.88)	0.95 (0.90, 1.01)
Internalising problems at age 16	3,152 (39.6)	1.03 (1.00, 1.05)	1.04 (0.99, 1.09)
Externalising problems at age 16	3,152 (39.6)	1.05 (1.03, 1.07)	1.08 (1.04, 1.12)
Poor self-perceived general health at age 46-48	5 (0.1)	1.40 (1.33, 1.47)	2.55 (2.34, 2.77)
Ever smoked cigarettes regularly (ever – reference) at age 46-48	0 (0)	0.96 (0.91, 1.02)	1.28 (1.17, 1.41)

Appendix 2E Multimorbidity prevalence at age 46-48 based on different sample definition.

Sample definition	% prevalence
Participated at age 46-48 (n total=7,951; imputed n=3,793)[1]	33.8 (32.6, 35.0)
Alive and not permanent emigrants at age 46-48 (n total=15,821; imputed n=11,575)[1]	35.9 (34.9, 37.0)
Complete cases only (n total=4,158)	30.5 (29.1, 31.9)
Participated at age 46-48 and had no missing values on objectively measured health outcomes (n total=4,963; imputed n=1,170)[2]	32.8 (31.4, 34.2)
Participated at age 46-48 and had no missing values on self-reported health outcomes (n total=6,368; imputed n=2,122)[2]	32.3 (31.1, 33.5)

[1]50 imputations used.
[2]20 imputations used.

Appendix 2F The risk ratio and E-values for the association between each exposure and multimorbidity at age 46-48 in the most adjusted models.

	Risk Ratio (95%CI)	E-value (point estimate)
Father's social class at birth (unskilled vs professional)	1.43 (1.18, 1.74)	2.21
Birthweight	0.90 (0.84, 0.96)	1.46
Cognitive ability (age 10)	0.91 (0.68, 1.00)	1.43
BMI (age 10)	1.03 (1.01, 1.05)	1.21
Internalising problems (age 16)	1.04 (1.00, 1.08)	1.24
Externalising problems (age 16)	1.06 (1.03, 1.09)	1.31

Appendix 3A The longitudinal examination of the measurement equivalence of the Malaise Inventory in the NCDS and BCS70 (adapted from Ploubidis, McElroy & Moreira, 2019).

		Chi-square (d.f.)	RMSEA	CFI	TLI	ΔRMSEA	ΔCFI	ΔTLI
***NCDS 23, 33, 42, 50**	Configural	1500.343 (216)	0.033 (0.031 to 0.034	0.988	0.984			
	Scalar	2482.153 (265)	0.039 (0.037 to 0.040)	0.979	0.977	0.006	0.009	0.007
****BCS70 26, 30, 34, 42, 46**	Configural	2169.417 (270)	0.039 (0.038 to 0.041)	0.986	0.982			
	Scalar	2815.072 (333)	0.040 (0.039 to 0.042)	0.982	0.981	0.001	0.004	0.001
*****NCDS & BCS70 23/26, 33/34, 42**	Configural	2354.059 (324)	0.035 (0.033 to 0.036)	0.986	0.981			
	Scalar	3774.957 (401)	0.040 (0.039 to 0.041)	0.976	0.974	0.005	0.010	0.007

***Eight independent groups multigroup models (4 waves, gender)
****Ten independent groups multigroup models (5 waves, gender)
***** Twelve independent groups multigroup models (3 waves, 2 cohorts, gender)

Appendix 3B Longitudinal examination of the measurement equivalence of seven harmonised items in the NSHD (adapted from McElroy, Villadsen, Patalay et al., 2020).

Model	N	Chi-square (DF)	RMSEA	CFI	TLI	ΔRMSEA	ΔCFI	ΔTLI
Configural	13,886	544.328 (70)	0.049	0.979	0.968			
Scalar*		1175.735 (94)	0.064	0.952	0.946	0.015	0.027	0.02
Partial Scalar*¥		1173.975 (95)	0.064	0.952	0.947			

*Latent variances fixed to 1

¥Threshold for 'tense' freed

Appendix 3C Longitudinal examination of the measurement equivalence of four harmonised items in the NSHD, NCDS and BCS70 (adapted from McElroy, Villadsen, Patalay et al., 2020).

Model	N	Chi-square (DF)	RMSEA	CFI	TLI	ΔRMSEA	ΔCFI	ΔTLI
Configural	65,997	269.102 (18)	0.044	0.994	0.983			
Scalar		4087.048 (66)	0.091	0.914	0.929	0.047	0.08	0.054
Partial Scalar*		1129.715 (58)	0.050	0.976	0.977	0.006	0.018	0.006
Partial Scalar 2**		444.496 (50)	0.033	0.991	0.990	0.011	0.003	0.007

*Threshold for 'tense' freed

**Thresholds for 'tense' and 'fatigue' freed

Appendix 3D Age profile of psychological distress in the NSHD, NCDS and BCS70—estimates from multilevel logit regression based on the binary outcome.

	NSHD	**NCDS**	**BCS70**
	Coef. (95%CI)	Coef. (95%CI)	Coef. (95%CI)
Intercept	-20.25 (-22.86, -17.65)	13.76 (9.99, 17.53)	14.43 (7.50, 21.36)
Intercept variance	7.43 (6.43, 8.59)	5.60 (5.06, 6.20)	5.70 (5.23, 6.21)
Age	0.55 (0.45, 0.64)	-1.73 (-2.06, -1.39)	-1.60 (-2.20, -1.00)
Age^2	-0.00 (-0.01, -0.00)	0.05 (0.04, 0.06)	0.04 (0.03, 0.06)
Age^3		-0.00 (-0.00, -0.00)	-0.00 (-0.00, -0.00)
Woman (vs man)	1.12 (0.91, 1.33)	1.20 (1.07, 1.34)	0.73 (0.61, 0.85)
Observations	12,229	41,177	41,466
Participants	3,093	13,250	12,019
AIC	16176.28	24799.77	31684.08
BIC	16213.33	24851.53	31735.87

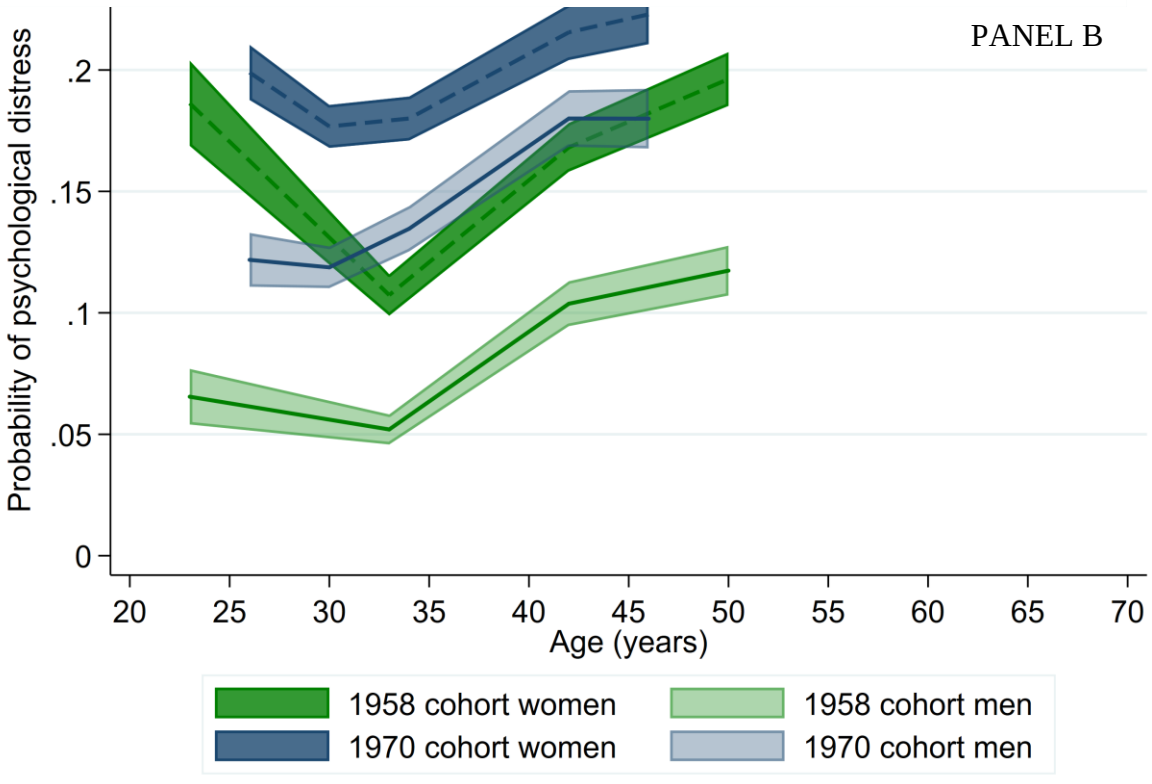
Note. AIC = Akaike information criterion; BIC = Bayesian information criterion.

Appendix 3E Age profile of psychological distress in the NSHD, NCDS and BCS70—estimates from multilevel Poisson regression based on the continuous outcome.

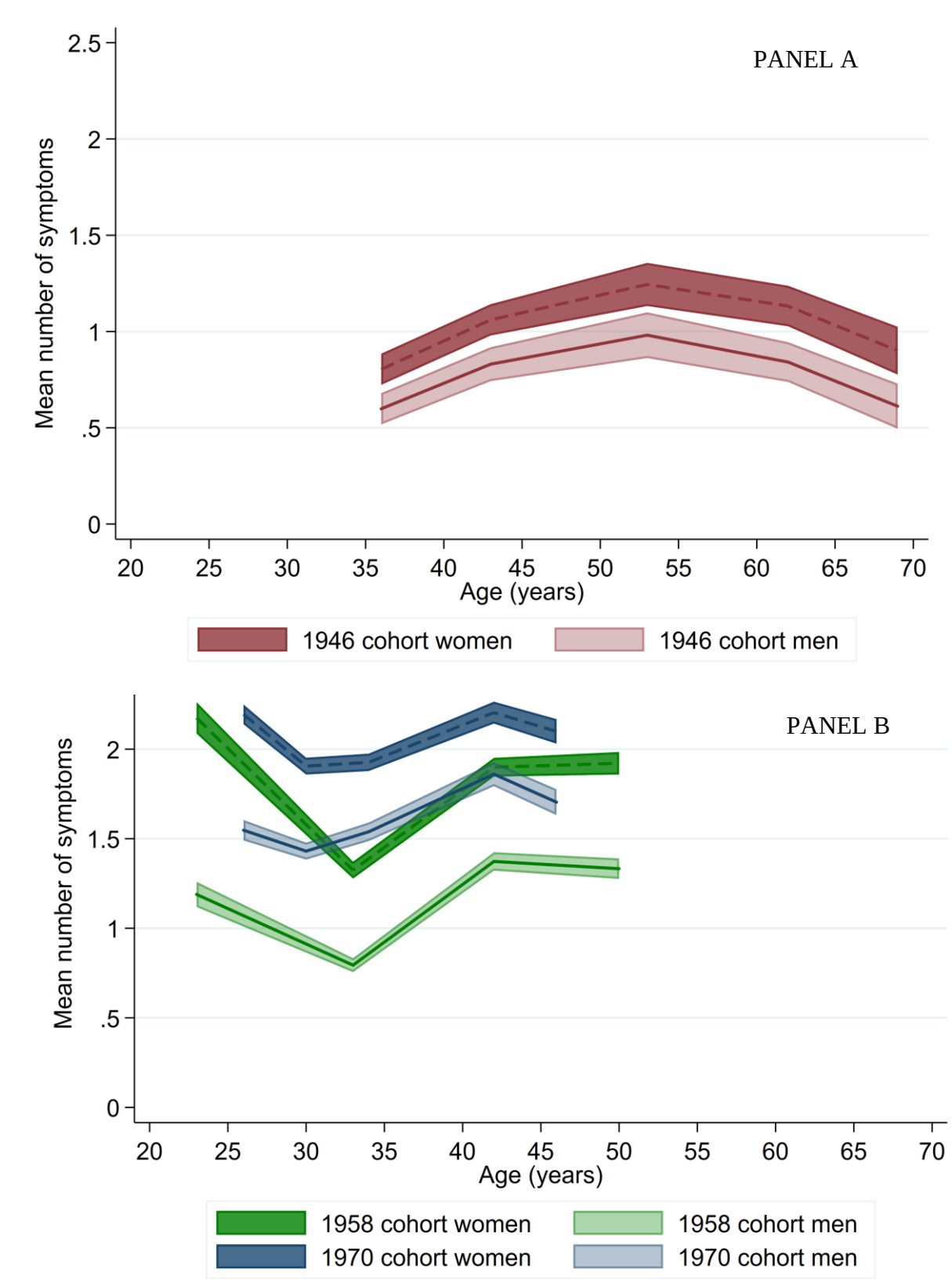
	NSHD	**NCDS**	**BCS70**
	Coef. (95%CI)	Coef. (95%CI)	Coef. (95%CI)
Intercept	-5.28 (-6.16, -4.40)	9.72 (8.90, 10.55)	1.41 (1.09, 1.84)
Intercept variance	2.17 (1.99, 2.37)	0.97 (0.93, 1.00)	0.78 (0.75, 0.81)
Age	0.16 (0.13, 0.20)	-0.97 (-1.04, -0.90)	-0.96 (-1.08, -0.83)
Age^2	-0.00 (-0.00, -0.00)	0.03 (0.03, 0.03)	0.03 (0.02, 0.03)
Age^3		-0.00 (-0.00, -0.00)	-0.00 (-0.00, -0.00)
Woman (vs man)	1.78 (1.59, 2.00)	0.59 (0.55, 0.64)	0.37 (0.33, 0.41)
Observations	12,229	41,177	41,466
Participants	3,093	13,250	12,019
AIC	55055.44	119340.8	135142.5
BIC	55085.08	119392.6	135194.3

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion.

Appendix 3F Gender-stratified age profile of psychological distress in the NSHD (1946 cohort), NCDS (1958 cohort) and BCS70 (1970 cohort)—estimates from multilevel logit regression based on the binary outcome.



Appendix 3G Gender-stratified age profile of psychological distress in the NSHD (1946 cohort), NCDS (1958 cohort) and BCS70 (1970 cohort)—estimates from multilevel Poisson regression based on the continuous outcome.



Appendix 4A Predictors of being excluded due to death or emigration.

	Died or emigrated before 1994	Died or emigrated in 1994-2008
	Odds ratio (CI95%)*	Odds ratio (CI95%)**
Women (vs men)	0.62 (0.58, 0.66)	0.66 (0.60, 0.73)
Parental SEP (high – reference)		
Medium	1.64 (1.48, 1.81)	4.04 (3.49, 4.69)
Low	2.61 (2.08, 2.46)	6.67 (5.91, 7.68)
Hospitalised in 1989-1993		3.79 (3.55, 4.06)

*Estimates from logit model: n=32,448-32,767. This sample includes individuals who did not contribute any data to the analyses.

**Estimates from multilevel logit model: n=28,238-28,448 (observations: n=112,952-113,792). This sample includes only individuals who contributed to at least one observation period.

Appendix 4B Conditions comprising the outcome variable and corresponding ICD10/9 codes.

Condition	ICD-10	ICD-9
Depression(477)	F20.4, F31.3, F31.4, F31.5, F32, F33, F34.1, F41.2, F43.2	296.2, 296.3, 296.5, 300.4, 309, 311
Asthma(478)	J45	493
Stroke or transient ischemic attack(479)	G45.0, G45.1, G45.2, G45.3, G45.8, G45.9, H34.1, I60, I61, I63, I64	362.3, 430, 431, 433.x1, 434.x1, 435, 436
Chronic kidney diseases(480)	N01, N02, N03, N04, N05, N06, N07, N08, N10, N11, N12, N13, N14, N15, N16, N17, N18, N19, N20, N21, N22, N23	583, 584, 585, 586, 592, 593.9
Chronic liver disease(481)	K70.0, K70.2, K73.X, K754, K758, K75.9, K76.0, B18.0, B18.1, B18.2, B18.8, B18.9	070.2X, 070.3X, 070.4X, 070.5X, 070.6, 070.9, 571.0, 571.3, 571.4X, 571.8, 573.1, 573.3
Chronic obstructive pulmonary disease(482)	J40, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9	492, 492.0, 492.8, 496.x
Dementia(477)	F00, F01, F02, F03, F051, G30, G31	290, 294.1, 331.2
Diabetes(483)	E10-E14	250
Heart failure (congestive heart failure; left ventricular failure; unspecified heart failure)(484)	I50	428
Cancer(477, 485))	C18, C19, C20, C21, C33, C34, C38.4, C45.0, C46.71, C50, C53, C61, C77, C78, C79, C80, C81, C82, C83, C84, C85, C88, C90.0, C90.2, C96, D05, D06, D01.0, D01.3, D02.2, D07.5	153, 154, 162, 163, 174, 180, 185, 196, 197, 198, 199, 200, 201, 202, 203.0, 230.3, 230.4, 230.5, 230.6, 231.2, 233.0, 233.1, 233.4, 238.6
Hypertension(486)	I10-I15	401-405
Coronary heart disease(484)	I20–I25	410-414
Migraine(487)	G43	346
Parkinson’s disease(488)	G20-G22	332
Rheumatoid arthritis(477)	M05, M06, M31.5, M32, M33, M34, M35.1, M35.3, M36.0	446.5, 710.0, 710.1, 710.2, 710.3, 710.4, 714.0, 714.1, 714.2, 714.8, 725
Schizophrenia or schizoaffective disorder(489)	F20, F21, F25	295

Appendix 4C Visualization of the data structure.

Observation period 1989-1993					*Observation period 1994-1998*					*Observation period 1999-2003*					*Observation period 2004-2008*					
1989	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	*Birth year*
17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	**1972**
18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	**1971**
19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	**1970**
20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	**1969**
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	**1968**
22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	**1967**
23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	**1966**
24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	**1965**
25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	**1964**
26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	**1963**
27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	**1962**
28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	**1961**
29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	**1960**
30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	**1959**
31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	**1958**
32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	**1957**
33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	**1956**
34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	**1955**
35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	**1954**
36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	**1953**
37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	**1952**
38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	**1951**
39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	**1950**
40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	**1949**
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	**1948**
42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	**1947**
43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	**1946**
44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	**1945**
45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	**1944**
46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	**1943**
47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	**1942**
48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	**1941**
49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	**1940**
50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	**1939**
51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	**1938**
60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	**1929**
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	**1928**
62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	**1927**
63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	**1926**
64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	**1925**
65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	**1924**
66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	**1923**
67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	**1922**
68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	**1921**
69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	**1920**
70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	**1919**
71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	**1918**
72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	**1917**
73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	**1916**
74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	**1915**
		↑					↑					↑					↑			
		Midpoint					Midpoint					Midpoint					Midpoint			

Generation 2

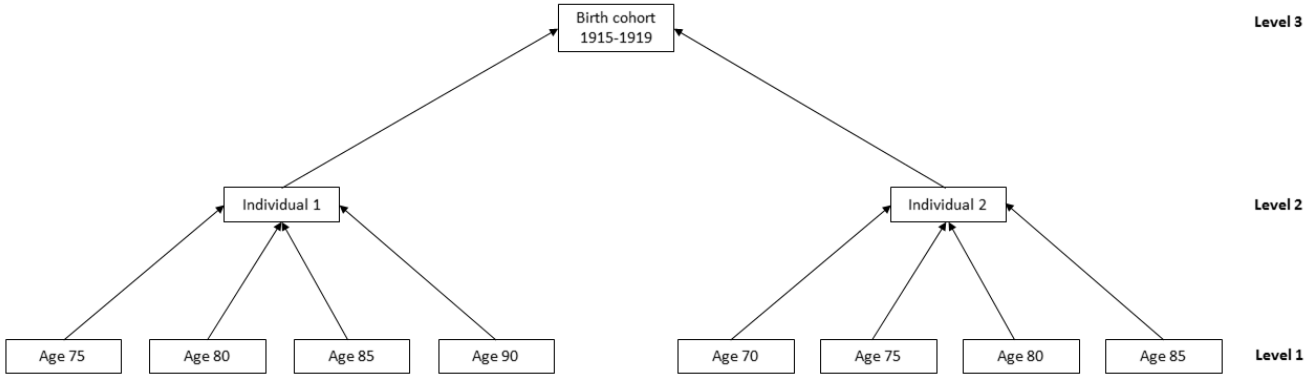
Generation 1

Observation period				
1989-1993	**1994-1998**	**1999-2003**	**2004-2008**	*Birth year*
19	24	29	34	**1972**
20	25	30	35	**1971**
21	26	31	36	**1970**
22	27	32	37	**1969**
23	28	33	38	**1968**
24	29	34	39	**1967**
25	30	35	40	**1966**
26	31	36	41	**1965**
27	32	37	42	**1964**
28	33	38	43	**1963**
29	34	39	44	**1962**
30	35	40	45	**1961**
31	36	41	46	**1960**
32	37	42	47	**1959**
33	38	43	48	**1958**
34	39	44	49	**1957**
35	40	45	50	**1956**
36	41	46	51	**1955**
37	42	47	52	**1954**
38	43	48	53	**1953**
39	44	49	54	**1952**
40	45	50	55	**1951**
41	46	51	56	**1950**
42	47	52	57	**1949**
43	48	53	58	**1948**
44	49	54	59	**1947**
45	50	55	60	**1946**
46	51	56	61	**1945**
47	52	57	62	**1944**
48	53	58	63	**1943**
49	54	59	64	**1942**
50	55	60	65	**1941**
51	56	61	66	**1940**
52	57	62	67	**1939**
53	58	63	68	**1938**
62	67	72	77	**1929**
63	68	73	78	**1928**
64	69	74	79	**1927**
65	70	75	80	**1926**
66	71	76	81	**1925**
67	72	77	82	**1924**
68	73	78	83	**1923**
69	74	79	84	**1922**
70	75	80	85	**1921**
71	76	81	86	**1920**
72	77	82	87	**1919**
73	78	83	88	**1918**
74	79	84	89	**1917**
75	80	85	90	**1916**
76	81	86	91	**1915**

Generation 2

Generation 1

Appendix 4D Visualization of the hierarchical data structure.



Appendix 4E Odds ratio with confidence intervals for the association between the exposures and hospitalisation. The most parsimonious models presented – with significant covariates only (at p<0.05).

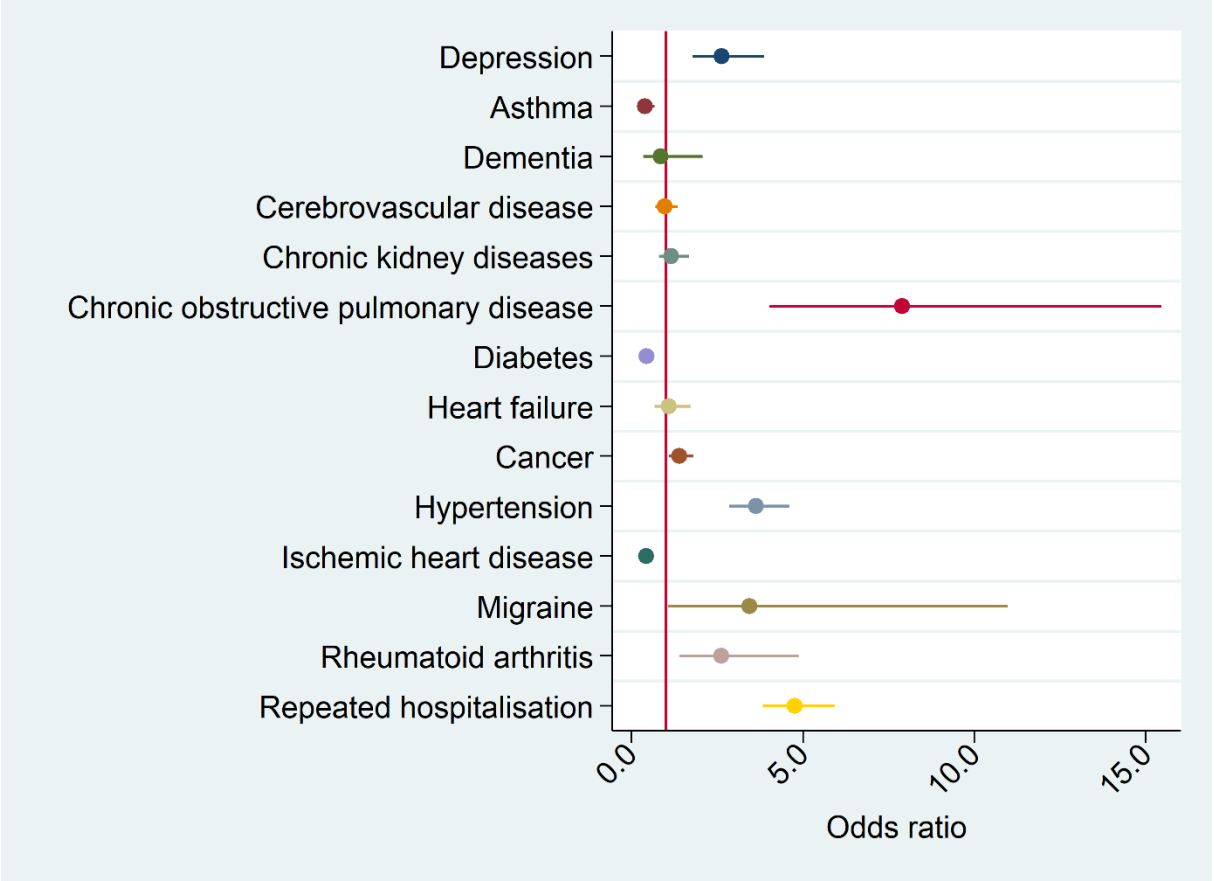
	Education	Income	SEP
Fixed effects			
Intercept	0.01 (0.01, 0.01)	0.02 (0.01, 0.02)	0.01 (0.01, 0.02)
Age	1.13 (1.12, 1.14)	1.13 (1.12, 1.14)	1.13 (1.12, 1.14)
Year-of-birth (YoB)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)	1.02 (1.01, 1.03)
Women (vs men)	0.88 (0.80, 0.96)	0.88 (0.80, 0.97)	0.88 (0.80, 0.96)
Parental SEP[a]			
Medium			1.11 (0.99, 1.27)
Low			1.24 (1.11, 1.39)
Parental education[b]			
Medium	1.21 (1.03, 1.41)		
Low	1.41 (1.21, 1.62)		
Parental income[c]		0.90 (0.85, 0.95)	
Random effects			
Level 2: individual (intercept)	3.39 (3.16, 3.65)	3.39 (3.13, 3.66)	3.29 (3.05, 3.60)
Level 3: family (intercept)	0.0002 (0.0001, 0.0004)	0.0004 (0.0002, 0.0007)	0.06 (0.04, 0.08)
Model fit			
DIC	27767.82	27705.63	27783.06
Observations	75,342	75,090	75,342

[a]Socioeconomic position (SEP) was defined in the same way as in the main analysis.

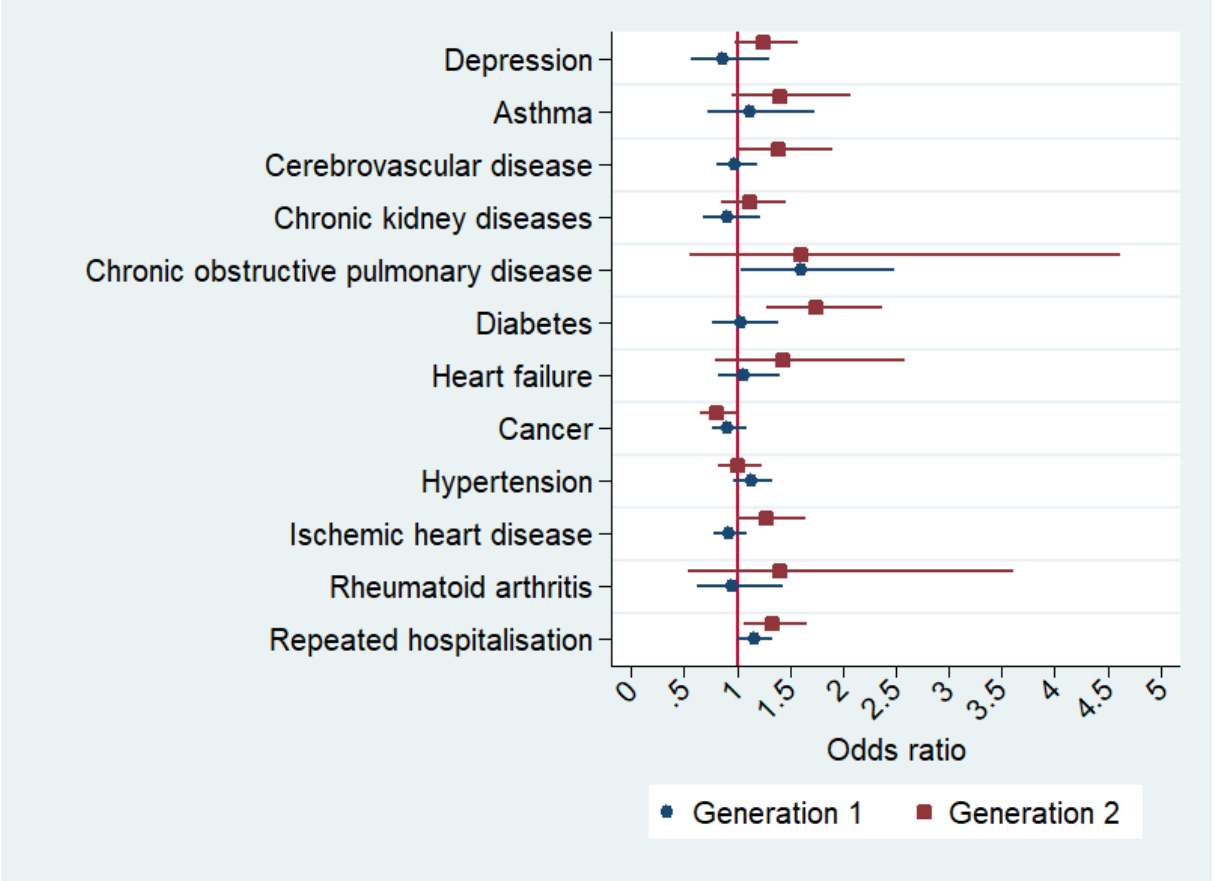
[b]A categorical variable (0 = High, 1 = Medium, 2 = Low), with categories grouped as: low (compulsory schooling), intermediate (upper-secondary schooling) and high (any postsecondary education). Parental education was measured as the highest lifetime education of either parent from Census and Education register in 1960-2008.

[c]A continuous individual disposable income standardised by age and gender in each calendar year (obtained from LOUISE and LISA registers 1990-2008 and Census 1970-1990) and then averaged across all available calendar years and both parents, when the parents were aged 25-65 and was obtained from Censuses 1970 and 1990 and from the LISA 1990–2008.

Appendix 4F Relative difference between children and parents (a reference group) in odds of hospitalisation due to individual conditions/group of conditions.



Appendix 4G Relative difference between low and medium/high SES (a reference group) in odds of hospitalisation due to individual conditions/group of conditions across both generations.



References

1. Office for National Statistics. Life Expectancy at Birth and at Age 65 by Local Areas in England and Wales: 2012 to 2014 2015 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/lifeexpectancyatbirthandatage65bylocalareasinenglandandwales/2015-11-04.
2. OECD. Health at a Glance 2017: OECD Indicators. Paris: OECD Publishing; 2017.
3. Eurostat. Population structure and ageing 2019 [Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php/Population_structure_and_ageing#Past_and_future_population_ageing_trends_in_the_EU.
4. Reither EN, Hauser RM, Yang Y. Do birth cohorts matter? Age-period-cohort analyses of the obesity epidemic in the United States. Soc Sci Med. 2009;69(10):1439-48.
5. "chronic.". In Merriam-Webster.com 2019 [Available from: https://www.merriam-webster.com.
6. Keyes KM, Utz RL, Robinson W, Li GH. What is a cohort effect? Comparison of three statistical methods for modeling cohort effects in obesity prevalence in the United States, 1971-2006. Soc Sci Med. 2010;70(7):1100-8.
7. Simpson JA, Weiner ESC. The Compact Oxford English Dictionary. 2nd ed. Oxford, England: Oxford University Press; 1991.
8. Tugwell P, Knottnerus JA. Multimorbidity and Comorbidity are now separate MESH headings. J Clin Epidemiol. 2019;105:vi-viii.
9. Organization WH. Health Impact Assessment. The determinants of health. 2019 [Available from: https://www.who.int/hia/evidence/doh/en/.
10. Doyal L. Sex and gender: The challenges for epidemiologists. Int J Health Serv. 2003;33(3):569-79.
11. Organization WH. Healthy life expectancy at birth. 2013.
12. National Institute for Health and Clinical Excellence. Common mental health disorders: identification and pathways to care. London: NICE; 2011.
13. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. J Gerontol a-Biol. 2004;59(3):255-63.
14. NICE. Multimorbidity. National Institute for Health and Care Excellence; 2017.
15. Crimmins EM. Lifespan and Healthspan: Past, Present, and Promise. Gerontologist. 2015;55(6):901-11.
16. Hiam L, Harrison D, McKee M, Dorling D. Why is life expectancy in England and Wales 'stalling'? Journal of Epidemiology & Community Health. 2018;72(5):404-8.
17. ONS. Healthcare expenditure, UK Health Accounts: 2017. 2017.
18. Miller RA. Genes Against Aging. J Gerontol a-Biol. 2012;67(5):495-502.
19. Sierra F, Hadley E, Suzman R, Hodes R. Prospects for Life Span Extension. Annu Rev Med. 2009;60:457-69.
20. Goldman DP, Cutler D, Rowe JW, Michaud PC, Sullivan J, Peneva D, et al. Substantial Health And Economic Returns From Delayed Aging May Warrant A New Focus For Medical Research. Health Affair. 2013;32(10):1698-705.
21. Gore PG, Kingston A, Johnson GR, Kirkwood TBL, Jagger C. New horizons in the compression of functional decline. Age Ageing. 2018;47(6):764-8.
22. Jagger C. Compression or expansion of morbidity - what clues the future hold? Age Ageing. 2000;29(2):93-4.
23. Fries JF. Aging, natural death, and the compression of morbidity. N Engl J Med. 1980;303(3):130-5.
24. Gruenberg EM. The failure of success. 1977;55:3-24.

25. Kramer M. The rising pandemic of mental disorders and associated chronic diseases and disabilites. Acta Psychiatrica Scandinavica Supplementum 1980;62:282–97.
26. Manton KG. Changing concepts of morbidity and mortality in the elderly population. Milbank Mem Fund Q Health Soc. 1982;60(2):183-244.
27. Fries JF. Aging, natural death, and the compression of morbidity. New England Journal of Medicine. 1980;303(3):130-5.
28. Rice DP, Haan MN, Selby JV, Satariano WA. Research agenda on the compression of morbidity. Journal of Aging and Health. 1991;3(2):301-4
29. Olshansky SJ, Rudberg MA, Carnes BA, Cassel CK, Brody JA. Trading off longer life for worsening health: The expansion of morbidity hypothesis. Journal of Aging and Health. 1991;3(2):194-216.
30. Howse K. Increasing life expectancy and the compression of morbidity: A critical review of the debate. Working Paper No.26. Oxford: Oxford Institute of Ageing, University of Oxford; 2006.
31. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. Lancet. 2015;385(9976):1397-405.
32. Leung AA, Nerenberg K, Daskalopoulou SS, McBrien K, Zarnke KB, Dasgupta K, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol. 2016;32(5):569-88.
33. Manton KG. Changing concepts of morbidity and mortality in the elderly population. Milbank Memorial Fund Quarterly. 1982;60(2):183-244.
34. Freedman VA, Spillman BC, Andreski PM, Cornman JC, Crimmins EM, Kramarow E, et al. Trends in late-life activity limitations in the United States: an update from five national surveys. Demography. 2013;50(2):661-71.
35. Chatterji S, Byles J, Cutler D, Seeman T, Verdes E. Health, functioning, and disability in older adults-present status and future implications. Lancet. 2015;385(9967):563-75.
36. Crimmins EM, Beltrán-Sánchez H. Mortality and morbidity trends: is there compression of morbidity? Journal of Gerontology: Social Sciences. 2010;66B(1):75–86.
37. Johnson W, Li L, Kuh D, Hardy R. How Has the Age-Related Process of Overweight or Obesity Development Changed over Time? Co-ordinated Analyses of Individual Participant Data from Five United Kingdom Birth Cohorts. Plos Med. 2015;12(5).
38. Ploubidis GB, Sullivan A, Brown M, Goodman A. Psychological distress in mid-life: evidence from the 1958 and 1970 British birth cohorts. Psychological Medicine. 2017;47(2):291-303.
39. Ploubidis GB, B. P. Self-rated Health Over the Life Course: Evidence from the 1958 and 1970 British Birth Cohorts. In: Ploubidis GB, Pongiglione B, De Stavola B, Daniel R, Benova L, Grundy E, et al., editors. Pathways to Health2019.
40. Wills AK, Lawlor DA, Matthews FE, Sayer AA, Bakra E, Ben-Shlomo Y, et al. Life course trajectories of systolic blood pressure using longitudinal data from eight UK cohorts. Plos Med. 2011;8(6):e1000440.
41. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93.
42. Ben-Shlomo Y, Cooper R, Kuh D. The last two decades of life course epidemiology, and its relevance for research on ageing. Int J Epidemiol. 2016;45(4):973-88.
43. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577-80.
44. Fuhrmann D, Knoll LJ, Blakemore SJ. Adolescence as a Sensitive Period of Brain Development. Trends in Cognitive Sciences. 2015;19(10):558-66.
45. Kadlecová P, Andel R, Mikulik R, Handing EP, Pedersen NL. Alcohol consumption at midlife and risk of stroke during 43 years of follow-up: cohort and twin analyses. Stroke. 2015;46(3):627–33.

46. Hardy R, Sovio U, King VJ, Skidmore PML, Helmsdal G, Olsen SF, et al. Birthweight and blood pressure in five European birth cohort studies: an investigation of confounding factors. European Journal of Public Health. 2006;16(1):21-30.
47. Lanier JB, Bury DC, Richardson SW. Diet and Physical Activity for Cardiovascular Disease Prevention. Am Fam Physician. 2016;93(11):919-24.
48. Lynch J, Smith GD. A life course approach to chronic disease epidemiology. Annual Review of Public Health. 2005;26:1-35.
49. Cohen S, Janicki-Deverts D, Chen E, Matthews KA. Childhood socioeconomic status and adult health. Ann N Y Acad Sci. 2010;1186:37-55.
50. Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. Journal of Epidemiology and Community Health. 2003;57(10):778-83.
51. Kuh D., Network NDoANP. A life course approach to healthy ageing, frailty and capability. Journal of Gerontology: Medical Sciences. 2007;62A:717–21.
52. Burton-Jeangros C, Cullati S, Sacker A, Blane D. A Life Course Perspective on Health Trajectories and Transitions. Cham, Switzerland: Springer; 2015.
53. Beltran-Sanchez H, Razak F, Subramanian SV. Going beyond the disability-based morbidity definition in the compression of morbidity framework. Glob Health Action. 2014;7:24766.
54. Pongiglione B, De Stavola BL, Ploubidis GB. A Systematic Literature Review of Studies Analyzing Inequalities in Health Expectancy among the Older Population. PLoS ONE. 2015;10(6):e0130747.
55. UN World Health Organization. World Report on Disability. Geneva (Switzerland): World Health Organization; 2011.
56. Parker MG, Thorslund M. Health trends in the elderly population: getting better and getting worse. Gerontologist. 2007;47(2):150-8.
57. Singh-Manoux A, Martikainen P, Ferrie J, Zins M, Marmot M, Goldberg M. What does self rated health measure? Results from the British Whitehall II and French Gazel cohort studies. Journal of Epidemiology and Community Health. 2006;60(4):364–72.
58. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. J Health Soc Behav. 1997;38(1):21-37.
59. Johnston DW, Propper C, Shields MA. Comparing subjective and objective measures of health: Evidence from hypertension for the income/health gradient. J Health Econ. 2009;28(3):540-52.
60. Yang Y, Land KC. Age-period-cohort analysis: new models, methods, and empirical applications. New York, USA: CRC Press; 2013.
61. Bell A, Jones K. The impossibility of separating age, period and cohort effects. Soc Sci Med. 2013;93:163-5.
62. Glenn ND. Cohort Analysis. London: Sage; 2005.
63. Sullivan A, Brown M, Bann D. Guest Editorial: Generation X enters middle age. Longitudinal and Life Course Studies. 2015;6(2):120 – 30.
64. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study.[Erratum appears in BMJ Open. 2016;6(5):e010210corr1; PMID: 27147381]. BMJ Open. 2016;6(1):e010210.
65. Hall KD. Did the Food Environment Cause the Obesity Epidemic? Obesity (Silver Spring). 2018;26(1):11-3.
66. Gluckman PD, Hanson MA. Developmental origins of disease paradigm: A mechanistic and evolutionary perspective. Pediatr Res. 2004;56(3):311-7.
67. Crimmins E, Kim JK, Vasunilashorn S. Biodemography: New Approaches to Understanding Trends and Differences in Population Health and Mortality. Demography. 2010;47:S41-S64.
68. Marmot M. Inclusion health: addressing the causes of the causes. Lancet. 2018;391(10117):186-8.

69. Psaltopoulou T, Hatzis G, Papageorgiou N, Androulakis E, Briasoulis A, Tousoulis D. Socioeconomic status and risk factors for cardiovascular disease: Impact of dietary mediators. Hell J Cardiol. 2017;58(1):32-42.
70. Joffe M, Gambhir M, Chadeau-Hyam M, Vineis P. Causal diagrams in systems epidemiology. Emerg Themes Epidemiol. 2012;9(1):1.
71. Lachman ME, Agrigoroaei S. Promoting Functional Health in Midlife and Old Age: Long-Term Protective Effects of Control Beliefs, Social Support, and Physical Exercise. Plos One. 2010;5(10).
72. Lachman ME, Teshale S, Agrigoroaei S. Midlife as a pivotal period in the life course: Balancing growth and decline at the crossroads of youth and old age. Int J Behav Dev. 2015;39(1):20-31.
73. Li L, Hardy R, Kuh D, Power C. Life-course body mass index trajectories and blood pressure in mid life in two British birth cohorts: stronger associations in the later-born generation. Int J Epidemiol. 2015;44(3):1018-26.
74. Cutler DM, Lleras-Muney A, Vogl T. Socioeconomic Status and Health: Dimensions and Mechanisms. In: Glied S, Smith P, editors. The Oxford Handbook of Health Economics. Oxford: Oxford University Press; 2011.
75. Moscelli G, Siciliania S, Gutacker N, Cookson R. Socioeconomic inequality of access to healthcare: Does choice explain the gradient? J Health Econ. 2018;57:290-314.
76. Burgard SA, Lin KY. Bad Jobs, Bad Health? How Work and Working Conditions Contribute to Health Disparities. Am Behav Sci. 2013;57(8).
77. Case A, Fertig A, Paxson C. The lasting impact of childhood health and circumstance. J Health Econ. 2005;24(2):365-89.
78. Calvin CM, Batty GD, Der G, Brett CE, Taylor A, Pattie A, et al. Childhood intelligence in relation to major causes of death in 68 year follow-up: prospective population study. BMJ. 2017;357:j2708.
79. Van Oyen H, Cox B, Demarest S, Deboosere P, Lorant V. Trends in health expectancy indicators in the older adult population in Belgium between 1997 and 2004. European Journal of Ageing 2008;5(2):137–46.
80. Jeune B, Bronnum-Hansen H. Trends in health expectancy at age 65 for various health indicators, 1987–2005, Denmark. European Journal of Ageing. 2008;5:279–85.
81. Moe JO, Hagen TP. Trends and variation in mild disability and functional limitations among older adults in Norway, 1986–2008. European Journal of Ageing. 2011;8(1):49–61.
82. Solé-Auró A, Alcañiz M. Are we living longer but less healthy? Trends in mortality and morbidity in Catalonia (Spain), 1994–2011. European Journal of Ageing 2015;12(1):61–70.
83. Sagardui-Villamor J, Guallar-Castillon P, Garcia-Ferruelo M, Banegas JR, Rodriguez-Artalejo F. Trends in disability and disability-free life expectancy among elderly people in Spain: 1986-1999. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2005;60(8):1028-34.
84. Cambois E, Clavel A, Romieu I, Robine JM. Trends in disability-free life expectancy at age 65 in France: consistent and diverging patterns according to the underlying disability measure. European Journal of Ageing. 2008;5:287–98.
85. Hossin MZ, Ostergren O, Fors S. Is the Association Between Late Life Morbidity and Disability Attenuated Over Time? Exploring the Dynamic Equilibrium of Morbidity Hypothesis. J Gerontol B-Psychol. 2019;74(8):E97-E106.
86. Murray CJL, Richards MA, Newton JN, Fenton KA, Anderson HR, Atkinson C, et al. UK health performance: Findings of the Global Burden of Disease Study 2010. The Lancet. 2013;381(9871):997-1020.
87. Newton JN, Briggs AD, Murray CJ, Dicker D, Foreman KJ, Wang H, et al. Changes in health in England, with analysis by English regions and areas of deprivation, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2257-74.
88. Lawlor DA, Tilling K, Smith GD. Triangulation in aetiological epidemiology. Int J Epidemiol. 2016;45(6):1866-86.

89. Miilunpalo S, Vuori I, Oja P, Pasanen M, Urponen H. Self-rated health status as a health measure: The predictive value of self-reported health status on the use of physician services and on mortality in the working-age population. Journal of Clinical Epidemiology. 1997;50(5):517-28.
90. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2009 [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
91. Scarborough P, Wickramasinghe K, Bhatnagar P, Rayner M. Trends in coronary heart disease 1961-2011. London: British Heart Foundation; 2011.
92. Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago?: Two population-based cross-sectional studies. Rheumatology. 2005;44(7):890-95.
93. Palmer KT, Walsh K, Bendall H, Cooper C, Coggon D. Back pain in Britain: comparison of two prevalence surveys at an interval of 10 years. BMJ. 2000;320:1577–8.
94. Gatling W, Budd S, Walters D, Mullee MA, Goddard JR, Hill RD. Evidence of an increasing prevalence of diagnosed diabetes mellitus in the Poole area from 1983 to 1996. Diabetic Medicine. 1998;15(12):1015-21.
95. Thomas MC, Hardoon SL, Papacosta AO, Morris RW, Wannamethee SG, Sloggett A, et al. Evidence of an accelerating increase in prevalence of diagnosed Type 2 diabetes in British men, 1978-2005. Diabetic Medicine. 2009;26(8):766-72.
96. Lampe FC, Morris RW, Whincup PH, Walker M, Ebrahim S, Shaper AG. Is the prevalence of coronary heart disease falling in British men? Heart. 2001;86(5):499-05.
97. Jarvis C, Tinker A. Trends in old age morbidity and disability in Britain. Ageing & Society. 1999;19(5):603-27.
98. Bebbington AC, Darton RA. Healthy life expectancy in England and Wales: recent evidence. PSSRU Discussion Paper 1205. Canterbury, Kent: PERSONAL SOCIAL SERVICES RESEARCH UNIT; 1996.
99. Kelly S, Baker A, Gupta S. Healthy life expectancy in Great Britain, 1980–96, and its use as an indicator in United Kingdom Government strategies. Health Statistics Quarterly 07. London: ONS; 2000.
100. Bebbington AC. The Expectation of life without disability in England and Wales. Soc Sci Med. 1988;27(4):321-6.
101. Robine JM, Ritchie K. Healthy life expectancy: evaluation of global indicator of change in population health. BMJ. 1991;302(6774):457-60.
102. Jagger C, Clarke M, Clarke SJ. Getting older--feeling younger: the changing health profile of the elderly. Internation Journal of Epidemiology. 1991;20(1):234-8.
103. Spiers N, Jagger C, Clarke M. Physical function and perceived health: cohort differences and interrelationships in older people. The Journals of Gerontology Series B, Psychological Sciences and Social Sciences. 1996;51(5):226-33.
104. Bajekal M. Healthy life expectancy by area deprivation: magnitude and trends in England, 1994-1999. Health statistics quarterly. 2005(25):18-27.
105. Davies AR, Smeeth L, Grundy EM. Contribution of changes in incidence and mortality to trends in the prevalence of coronary heart disease in the UK: 1996 2005. European Heart Journal. 2007;28(17):2142-7.
106. Simpson CR, Hannaford PC, Williams D. Evidence for inequalities in the management of coronary heart disease in Scotland. Heart. 2005;91(5):630-4.
107. Jivraj S, Goodman A, Pongiglione B, Ploubidis GB. Living longer but not necessairly healthier: The joint progress of health and mortality in the working age population in England. Manuscript submitted for publication. under review.
108. Jagger C, Matthews R, Matthews F, Robinson T, Robine JM, Brayne C. The burden of diseases on disability-free life expectancy in later life. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2007;62(4):408-14.

109. Lee S, Shafe AC, Cowie MR. UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database. BMJ Open. 2011;1(2):e000269.
110. Evans JM, Barnett KN, Ogston SA, Morris AD. Increasing prevalence of type 2 diabetes in a Scottish population: effect of increasing incidence or decreasing mortality? Diabetologia. 2007;50(4):729-32.
111. Gonzalez EL, Johansson S, Wallander MA, Rodriguez LA. Trends in the prevalence and incidence of diabetes in the UK: 1996-2005. Journal of Epidemiology and Community Health. 2009;63(4):332-6.
112. Groot W, van den Brink HM. Health-adjusted life expectancy of the British population. Applied Economics. 2008;40(11):1373-86.
113. Imkampe AK, Gulliford MC. Increasing socio-economic inequality in type 2 diabetes prevalence--repeated cross-sectional surveys in England 1994-2006. European Journal of Public Health. 2011;21(4):484-90.
114. Lafortune G, Balestat G, the Disability Study Expert Group Members. Trends in Severe Disability Among Elderly People: Assessing the Evidence in 12 OECD Countries and the Future Implications. Paris: Organisation for Economic Co-operation and Development 2007.
115. Lusignan S, Sismanidis C, Carey IM, DeWilde S, Richards N, Cook DG. Trends in the prevalence and management of diagnosed type 2 diabetes 1994-2001 in England and Wales. BMC Family Practice. 2005;6(1):13.
116. Morgan CL, Peters JR, Currie CJ. The changing prevalence of diagnosed diabetes and its associated vascular complications in a large region of the UK. Diabetic Medicine. 2010;27(6):673-8.
117. Newnham A, Ryan R, Khunti K, Majeed A. Prevalence of diagnosed diabetes mellitus in general practice in England and Wales, 1994 to 1998. Health Statistics Quarterly 2002;14:5-13.
118. Samaranayakaa S, Gulliforda MC. Trends in cardiovascular risk factors among people with diabetes in a population based study, Health Survey for England 1994–2009. Primary Care Diabetes 2013;7:193–8.
119. Bhatnagar P, Wickramasinghe K, Wilkins E, Townsend N. Trends in the epidemiology of cardiovascular disease in the UK. Heart. 2016;102(24):1945-52.
120. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, et al. Recent trends in physician diagnosed COPD in women and men in the UK. Thorax. 2000;55(9):789-94.
121. Soriano JB, Kiri VA, Maier WC, Strachan D. Increasing prevalence of asthma in UK primary care during the 1990s. International Journal of Tuberculosis and Lung Disease. 2003;7(5):415-21.
122. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. Journal of the Royal Society of Medicine. 2010;103(3):98-106.
123. Simpson CR, Hippisley-Cox J, Sheikh A. Trends in the epidemiology of chronic obstructive pulmonary disease in England: a national study of 51 804 patients. British Journal of General Practice. 2010;60(576):277-84.
124. British Lung Foundation. Lung cancer statistics 2017 [Available from: https://statistics.blf.org.uk/lung-cancer.
125. Ahmadi-Abhari S, Guzman-Castillo M, Bandosz P, Shipley MJ, Muniz-Terrera G, Singh-Manoux A, et al. Temporal trend in dementia incidence since 2002 and projections for prevalence in England and Wales to 2040: modelling study. BMJ. 2017;358:j2856.
126. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2013;382(9902):1405-12.
127. Jagger C. Trends in life expectancy and healthy life expectancy. Future of an ageing population: evidence review. London: Foresight, Government Office for Science; 2015.
128. Smith MP, Olatunde O, White C. Inequalities in disability-free life expectancy by area deprivation: England, 2001–04 and 2005–08. Health Statistics Quarterly. 2010;48:1-22.

129. Wohland P, Rees P, Gillies C, Alvanides S, Matthews FE, O'Neill V, et al. Drivers of inequality in disability-free expectancy at birth and age 85 across space and time in Great Britain. Journal of epidemiology and community health. 2014;68(9):826-33.
130. Morciano M, Hancock RM, Pudney SE. Birth-cohort trends in older-age functional disability and their relationship with socio-economic status:Evidence from a pooling of repeated cross-sectional population-based studies for the UK. Social Science & Medicine 2015;136-137:1-9.
131. Congdon P. Modelling changes in small area disability free life expectancy: Trends in London wards between 2001 and 2011. Statistics in Medicine. 2014;33(29):5138-50.
132. Jagger C, Matthews FE, Wohland P, Fouweather T, Stephan BC, Robinson L, et al. A comparison of health expectancies over two decades in England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2016;387(10020):779-86.
133. Donald IP, Foy C, Jagger C. Trends in disability prevalence over 10 years in older people living in Gloucestershire. Age Ageing. 2010;39(3):337-42.
134. Martin LG, Schoeni RF, Andreski PM, Jagger C. Trends and inequalities in late-life health and functioning in England. Journal of Epidemiology and Community Health. 2012;66(10):874-80.
135. Public Health England. Chapter 1: life expectancy and healthy life expectancy. Health profile for England A report combining Public Health England (PHE) data and knowledge on the health of the population in England in 2017: Public Health England 2017.
136. Fleming KM, Aithal GP, Solaymani-Dodaran M, Card TR, West J. Incidence and prevalence of cirrhosis in the United Kingdom, 1992-2001: a general population-based study. Journal of Hepatology. 2008;49(5):732-8.
137. Hamer M, Kengne AP, Batty GD, Cooke D, Stamatakis E. Temporal trends in diabetes prevalence and key diabetes risk factors in Scotland, 2003-2008. Diabetic Medicine. 2011;28(5):595-8.
138. Public Health England. Chapter 2: major causes of death and how they have changed. 2017.
139. Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. Br J Gen Pract. 2016;66(644):e152-7.
140. Horsfall L, Petersen I, Walters K, Schrag A. Time trends in incidence of Parkinson's disease diagnosis in UK primary care. Journal of Neurology. 2013;260(5):1351-7.
141. The NHS Confederation. Investing in General Practice: The New General Medical Services Contract.
142. Alageel S, Wright AJ, Gulliford MC. Changes in cardiovascular disease risk and behavioural risk factors before the introduction of a health check programme in England. Preventive Medicine. 2016;91:158-63.
143. Verbrugge LM. Disability Experience and Measurement. Journal of Aging and Health. 2016;28(7):1124-58.
144. Eurostat. Disability statistics - prevalence and demographics. 2016.
145. Pongiglione B, Ploubidis GB, De Stavola BL. Levels of disability in the older population of England: Comparing binary and ordinal classifications. Disability and Health Journal. 2017;10(4):509-17.
146. Maestas N, Mullen KJ, Powell D. The Effect of Population Aging on Economic Growth, the Labor Force and Productivity. Santa Monica, CA: RAND Corporation; 2016.
147. McCormick J, Clifton J, Sachrajda A, Cherti M, McDowell E. Getting On: Well-being in later life. London: Institute for Public Policy Research 2009.
148. Age UK. Healthy Ageing Evidence Review. London: Age UK; 2011.
149. Wadsworth M, Kuh D, Richards M, Hardy R. Cohort Profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). Int J Epidemiol. 2006;35(1):49-54.
150. Kuh D, Wong A, Shah I, Moore A, Popham M, Curran P, et al. The MRC National Survey of Health and Development reaches age 70: maintaining participation at older ages in a birth cohort study. Eur J Epidemiol. 2016;31(11):1135-47.

151. Kuh D, Pierce M, Adams J, Deanfield J, Ekelund U, Friberg P, et al. Cohort profile: updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. Int J Epidemiol. 2011;40(1):e1-9.
152. Stafford M, Black S, Shah I, Hardy R, Pierce M, Richards M, et al. Using a birth cohort to study ageing: representativeness and response rates in the National Survey of Health and Development. Eur J Ageing. 2013;10(2):145-57.
153. Power C, Elliott J. Cohort profile: 1958 British birth cohort (National Child Development Study). Int J Epidemiol. 2006;35(1):34-41.
154. Plewis I, Calderwood L, Hawkes D, Nathan G. Changes in the NCDS and BCS70 populations and samples over time. CLS Technical Report. London: CLS, Institute of Education; 2004.
155. Elliott J, Shepherd P. Cohort profile: 1970 British Birth Cohort (BCS70). International Journal of Epidemiology. 2006;35(4):836-43.
156. Mostafa T, Wiggins R. The impact of attrition and non-response in birth cohort studies: a need to incorporate missingness strategies. Longitudinal and Life Course Studies. 2015;6(2):131 – 46

157. Koupil I. The Uppsala studies on developmental origins of health and disease. J Intern Med. 2007;261(5):426-36.
158. Koupil I, Goodman A. Health Equity: A life course approach. Public Service Review: European Union. 2011;11:382-3.
159. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
160. Goodman A, Koupil I. Social and biological determinants of reproductive success in Swedish males and females born 1915–1929. . Evol Hum Behav 2009;30:329–41.
161. Rajaleid K, Manor O, Koupil I. Does the strength of the association between foetal growth rate and ischaemic heart disease mortality differ by social circumstances in early or later life? J Epidemiol Community Health. 2008;62(5):e6.
162. Goodman A, Koupil I, Lawson DW. Low fertility increases descendant socioeconomic position but reduces long-term fitness in a modern post-industrial society. Proc Biol Sci. 2012;279(1746):4342-51.
163. Kingston A, Robinson L, Booth H, Knapp M, Jagger C, Project M. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age Ageing. 2018;47(3):374-80.
164. Tran J, Norton R, Conrad N, Rahimian F, Canoy D, Nazarzadeh M, et al. Patterns and temporal trends of comorbidity among adult patients with incident cardiovascular disease in the UK between 2000 and 2014: A population-based cohort study. Plos Med. 2018;15(3).
165. World Health Organization. Multimorbidity: Technical Series on Safer Primary Care. Geneva: World Health Organization; 2016.
166. Canizares M, Hogg-Johnson S, Gignac MAM, Glazier RH, Badley EM. Increasing Trajectories of Multimorbidity Over Time: Birth Cohort Differences and the Role of Changes in Obesity and Income. J Gerontol B-Psychol. 2018;73(7):1303-14.
167. Lehnert T, Heider D, Leicht H, Heinrich S, Corrieri S, Luppa M, et al. Review: health care utilization and costs of elderly persons with multiple chronic conditions. Med Care Res Rev. 2011;68(4):387-420.
168. Academy of Medical Sciences. Multimorbidity: a priority for global health research. London: Academy of Medical Sciences; 2018.
169. Stirland LE, Gonzalez-Saavedra L, Mullin DS, Ritchie CW, Muniz-Terrera G, Russ TC. Measuring multimorbidity beyond counting diseases: systematic review of community and population studies and guide to index choice. BMJ. 2020;368:m160.

170. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW. Defining and measuring multimorbidity: a systematic review of systematic reviews. European Journal of Public Health. 2019;29(1):182-9.
171. Diederichs C, Berger K, Bartels DB. The Measurement of Multiple Chronic Diseases-A Systematic Review on Existing Multimorbidity Indices. J Gerontol a-Biol. 2011;66(3):301-11.
172. National Institute for Health and Care Excellence (NICE). Multimorbidity: clinical assessment and management. 2016.
173. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, Determinants and Patterns of Multimorbidity in Primary Care: A Systematic Review of Observational Studies. Plos One. 2014;9(7).
174. Fortin M, Stewart M, Poitras ME, Almirall J, Maddocks H. A Systematic Review of Prevalence Studies on Multimorbidity: Toward a More Uniform Methodology. Ann Fam Med. 2012;10(2):142-51.
175. van den Akker M, Buntinx F, Roos S, Knottnerus JA. Problems in determining occurrence rates of multimorbidity. Journal of Clinical Epidemiology. 2001;54(7):675-9.
176. Salive ME. Multimorbidity in Older Adults. Epidemiol Rev. 2013;35:75-83.
177. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. British Journal of General Practice. 2011;61(582).
178. Department of Health. Long term conditions compendium of information: third edition. 2012.
179. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43.
180. Department of Health, NHS England, England PH. Comorbidities: a framework of principles for system-wide action. 2014.
181. Lehman BJ, David DM, Gruber JA. Rethinking the biopsychosocial model of health: Understanding health as a dynamic system. Soc Personal Psychol. 2017;11(8).
182. Solis CB, Kelly-Irving M, Fantin R, Darnaudery M, Torrisani J, Lang T, et al. Adverse childhood experiences and physiological wear- and-tear in midlife: Findings from the 1958 British birth cohort. P Natl Acad Sci USA. 2015;112(7):E738-E46.
183. Blane D, Kelly-Irving M, d'Errico A, Bartley M, Montgomery S. Social-biological transitions: how does the social become biological? Longitudinal and Life Course Studies. 2013;4(2):136–46.
184. Gilbert LK, Breiding MJ, Merrick MT, Thompson WW, Ford DC, Dhingra SS, et al. Childhood adversity and adult chronic disease: an update from ten states and the District of Columbia, 2010. Am J Prev Med. 2015;48(3):345-9.
185. Anda RF, Butchart A, Felitti VJ, Brown DW. Building a framework for global surveillance of the public health implications of adverse childhood experiences. Am J Prev Med. 2010;39(1):93-8.
186. Gondek D, Ning K, Ploubidis GB, Nasim B, Goodman A. The impact of health on economic and social outcomes in the United Kingdom: A scoping literature review. Plos One. 2018;13(12).
187. Kristensen P. Social Inequalities in Health: New Evidence and Policy Implications. BMJ. 2006;333(7579):1177-.
188. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav R. 2010;35(1):2-16.
189. Colman I, Jones PB, Kuh D, Weeks M, Naicker K, Richards M, et al. Early development, stress and depression across the life course: pathways to depression in a national British birth cohort. Psychological Medicine. 2014;44(13):2845-54.
190. Pote I, Doubell L, Brims L, Larbie J, Stock L, B. L. Engaging disadvantaged and vulnerable parents: An evidence review. 2019.
191. Sauce B, Matzel LD. The Paradox of Intelligence: Heritability and Malleability Coexist in Hidden Gene-Environment Interplay. Psychol Bull. 2018;144(1):26-47.

192. Ramsden S, Richardson FM, Josse G, Thomas MSC, Ellis C, Shakeshaft C, et al. Verbal and non-verbal intelligence changes in the teenage brain (vol 479, pg 113, 2011). Nature. 2012;485(7400):666-.
193. Kendler KS, Turkheimer E, Ohlsson H, Sundquist J, Sundquist K. Family environment and the malleability of cognitive ability: A Swedish national home-reared and adopted-away cosibling control study. P Natl Acad Sci USA. 2015;112(15):4612-7.
194. Heckman JJ, Stixrud J, Urzua S. The effects of cognitive and noncognitive abilities on labor market outcomes and social behavior. J Labor Econ. 2006;24(3):411-82.
195. Ford CA, Mirman JH, Garcia-Espana JF, Thiel MCF, Friedrich E, Salek EC, et al. Effect of Primary Care Parent-Targeted Interventions on Parent-Adolescent Communication About Sexual Behavior and Alcohol Use A Randomized Clinical Trial. Jama Netw Open. 2019;2(8).
196. Jensen B, Currie C, Dyson A, al. e. European Review of Social Determinants of Health and the Health Divide in the WHO European Region. Copenhagen, Denmark: WHO Regional Office for Europe; 2013.
197. Patalay P, Gondek D, Moltrecht B, Giese L, Curtin C, Stankovic M, et al. Mental health provision in schools: approaches and interventions in 10 European countries. Glob Ment Health (Camb). 2017;4:e10.
198. Gondek D, Lereya T. What Are the Challenges Involved in the Prevention of Depression in Schools? Contemporary School Psychology. 2018;22(4):395-400.
199. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58:295–300.
200. Lebenbaum M, Zaric GS, Thind A, Sarma S. Trends in obesity and multimorbidity in Canada. Prev Med. 2018;116:173-9.
201. Sellers R, Warne N, Pickles A, Maughan B, Thapar A, Collishaw S. Cross-cohort change in adolescent outcomes for children with mental health problems. J Child Psychol Psychiatry. 2019;60(7):813-21.
202. Gale CR, Hatch SL, Batty GD, Deary IJ. Intelligence in childhood and risk of psychological distress in adulthood: The 1958 National Child Development Survey and the 1970 British Cohort Study. Intelligence. 2009;37(6):592-9.
203. Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. J Gerontol a-Biol. 2016;71(2):205-14.
204. Sinnige J, Braspenning J, Schellevis F, Stirbu-Wagner I, Westert G, Korevaar J. The Prevalence of Disease Clusters in Older Adults with Multiple Chronic Diseases - A Systematic Literature Review. Plos One. 2013;8(11).
205. Mujica-Mota RE, Roberts M, Abel G, Elliott M, Lyratzopoulos G, Roland M, et al. Common patterns of morbidity and multi-morbidity and their impact on health-related quality of life: evidence from a national survey. Qual Life Res. 2015;24(4):909-18.
206. Vetrano DL, Rizzuto D, Calderon-Larranaga A, Onder G, Welmer AK, Bernabei R, et al. Trajectories of functional decline in older adults with neuropsychiatric and cardiovascular multimorbidity: A Swedish cohort study. Plos Med. 2018;15(3).
207. Gallo JJ, Hwang S, Joo JH, Bogner HR, Morales KH, Bruce ML, et al. Multimorbidity, Depression, and Mortality in Primary Care: Randomized Clinical Trial of an Evidence-Based Depression Care Management Program on Mortality Risk. J Gen Intern Med. 2016;31(4):380–6.
208. Bobo WV, Yawn BP, St Sauver JL, Grossardt BR, Boyd CM, Rocca WA. Prevalence of Combined Somatic and Mental Health Multimorbidity: Patterns by Age, Sex, and Race/Ethnicity. J Gerontol a-Biol. 2016;71(11):1483-91.
209. Cassell A, Edwards D, Harshfield A, Rhodes K, Brimicombe J, Payne R, et al. The epidemiology of multimorbidity in primary care: a retrospective cohort study. British Journal of General Practice. 2018;68(669):E245-E51.

210. Booth HP, Prevost AT, Gulliford MC. Impact of body mass index on prevalence of multimorbidity in primary care: cohort study. Fam Pract. 2014;31(1):38-43.
211. Johnston MC, Black C, Mercer SW, Prescott GJ, Crilly MA. Impact of educational attainment on the association between social class at birth and multimorbidity in middle age in the Aberdeen Children of the 1950s cohort study. Bmj Open. 2019;9(1).
212. Humphreys J, Jameson K, Cooper C, Dennison E. Early-life predictors of future multi-morbidity: results from the Hertfordshire Cohort. Age Ageing. 2018;47(3):474-8.
213. Neeleman J, Sytema S, Wadsworth M. Propensity to psychiatric and somatic ill-health: evidence from a birth cohort. Psychol Med. 2002;32(5):793-803.
214. Belbasis L, Savvidou MD, Kanu C, Evangelou E, Tzoulaki I. Birth weight in relation to health and disease in later life: an umbrella review of systematic reviews and meta-analyses. Bmc Med. 2016;14.
215. Mensah FK, Hobcraft J. Childhood deprivation, health and development: associations with adult health in the 1958 and 1970 British prospective birth cohort studies. Journal of Epidemiology and Community Health. 2008;62(7):599-606.
216. Cooper R, Power C. Sex differences in the associations between birthweight and lipid levels in middle-age: Findings from the 1958 British birth cohort. Atherosclerosis. 2008;200(1):141-9.
217. Hardy R, Kuh D, Langenberg C, Wadsworth MEJ. Birthweight, childhood social class, and change in adult blood pressure in the 1946 British birth cohort. Lancet. 2003;362(9391):1178-83.
218. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. Int J Epidemiol. 2013;42(5):1511-9.
219. Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol. 2006;16(2):91-104.
220. Singh-Manoux A, Ferrie JE, Lynch JW, Marmot M. The role of cognitive ability (intelligence) in explaining the association between socioeconomic position and health: Evidence from the Whitehall II prospective cohort study. Am J Epidemiol. 2005;161(9):831-9.
221. Park MH, Falconer C, Viner RM, Kinra S. The impact of childhood obesity on morbidity and mortality in adulthood: a systematic review. Obes Rev. 2012;13(11):985-1000.
222. Henderson M, Richards M, Stansfeld S, Hotopf M. The association between childhood cognitive ability and adult long-term sickness absence in three British birth cohorts: :a cohort study. Bmj Open. 2012;2(2).
223. Buchanan A, Flouri E, Ten Brinke J. Emotional and behavioural problems in childhood and distress in adult life: risk and protective factors. Aust N Z J Psychiatry. 2002;36(4):521-7.
224. Henderson M, Hotopf M, Leon DA. Childhood temperament and long-term sickness absence in adult life. Brit J Psychiat. 2009;194(3):220-3.
225. Kuh D, Pierce M, Adams J, Deanfield J, Ekelund U, Friberg P, et al. Cohort profile: updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research. Int J Epidemiol. 2011;40(1):e1-9.
226. Power C, Elliott J. Cohort profile: 1958 British Birth Cohort (National Child Development Study). Int J Epidemiol. 2006;35(1):34-41.
227. Wadsworth M, Bynner J. A Companion to Life Course Studies: the social and historical context of the British birth cohort studies. London: Routledge; 2011.
228. Brown M, Peters A. 1970 British Cohort Study. Age 46 Survey User Guide. Institute of Education; 2019.
229. Elliot J, Johnson J, Shepherd P. User guide to the biomedical survey 2002–2004 dataset. Centre for Longitudinal Studies, Bedford Group for Lifecourse & Statistical Studies, Institute of Education, University of London; 2008.
230. Rutter M, Tizard J, Whitmore K. Education, Health and Behaviour. London: Longmans; 1970.
231. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med. 2017;5(7).

232. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 2). J Epidemiol Community Health. 2006;60(2):95-101.
233. Douglas JWB. The Home and the School. . London: McGibbon and Kee; 1964.
234. Elliott C, Murray D, Pearson L. British Ability Scales. . Windsor: National Foundation for Educational Research; 1978.
235. Schoon I. Childhood Cognitive Ability and Adult Academic Attainment: Evidence from Three British Cohort Studies. Longitudinal and Life Course Studies. 2010;1(3):241-58.
236. Babor TF, Higgins-Biddle JC, Saunders JB, et al., AUDIT. AUDIT: The Alcohol Use Disorders Identification Test. Guidelines for Use in Primary Care. Geneva, Switzerland: World Health Organization; 2001.
237. Gómez A, Conde A, Santana JM, Jorrín A. Diagnostic usefulness of brief versions of Alcohol Use Disorders Identification Test (AUDIT) for detecting hazardous drinkers in primary care settings. Journal of Studies on Alcohol. 2005;66:305-8.
238. Rodgers B, Pickles A, Power C, Collishaw S, Maughan B. Validity of the Malaise Inventory in general population samples. Soc Psychiatry Psychiatr Epidemiol. 1999;34(6):333-41.
239. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. WHO Technical Report Series 854. Geneva: World Health Organization; 1995.
240. Cohort and Longitudinal Studies Enhancement Resources. Harmonised Height, Weight and BMI in Five Longitudinal Cohort Studies: Avon Longitudinal Study of Parents and Children: Special Licence Access.2017.
241. Elliott J, Johnson J, Shepherd P. National Child Development Study User Guide to the Biomedical Survey 2002-2004 Dataset. London: Centre for Longitudinal Studies, Institute of Education; 2008.
242. Verberk WJ, Kessels AGH, Thien T. Blood Pressure Measurement Method and Inter-Arm Differences: A Meta-Analysis. Am J Hypertens. 2011;24(11):1201-8.
243. American Diabetes Association. Executive summary: standards of medical car in diabetes – 2010. Diabetes Care. 2010;33:S4-S10.
244. Gillett MJ. International Expert Committee report on the role of the A1c assay in the diagnosis of diabetes: Diabetes Care 2009; 32(7): 1327-1334. Clin Biochem Rev. 2009;30(4):197-200.
245. Ploubidis GB, Sullivan A, Brown M, Goodman A. Psychological distress in mid-life: evidence from the 1958 and 1970 British birth cohorts. Psychol Med. 2017;47(2):291-303.
246. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30(4):377–99.
247. Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychological Methods. 2001;6(4):330-51.
248. Little R, Rubin DB. Statistical analysis with missing data. Hoboken, N.J: Wiley; 2002.
249. StataCorp. Stata Statistical Software: Release 14. . College Station, TX: StataCorp LP. ; 2015.
250. Rubin DB. Multiple imputation for nonresponse in surveys. New York: Sons; 1987.
251. Zapata-Diomedi B, Barendregt JJ, Veerman JL. Population attributable fraction: names, types and issues with incorrect interpretation of relative risks. Brit J Sport Med. 2018;52(4):212-3.
252. Klein D. MIMRGNS: Stata module to run margins after mi estimate. Statistical Software Components; 2014.
253. VanderWeele TJ, Mathur MB. Some Desirable Properties of the Bonferroni Correction: Is the Bonferroni Correction Really So Bad? Am J Epidemiol. 2019;188(3):617-8.
254. Tobin MD, Sheehan NA, Scurrah KJ, Burton PR. Adjusting for treatment effects in studies of quantitative traits: antihypertensive therapy and systolic blood pressure. Statistics in Medicine. 2005;24(19):2911-35.
255. Bennett WL, Bass EB, Bolen S. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations (vol 154, pg 602, 2011). Ann Intern Med. 2011;155(1):67-+.

256. Katikireddi SV, Skivington K, Leyland AH, Hunt K, Mercer SW. The contribution of risk factors to socioeconomic inequalities in multimorbidity across the lifecourse: a longitudinal analysis of the Twenty-07 cohort. Bmc Med. 2017;15.
257. Li J, Green M, Kearns B, Holding E, Smith C, Haywood A, et al. Patterns of multimorbidity and their association with health outcomes within Yorkshire, England: baseline results from the Yorkshire Health Study. Bmc Public Health. 2016;16.
258. Uijen AA, van de Lisdonk EH. Multimorbidity in primary care: prevalence and trend over the last 20 years. Eur J Gen Pract. 2008;14 Suppl 1:28-32.
259. Roberts K. Leisure: Stability and change. In: Wadsworth M, Bynner J, editors. A companion to life course studies: the social and historical context of the British birth cohort studies. Oxford: Routledge; 2011.
260. Maggs JL, Patrick ME, Feinstein L. Childhood and adolescent predictors of alcohol use and problems in adolescence and adulthood in the National Child Development Study. Addiction. 2008;103:7-22.
261. Hahn RA, Truman BI. Education Improves Public Health and Promotes Health Equity. Int J Health Serv. 2015;45(4):657-78.
262. McCulloch G. Education policy and practice. In: Wadsworth M, Bynner J, editors. A companion to life course studies: the social and historical context of the British birth cohort studies. Oxford: Routledge; 2011.
263. Lyall DM, Celis-Morales C, Ward J, Iliodromiti S, Anderson JJ, Gill JMR, et al. Association of Body Mass Index With Cardiometabolic Disease in the UK Biobank A Mendelian Randomization Study. Jama Cardiol. 2017;2(8):882-9.
264. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-51.
265. Bell JA, Hamer M, Batty GD, Singh-Manoux A, Sabia S, Kivimaki M. Incidence of Metabolic Risk Factors Among Healthy Obese Adults 20-Year Follow-Up. J Am Coll Cardiol. 2015;66(7):871-3.
266. Caserta MT, Wyman PA, Wang HY, Moynihan J, O'Connor TG. Associations among depression, perceived self-efficacy, and immune function and health in preadolescent children. Dev Psychopathol. 2011;23(4):1139-47.
267. Stone AL, Becker LG, Huber AM, Catalano RF. Review of risk and protective factors of substance use and problem use in emerging adulthood. Addict Behav. 2012;37(7):747-75.
268. Dyer ML, Easey KE, Heron J, Hickman M, Munafo MR. Associations of child and adolescent anxiety with later alcohol use and disorders: a systematic review and meta-analysis of prospective cohort studies. Addiction. 2019;114(6):968-82.
269. Goodman A, Joyce R, Smith JP. The long shadow cast by childhood physical and mental problems on adult life. P Natl Acad Sci USA. 2011;108(15):6032-7.
270. Gottfredson LS, Deary IJ. Gottfredson LS, Deary IJ. Intelligence predicts health and longevity, but why? Curr Direct Psychol Sci. 2004;13:1-4.
271. Bann D, Johnson W, Li L, Kuh D, Hardy R. Socioeconomic Inequalities in Body Mass Index across Adulthood: Coordinated Analyses of Individual Participant Data from Three British Birth Cohort Studies Initiated in 1946, 1958 and 1970. Plos Med. 2017;14(1).
272. Birnie K, Cooper R, Martin RM, Kuh D, Sayer AA, Alvarado BE, et al. Childhood Socioeconomic Position and Objectively Measured Physical Capability Levels in Adulthood: A Systematic Review and Meta-Analysis. Plos One. 2011;6(1).
273. Yang YC, Gerken K, Schorpp K, Boen C, Harris KM. Early-Life Socioeconomic Status and Adult Physiological Functioning: A Life Course Examination of Biosocial Mechanisms. Biodemogr Soc Biol. 2017;63(2):87-103.
274. Saxton K, Chyu L. Early life adversity increases the salience of later life stress: an investigation of interactive effects in the PSID. J Dev Orig Health Dis. 2020;11(1):25-36.
275. Evans GW, Kim P. Childhood poverty and health: cumulative risk exposure and stress dysregulation. Psychol Sci. 2007;18(11):953-7.

276. Wang TG, Huang T, Li YP, Zheng Y, Manson JE, Hu FB, et al. Low birthweight and risk of type 2 diabetes: a Mendelian randomisation study. Diabetologia. 2016;59(9):1920-7.
277. Zanetti D. Birthweight, Type 2 Diabetes Mellitus, and Cardiovascular Disease: Addressing the Barker Hypothesis With Mendelian Randomization (vol 11, e002054, 2018). Circ-Genom Precis Me. 2018;11(9).
278. Myatt L. Placental adaptive responses and fetal programming. J Physiol-London. 2006;572(1):25-30.
279. Santos MS, Joles JA. Early determinants of cardiovascular disease. Best Pract Res Cl En. 2012;26(5):581-97.
280. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-+.
281. Madley-Dowd P, Hughesa R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. Journal of Clinical Epidemiology. 2019;110:63-73.
282. Fernández-Reino M. The health of migrants in the UK. Migration Observatory briefing, COMPAS, University of Oxford. 2020.
283. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013;9(382(9904)).
284. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1545-602.
285. World Health Organization. Risks to mental health: an overview of vulnerabilities and risk factors. Geneva: World Health Organization; 2012.
286. Blanchflower DG, Oswald AJ. The U-shape without controls: A response to Glenn. Soc Sci Med. 2009;69(4):486-8.
287. Glenn N. Is the apparent U-shape of well-being over the life course a result of inappropriate use of control variables? A commentary on Blanchflower and Oswald (66:8,2008,1733-1749). Soc Sci Med. 2009;69(4):481-5.
288. Schisterman EF, Cole SR, Platt RW. Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology. 2009;20(4):488-95.
289. Bell A. Life-course and cohort trajectories of mental health in the UK, 1991-2008-A multilevel age-period-cohort analysis. Soc Sci Med. 2014;120:21-30.
290. Rudolph KE, Goin DE, Paksarian D, Crowder R, Merikangas KR, Stuart EA. Causal Mediation Analysis With Observational Data: Considerations and Illustration Examining Mechanisms Linking Neighborhood Poverty to Adolescent Substance Use. Am J Epidemiol. 2019;188(3):598-608.
291. Sacker A, Wiggins RD. Age-period-cohort effects on inequalities in psychological distress, 1981-2000. Psychological Medicine. 2002;32(6):977-90.
292. Sullivan A, Brown M, Bann D. Guest Editorial: Generation X enters middle age. Longitudinal and Life Course Studies. 2015;6(2):120 – 30.
293. Spiers N, Brugha TS, Bebbington P, McManus S, Jenkins R, Meltzer H. Age and birth cohort differences in depression in repeated cross-sectional surveys in England: the National Psychiatric Morbidity Surveys, 1993 to 2007. Psychological Medicine. 2012;42(10):2047-55.
294. Frasquilho D, Matos MG, Salonna F, Guerreiro D, Storti CC, Gaspar T, et al. Mental health outcomes in times of economic recession: a systematic literature review. Bmc Public Health. 2016;16.
295. Smith HL. Advances in age-period-cohort analysis. Sociol Method Res. 2008;36(3):287-96.
296. Jorm AF. Does old age reduce the risk of anxiety and depression? A review of epidemiological studies across the adult life span. Psychological Medicine. 2000;30(1):11-22.
297. Blanchflower DG, Oswald AJ. Is well-being U-shaped over the life cycle? Soc Sci Med. 2008;66(8):1733-49.

298. Keyes KM, Nicholson R, Kinley J, Raposo S, Stein MB, Goldner EM, et al. Age, Period, and Cohort Effects in Psychological Distress in the United States and Canada. Am J Epidemiol. 2014;179(10):1216-27.
299. Sunderland M, Slade T, Carragher N, Batterham P, Buchan H. Age-related differences in internalizing psychopathology amongst the Australian general population. J Abnorm Psychol. 2013;122(4):1010-20.
300. Vestergaard S, Thinggaard M, Jeune B, Vaupel JW, McGue M, Christensen K. Physical and mental decline and yet rather happy? A study of Danes aged 45 and older. Aging & Mental Health. 2015;19(5):400-8.
301. Jokela M, Batty GD, Kivimaki M. Ageing and the prevalence and treatment of mental health problems. Psychol Med. 2013;43(10):2037-45.
302. Tampubolon G, Maharani A. When Did Old Age Stop Being Depressing? Depression Trajectories of Older Americans and Britons 2002–2012. Am J Geriatr Psychiatry 2017;25:1187–95.
303. Brault MC, Meuleman B, Bracke P. Depressive symptoms in the Belgian population: disentangling age and cohort effects. Soc Psychiatry Psychiatr Epidemiol. 2012;47(6):903-15.
304. Calling S, Midlov P, Johansson SE, Sundquist K, Sundquist J. Longitudinal trends in self-reported anxiety. Effects of age and birth cohort during 25 years. Bmc Psychiatry. 2017;17.
305. Lucke JC, Brown W, Tooth L, Loxton D, Byles J, Spallek M, et al. Health Across Generations: Findings From the Australian Longitudinal Study on Women's Health. Biol Res Nurs. 2010;12(2):162-70.
306. Zimmerman M, Morgan TA, Stanton K. The severity of psychiatric disorders. World Psychiatry. 2018;17(3):258-75.
307. Wing JK, Cooper JE, Sartorius N. The measurement and classification of psychiatric symptoms. Cambridge, UK: Cambridge University Press; 1974.
308. Lindelow M, Hardy R, Rodgers B. Development of a scale to measure symptoms of anxiety and depression in the general UK population: the psychiatric symptom frequency scale. Journal of Epidemiology and Community Health. 1997;51(5):549-57.
309. Goldberg DP, Hillier VF. A scaled version of the General Health Questionnaire. Psychological Medicine. 1979;9(1):139-45.
310. Ploubidis G, McElroy E, Moreira H. A longitudinal examination of the measurement equivalence of mental health assessments in two British birth cohorts. Longitudinal and Life Course Studies 2019;10(4):471-89.
311. McGee R, Williams S, Silva PA. An evaluation of the Malaise inventory. Journal of Psychosomatic Research. 1986;30(2):147-52.
312. Furnham A, Cheng H. The stability and change of malaise scores over 27 years: Findings from a nationally representative sample. Personality and Individual Differences. 2015;79:30-4.
313. Goldberg DP, Gater R, Sartorius N, Ustun TB, Piccinelli M, Gureje O, et al. The validity of two versions of the GHQ in the WHO study of mental illness in general health care. Psychol Med. 1997;27(1):191-7.
314. Florkowski CM. Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. Clin Biochem Rev. 2008;29 Suppl 1:S83-7.
315. McElroy E, Villadsen A, Patalay P, Goodman A, Richards M, Northstone K, et al. Harmonisation of Mental Health Measures in the British Birth Cohorts. UK: CLOSER; 2020.
316. Meredith W. Measurement Invariance, Factor-Analysis and Factorial Invariance. Psychometrika. 1993;58(4):525-43.
317. Asparouhov T, Muthen B. Multiple-Group Factor Analysis Alignment. Struct Equ Modeling. 2014;21(4):495-508.
318. Raudenbush SW, Bryk AS. Hierarchical linear models: Applications and data analysis methods (2nd ed.). Thousand Oaks: Sage Publications; 2002.
319. Suzuki E. Time changes, so do people. Soc Sci Med. 2012;75(3):452-6.

320. Singer JD, Willet JB. Applied Longitudinal Data Analysis. Oxford; United Kingdom: Oxford University Press; 2003.
321. StataCorp. Stata Statistical Software: Release 15. . College Station, TX: StataCorp LLC; 2017.
322. Blanchflower DG, Oswald AJ. Is well-being U-shaped over the life cycle? Social Science & Medicine. 2008;66(8):1733-49.
323. Arnett JJ, Zukauskiene R, Sugimura K. The new life stage of emerging adulthood at ages 18-29 years: implications for mental health. Lancet Psychiatry. 2014;1(7):569–76.
324. Gustavson K, Knudsen AK, Nesvåg R, Knudsen GP, Vollset SE, Reichborn-Kjennerud T. Prevalence and stability of mental disorders among young adults: findings from a longitudinal study. Bmc Psychiatry. 2018;18.
325. Willis SL, Martin M, Rocke C. Longitudinal perspectives on midlife development: stability and change. European Journal of Ageing. 2010;7(3):131-4.
326. Health and Safety Executive. Work-related stress, Depression or Anxiety Statistics in Great Britain 2017. This document is available from www.hse.gov.uk/statistics/; 2017.
327. Otterbach S, Sousa-Poza A, Møller V. A cohort analysis of subjective wellbeing and ageing: heading towards a midlife crisis? Longitudinal and Life Course Studies. 2018;9(4):382-411.
328. Office for National Statistics. Statistical bulletin: Divorces in England and Wales: 2013 2015 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/divorce/bulletins/divorcesinenglandandwales/2013.
329. Britton A, Ben-Shlomo Y, Benzeval M, Kuh D, Bell S. Life course trajectories of alcohol consumption in the United Kingdom using longitudinal data from nine cohort studies. Bmc Med. 2015;13(47).
330. Office for National Statistics , National Records of Scotland , Northern Ireland Statistics and Research Agency. 2011 Census aggregate data. UK Data Service (Edition: June 2016). 2016.
331. Archer G, Kuh D, Hotopf M, Stafford M, Richards M. Adolescent affective symptoms and mortality. Brit J Psychiat. 2018;213(1):419-24.
332. Wadsworth MEJ, Mann SL, Rodgers B, Kuh DJL, Hilder WS, Yusuf EJ. Loss and Representativeness in a 43 Year Follow-up of a National Birth Cohort. Journal of Epidemiology and Community Health. 1992;46(3):300-4.
333. Stone AA, Schneider S, Broderick JE. Psychological stress declines rapidly from age 50 in the United States: Yet another well-being paradox. Journal of Psychosomatic Research. 2017;103:22-8.
334. Carstensen LL, Fung HH, Charles ST. Socioemotional selectivity theory and the regulation of emotion in the second half of life. Motivation and Emotion. 2003;27:103-23.
335. Mezuk B, Kendler KS. Examining variation in depressive symptoms over the life course: a latent class analysis. Psychol Med. 2012;42(10):2037-46.
336. Christensen H, Jorm AF, Mackinnon AJ, Korten AE, Jacomb PA, Henderson AS, et al. Age differences in depression and anxiety symptoms: a structural equation modelling analysis of data from a general population sample. Psychological Medicine. 1999;29(2):325-39.
337. Gili M, Lopez-Navarro E, Castro A, Homar C, Navarro C, Garcia-Toro M, et al. Gender differences in mental health during the economic crisis. Psicothema. 2016;28(4):407-13.
338. Ashton D, Bynner J. Labour market, employment and skills. In: Wadsworth M, Bynner J, editors. A companion to life course studies: the social and historical context of the British birth cohort studies. Oxford: Routledge; 2011.
339. Luechinger S, Meier S, Stutzer A. Why Does Unemployment Hurt the Employed? Evidence from the Life Satisfaction Gap between the Public and the Private Sector. IZA Discussion Paper No. 3385 2008.
340. Dickerson S, Kemeny M. Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. Psychol Bull. 2004;130(3):355–91.
341. Umberson D, Montez JK. Social relationships and health: a flashpoint for health policy. J Health Soc Behav. 2010;51 Suppl:S54-66.

342. Frank R. Falling Behind: How Rising Inequality Harms the Middle Class. Berkeley and Los Angeles: University of California Press; 2007.
343. Clarke L, Roberts C. Family structure and family policy and practice. In: Wadsworth M, Bynner J, editors. A companion to life course studies: the social and historical context of the British birth cohort studies. Oxford: Routledge; 2011.
344. Richards M, Hardy R, Wadsworth M. The effects of divorce and separation on mental health in a national UK birth cohort. Psychol Med. 1997;27(5):1121-8.
345. Chiu M, Rahman F, Kurdyak P, Cairney J, Jembere N, Vigod S. Self-rated health and mental health of lone fathers compared with lone mothers and partnered fathers: a population-based cross-sectional study. J Epidemiol Community Health. 2017;71(5):417-23.
346. Holt-Lunstad J, Birmingham W, Jones BQ. Is There Something Unique about Marriage? The Relative Impact of Marital Status, Relationship Quality, and Network Social Support on Ambulatory Blood Pressure and Mental Health. Annals of Behavioural Medicine. 2008;35:239–44.
347. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.
348. Enders CE. Applied missing data analysis. New York: Guilford; 2010.
349. Lomax N, Wohland P, Rees P, Norman P. The impacts of international migration on the UK's ethnic populations. Journal of Ethnic and Migration Studies. 2019:1-23.
350. Helgesson M, Johansson B, Nordquist T, Vingard E, Svartengren M. Healthy migrant effect in the Swedish context: a register-based, longitudinal cohort study. Bmj Open. 2019;9(3).
351. Salomon JA, Wang H, Freeman MK, Vos T, Flaxman AD, Lopez AD, et al. Healthy life expectancy for 187 countries, 1990-2010: a systematic analysis for the Global Burden Disease Study 2010. Lancet. 2012;380(9859):2144-62.
352. Gondek D, Bann D, Ning K, Grundy E, Ploubidis GB. Post-war (1946-2017) population health change in the UK: A systematic review PLoS One. 2019.
353. Erler A, Bodenheimer T, Baker R, Goodwin N, Spreeuwenberg C, Vrijhoef HJ, et al. Preparing primary care for the future - perspectives from the Netherlands, England, and USA. Z Evid Fortbild Qual Gesundhwes. 2011;105(8):571-80.
354. Crimmins EM, Reynolds SL, Saito Y. Trends in health and ability to work among the older working-age population. J Gerontol B Psychol Sci Soc Sci. 1999;54(1):S31–S40.
355. Fors S, Lennartsson C, Lundberg O. Health inequalities among older adults in Sweden 1991-2002. Eur J Public Health. 2008;18(2):138-43.
356. Fritzell J, Lennartsson C, Lundberg O. Health and inequalities in Sweden: long and short term perspectives. In: Fritzell J, Lundberg O, editors. Health inequalities and welfare resources. Bristol: Policy Press; 2007.
357. Kunst AE, Bos V, Lahelma E, Bartley M, Lissau I, Regidor E, et al. Trends in socioeconomic inequalities in self-assessed health in 10 European countries. Int J Epidemiol. 2005;34(2):295-305.
358. Lahelma E, Kivela K, Roos E, Tuominen T, Dahl E, Diderichsen F, et al. Analysing changes of health inequalities in the Nordic welfare states. Soc Sci Med. 2002;55(4):609-25.
359. Meinow B, Kåreholt I, Thorslund M, Parker MG. Complex health problems among the oldest old in Sweden: increased prevalence rates between 1992 and 2002 and stable rates thereafter. European journal of ageing. 2015;12(4):285–97.
360. Lundberg O. The next step towards more equity in health in Sweden: how can we close the gap in a generation? Scand J Public Health. 2018;46(22_suppl):19-27.
361. Andersson T, Ahlbom A, Carlsson S. Diabetes Prevalence in Sweden at Present and Projections for Year 2050. PLoS One. 2015;10(11):e0143084.
362. Paren P, Schaufelberger M, Bjorck L, Lappas G, Fu M, Rosengren A. Trends in prevalence from 1990 to 2007 of patients hospitalized with heart failure in Sweden. Eur J Heart Fail. 2014;16(7):737-42.
363. Rosen M, Haglund B. From healthy survivors to sick survivors–implications for the twenty-first century. Scand J Public Health. 2005;33:151–5.

364. Sundberg L, Agahi N, Fritzell J, Fors S. Trends in health expectancies among the oldest old in Sweden, 1992-2011. Eur J Public Health. 2016;26(6):1069-74.
365. Hu Y, van Lenthe FJ, Borsboom GJ, al. e. Trends in socioeconomic inequalities in self-assessed health in 17 European countries between 1990 and 2010. J Epidemiol Community Health. 2016;70:644-52.
366. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. J Epidemiol Community Health. 2015;69(4):316-21.
367. Bann D, Johnson W, Li L, Kuh D, Hardy R. Socioeconomic Inequalities in Body Mass Index across Adulthood: Coordinated Analyses of Individual Participant Data from Three British Birth Cohort Studies Initiated in 1946, 1958 and 1970. PLoS Med. 2017;14(1):e1002214.
368. Lofqvist T, Burstrom B, Walander A, Ljung R. Inequalities in avoidable hospitalisation by area income and the role of individual characteristics: a population-based register study in Stockholm County, Sweden. BMJ Qual Saf. 2014;23(3):206-14.
369. Fleury MJ, Ngui AN, Bamvita JM, Grenier G, Caron J. Predictors of healthcare service utilization for mental health reasons. Int J Environ Res Public Health. 2014;11(10):10559-86.
370. Farkas J, Kosnik M, Flezar M, Suskovic S, Lainscak M. Self-rated health predicts acute exacerbations and hospitalizations in patients with COPD. Chest. 2010;138(2):323-30.
371. OECD/EU. Health at a Glance: Europe 2016 – State of Health in the EU Cycle. Paris: OECD Publishing; 2016.
372. Pezzin LE, Bogner HR, Kurichi JE, Kwong PL, Streim JE, Xie D, et al. Preventable hospitalizations, barriers to care, and disability. Medicine (Baltimore). 2018;97(19):e0691.
373. Kelly E, Stoye G, Vera-Hernández M. Public Hospital Spending in England: Evidence from National Health Service Administrative Records. Fiscal Studies. 2016;37(3-4):433-59.
374. Barnett R, Lauer G. Urban deprivation and public hospital admissions in Christchurch, New Zealand, 1990-1997. Health Soc Care Community. 2003;11(4):299-313.
375. Carlsen F, Grytten J, Kjelvik J, Skau I. Better primary physician services lead to fewer hospital admissions. Eur J Health Econ. 2007;8(1):17-24.
376. Brameld KJ, Holman CD. The use of end-quintile comparisons to identify under-servicing of the poor and over-servicing of the rich: a longitudinal study describing the effect of socioeconomic status on healthcare. BMC Health Serv Res. 2005;5(61).
377. Asada Y, Kephart G. Equity in health services use and intensity of use in Canada. BMC Health Serv Res. 2007;7(41).
378. Antonelli-Incalzi R, Ancona C, Forastiere F, Belleudi V, Corsonello A, Perucci CA. Socioeconomic status and hospitalization in the very old: a retrospective study. Bmc Public Health. 2007;7(227).
379. Taylor CB, Ahn D, Winkleby MA. Neighborhood and individual socioeconomic determinants of hospitalization. Am J Prev Med. 2006;31(2):127-34.
380. Birnie K, Cooper R, Martin RM, Kuh D, Sayer AA, Alvarado BE, et al. Childhood socioeconomic position and objectively measured physical capability levels in adulthood: a systematic review and meta-analysis. PLoS One. 2011;6(1):e15564.
381. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31(2):285-93.
382. Warren JR. Socioeconomic Status and Health across the Life Course: A Test of the Social Causation and Health Selection Hypotheses. Soc Forces. 2009;87(4):2125-53.
383. Cockerham WC, Hamby BW, Oates GR. The Social Determinants of Chronic Disease. Am J Prev Med. 2017;52(1S1):S5-S12.
384. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. Bmc Public Health. 2011;11:450.

385. Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak. 2015;15:31.
386. Statistics Sweden. Socioekonomisk indelning (SEI). Meddelande i Samordningsfrågor [Swedish Socioeconomic Classification (SEI). Reports on statistical coordination]. Orebro: Statistics Sweden; 1984.
387. Sidorchuk A, Goodman A, Koupil I. Social class, social mobility and alcohol-related disorders in Swedish men and women: A study of four generations. PLoS One. 2018;13(2):e0191855.
388. Yang Y. Is old age depressing? Growth trajectories and cohort variations in late-life depression. J Health Soc Behav. 2007;48(1):16-32.
389. Charlton C, Rasbash J, Browne WJ, Healy M, Cameron B. MLwiN Version 3.03. Centre for Multilevel Modelling, University of Bristol.; 2019.
390. Leckie G, Charlton C. runmlwin - A Program to Run the MLwiN Multilevel Modelling Software from within Stata. Journal of Statistical Software. 2013;52(11):1-40.
391. Iacobucci D, Schneider MJ, Popovich DL, Bakamitsos GA. Mean centering helps alleviate "micro" but not "macro" multicollinearity. Behav Res Methods. 2016;48(4):1308-17.
392. van Oostrom SH, Gijsen R, Stirbu I, Korevaar JC, Schellevis FG, Picavet HS, et al. Time Trends in Prevalence of Chronic Diseases and Multimorbidity Not Only due to Aging: Data from General Practices and Health Surveys. PLoS One. 2016;11(8):e0160264.
393. Gruenberg EM. The failures of success. Milbank Memorial Fund Quart/Health Soc. 1977;55:3–24.
394. Ng N, Carlberg B, Weinehall L, Norberg M. Trends of blood pressure levels and management in Vasterbotten County, Sweden, during 1990-2010. Glob Health Action. 2012;5.
395. Patja K, Hakala SM, Boström G, Nordgren P, Haglund M. Trends of tobacco use in Sweden and Finland: do differences in tobacco policy relate to tobacco use? Scand J Public Health. 2009;37(2):153-60.
396. Heckley G, Jarl J, Gerdtham UG. Frequency and intensity of alcohol consumption: new evidence from Sweden. Eur J Health Econ. 2017;18(4):495-517.
397. Johansson I, Nilsson LM, Stegmayr B, Boman K, Hallmans G, Winkvist A. Associations among 25-year trends in diet, cholesterol and BMI from 140,000 observations in men and women in Northern Sweden. Nutrition Journal 2012;11(40).
398. Davies AR, Grundy E, Nitsch D, Smeeth L. Constituent country inequalities in myocardial infarction incidence and case fatality in men and women in the United Kingdom, 1996-2005. Journal of Public Health. 2011;33(1):131-8.
399. Barasa A, Schaufelberger M, Lappas G, Swedberg K, Dellborg M, Rosengren A. Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden. Eur Heart J. 2014;35(1):25-32.
400. Moller T, Anderson H, Aareleid T, Hakulinen T, Storm H, Tryggvadottir L, et al. Cancer prevalence in Northern Europe: the EUROPREVAL study. Ann Oncol. 2003;14(6):946-57.
401. Bardsley M, Blunt I, Davies S, Dixon J. Is secondary preventive care improving? Observational study of 10-year trends in emergency admissions for conditions amenable to ambulatory care. BMJ Open. 2012.
402. Jansson SP, Fall K, Brus O, Magnuson A, Wandell P, Ostgren CJ, et al. Prevalence and incidence of diabetes mellitus: a nationwide population-based pharmaco-epidemiological study in Sweden. Diabet Med. 2015;32(10):1319-28.
403. Backman H, Räisänen P, Hedman L, Stridsman C, Andersson M, Lindberg A, et al. Increased prevalence of allergic asthma from 1996 to 2006 and further to 2016-results from three population surveys. Clin Exp Allergy. 2017.
404. Dannefer D. Cumulative advantage/disadvantage and the life course: cross-fertilizing age and social science theory. J Gerontol B Psychol Sci Soc Sci 2003;327:327–37.

405. Burstrom B. Market-oriented, demand-driven health care reforms and equity in health and health care utilization in Sweden. Int J Health Serv. 2009;39(2):271-85.
406. Eikemo TA, Bambra C, Judge K, Ringdal K. Welfare state regimes and differences in self-perceived health in Europe: A multilevel analysis. Soc Sci Med. 2008;66:2281–95.
407. Breen R, Jonsson JO. Explaining change in social fluidity: educational equalization and educational expansion in twentieth century Sweden. American Journal of Sociology. 2007;112(6):1775–810.
408. Härkönen J, Bihagen E. Occupational attainment and career progression in Sweden. European Societies. 2011;13(3):451–79.
409. Johansson G, Huang Q, Lindfors P. A life-span perspective on women's careers, health, and well-being. Soc Sci Med. 2007;65(4):685–97.
410. Billingsley S. Intragenerational social mobility and cause-specific premature mortality. PLoS One. 2019;14(2):e0211977.
411. Jonsson F, Sebastian MS, Hammarström A, Gustafsson PE. Intragenerational social mobility and functional somatic symptoms in a northern Swedish context: analyses of diagonal reference models. . International Journal for Equity in Health. 2017;16(1).
412. Mishra GD, Chiesa F, Goodman A, De Stavola B, Koupil I. Socio-economic position over the life course and all-cause, and circulatory diseases mortality at age 50-87 years: results from a Swedish birth cohort. Eur J Epidemiol. 2013;28(2):139-47.
413. Statistics Sweden. Sveriges framtida befolkning 2015–2060 – The future population of Sweden 2015–2060 2017 [Available from: https://www.scb.se/Statistik/_Publikationer/BE0401_2015I60_BR_BE51BR1502.pdf.
414. British Geriatrics Society. Quest for Quality. An Inquiry into the Quality of Healthcare Support for Older People in Care Homes: a Call for Leadership, Partnership and Improvement 2011 [Available from: http://www.bgs.org.uk/campaigns/carehomes/quest_quality_care_homes.pdf
415. Mostafa T, Wiggins R. The impact of attrition and non-response in birth cohort studies: a need to incorporate missingness strategies. Longitudinal and Life Course Studies. 2015;6(2):131 – 46

416. Goodman A, Butler NR. BCS70 - The 1970 British Cohort Study: The Sixteen-year Follow-up. London: Social Statistics Research Unit; 1987.
417. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res. 2007;16(3):219–42.
418. Morris TP, White IR, Royston P. Tuning multiple imputation by predictive mean matching and local residual draws. BMC Med Res Methodol. 2014;14:75.
419. Counsell N, Cortina-Borja M, Lehtonen A, Stein A. Modelling psychiatric measures using Skew-Normal distributions. Eur Psychiat. 2011;26(2):112-4.
420. Misselbrook D. W is for wellbeing and the WHO definition of health. The British journal of general practice : the journal of the Royal College of General Practitioners. 2014;64(628).
421. van der Heide I, Wang J, Droomers M, Spreeuwenberg P, Rademakers J, Uiters E. The relationship between health, education, and health literacy: results from the Dutch Adult Literacy and Life Skills Survey. Journal of health communication. 2013;18:172–84.
422. Bhavsar V, Schofield P, Das-Munshi J, Henderson C. Regional differences in mental health stigma-Analysis of nationally representative data from the Health Survey for England, 2014. PLoS One. 2019;14(1):e0210834.
423. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemiere C, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. JAMA. 2017;317(3):269-79.
424. Allan CE, Valkanova V, Ebmeier KP. Depression in older people is underdiagnosed. Practitioner. 2014;258(1771):19-2.
425. Simpson CR, Hippisley-Cox J, Sheikh A. Trends in the epidemiology of smoking recorded in UK general practice. Br J Gen Pract. 2010;60(572):e121-7.
426. Drummond C, McBride O, Nicola F, Elizabeth F. Alcohol Dependence. 2016.

427. Morgan C, Webb RT, Carr MJ, Kontopantelis E, Green J, Chew-Graham CA, et al. Incidence, clinical management, and mortality risk following self harm among children and adolescents: cohort study in primary care. BMJ. 2017;359:j4351.
428. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. Scand J Public Health. 2017;45(17):14-9.
429. De Stavola BL, Daniel RM, Ploubidis GB, Micali N. Mediation analysis with intermediate confounding: structural equation modeling viewed through the causal inference lens. Am J Epidemiol. 2015;181(1):64-80.
430. Palladino R, Pennino F, Finbarr M, Millett C, Triassi M. Multimorbidity And Health Outcomes In Older Adults In Ten European Health Systems, 2006-15. Health Aff (Millwood). 2019;38(4):613-23.
431. Kelishadi R, Azizi-Soleiman F. Controlling childhood obesity: A systematic review on strategies and challenges. J Res Med Sci. 2014;19(10):993-1008.
432. Love R, Adams J, van Sluijs EMF. Are school-based physical activity interventions effective and equitable? A meta-analysis of cluster randomized controlled trials with accelerometer-assessed activity. Obes Rev. 2019;20(6):859-70.
433. Gortmaker YSL, Wang C, Long MW, Giles CM, Ward ZJ, Barrett JL, et al. Three Interventions That Reduce Childhood Obesity Are Projected To Save More Than They Cost To Implement. Health Affair. 2015;34(11):1932-9.
434. Corrieri S, Heider D, Conrad I, Blume A, Konig HH, Riedel-Heller SG. School-based prevention programs for depression and anxiety in adolescence: a systematic review. Health Promot Int. 2014;29(3):427-41.
435. Bowling A, Blaine RE, Kaur R, Davison KK. Shaping healthy habits in children with neurodevelopmental and mental health disorders: parent perceptions of barriers, facilitators and promising strategies. Int J Behav Nutr Phy. 2019;16.
436. (NICE) NIfHaCE. Dementia, disability and frailty in later life – mid-life approaches to delay or prevent onset 2015 [Available from: https://www.nice.org.uk/guidance/ng16/chapter/What-is-this-guideline-about.
437. Buck D, Frosini F. Clustering of unhealthy behaviours over time. Implications for policy and practice. London: The King's Fund; 2012.
438. Brown AF, Ma GX, Miranda J, Eng E, Castille D, Brockie T, et al. Structural Interventions to Reduce and Eliminate Health Disparities. Am J Public Health. 2019;109(S1):S72-S8.
439. Mackenbach JP, Valverde JR, Artnik B, Bopp M, Bronnum-Hansen H, Deboosere P, et al. Trends in health inequalities in 27 European countries. Proc Natl Acad Sci U S A. 2018;115(25):6440-5.
440. Mackenbach JP, Bakker MJ, European Network on I, Policies to Reduce Inequalities in H. Tackling socioeconomic inequalities in health: analysis of European experiences. Lancet. 2003;362(9393):1409-14.
441. Burstrom B, Whitehead M, Lindholm C, Diderichsen F. Inequality in the social consequences of illness: how well do people with long-term illness fare in the British and Swedish labor markets? Int J Health Serv. 2000;30(3):435-51.
442. Statistics OfN. How would you support our ageing population? 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/ageing/articles/howwouldyousupportourageingpopulation/2019-06-24#:~:text=Despite%20more%20people%20working%20beyond,has%20only%20risen%20by%20800%2C000.
443. Parker M, Bucknall M, Jagger C, Wilkie R. Population-based estimates of healthy working life expectancy in England at age 50 years: analysis of data from the English Longitudinal Study of Ageing. The Lancet Public Health. 2020;5(7):E395-E403.
444. Hacking JM, Muller S, Buchan IE. Trends in mortality from 1965 to 2008 across the English north-south divide: comparative observational study. BMJ. 2011;342:d508.

445. TUC. Postponing the pension: are we all working longer? Trades Union Congress analysis of issues being considered by the Independent Review of State Pension age. 2016.
446. Harvey SB, Henderson M, Lelliott P, Hotopf M. Mental health and employment: much work still to be done. Brit J Psychiat. 2009;194:201–03.
447. Harvey SB, Sellahewa DA, Wang MJ, Milligan-Saville J, Bryan BT, Henderson M, et al. The role of job strain in understanding midlife common mental disorder: a national birth cohort study. Lancet Psychiatry. 2018;5(6):498-506.
448. Psychiatrists RCo. No health without public mental health: the case for action Position statement PS4/2010. Royal College of Psychiatrists: London; 2010.
449. Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, Morris RW. 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. 2008;117(5):598–604.
450. Tunstall-Pedoe H, Kuulasmaa K, Mahonen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations. Monitoring trends and determinants in cardiovascular disease. Lancet. 1999;353(9164):1547-57.
451. Heuschmann PU, Grieve AP, Toschke AM, Rudd AG, Wolfe CD. Ethnic group disparities in 10-year trends in stroke incidence and vascular risk factors: the South London Stroke Register (SLSR). Stroke. 2008;39(8):2204-10.
452. Lovelock CE, Molyneux AJ, Rothwell PM, Oxford Vascular S. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study.[Erratum appears in Lancet Neurol. 2007 Sep;6(9):757]. Lancet Neurology. 2007;6(6):487-93.
453. Macpherson KJ, Lewsey JD, Jhund PS, Gillies M, Chalmers JWT, Redpath A, et al. Trends in incidence and in short term survival following a subarachnoid haemorrhage in Scotland, 1986 - 2005: A retrospective cohort study. BMC Neurology. 2011;11 (no pagination)(38).
454. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363(9425):1925-33.
455. Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R, Bull LM, et al. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. Circulation. 2014;130(15):1236-44.
456. Pollock AM, Benster R, Vickers N. Why did treatment rates for colorectal cancer in south east England fall between 1982 and 1988? The effect of case ascertainment and registration bias. Journal of Public Health Medicine. 1995;17(4):419-28.
457. Quinn M, Babb P, Brock A, Kirby L, Jones J. Cancer trends in England and Wales 1950–1999. Studies on Medical and Population Subjects No. 66. London: The Office for National Statistics 2001.
458. Harris V, Sandridge AL, Black RJ, Brewster DH, Gould A. Cancer Registration Statistics Scotland 1986 - 1995. Edinburgh: ISD Scotland Publications; 1998.
459. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JW. Recent trends of cancer in Europe: a combined approach of incidence, survival and mortality for 17 cancer sites since the 1990s. Eur J Cancer. 2008;44(10):1345-89.
460. Arnold M, Karim-Kos HE, Coebergh JW, Byrnes G, Antilla A, Ferlay J, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: Analysis of the European Cancer Observatory. European Journal of Cancer. 2015;51:1164– 87.
461. Hery C, Ferlay J, Boniol M, Autier P. Quantification of changes in breast cancer incidence and mortality since 1990 in 35 countries with Caucasian-majority populations. Annals of Oncology. 2008;19:1187–94.
462. Gillis CR, Hole DJ, Lamont DW, Graham AC, Ramage S. The incidences oflung cancer and breast cancer in women in Glasgow. BMJ. 1992;305(6865):1331.

463. Ellis L, Woods LM, Esteve J, Eloranta S, Coleman MP, Rachet B. Cancer incidence, survival and mortality: explaining the concepts. Int J Cancer. 2014;135(8):1774-82.
464. Hery C, Ferlay J, Boniol M, Autier P. Changes in breast cancer incidence and mortality in middle-aged and elderly women in 28 countries with Caucasian majority populations. Ann Oncol. 2008;19(5):1009-18.
465. Abdulrahman GO, Jnr. Alzheimer's disease: Current Trends in Wales. Oman Med J. 2014;29(4):280-4.
466. Riaz SP, Luchtenborg M, Coupland VH, Spicer J, Peake MD, Moller H. Trends in incidence of small cell lung cancer and all lung cancer. Lung Cancer. 2012;75(3):280-4.
467. Janssen-Heijnen ML, Coebergh JW. The changing epidemiology of lung cancer in Europe. Lung Cancer. 2003;41(3):245-58.
468. Lortet-Tieulent J, Renteria E, Sharp L, Weiderpass E, Comber H, Baas P, et al. Convergence of decreasing male and increasing female incidence rates in major tobacco-related cancers in Europe in 1988-2010. Eur J Cancer. 2015;51(9):1144-63.
469. Hardoon SL, Morris RW, Thomas MC, Wannamethee SG, Lennon LT, Whincup PH. Is the Recent Rise in Type 2 Diabetes Incidence From 1984 to 2007 Explained by the Trend in Increasing BMI. Diabetes Care 2010;33:1494–6.
470. Ryan R, Newnham A, Khunti K, Majeed A. New cases of diabetes mellitus in England and Wales, 1994-1998: database study. Public Health. 2005;119(10):892-9.
471. Holden SH, Barnett AH, Peters JR, Jenkins-Jones S, Poole CD, Morgan CL, et al. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. Diabetes Obes Metab. 2013;15(9):844-52.
472. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. British Journal of General Practice. 2010;60(572):e128–e36.
473. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69(1):4-14.
474. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. Pharmacoepidemiol Drug Saf. 2007;16(4):393-401.
475. Althubaiti A. Information bias in health research: definition, pitfalls, and adjustment methods. J Multidiscip Healthc. 2016;9:211-7.
476. Wood N, Stafford M, O'Neill D. CLOSER work package 9: Harmonised childhood environment and adult wellbeing measures user guide. London: CLOSER; 2019.
477. Quan H, Li B, Saunders LD, Parsons GA, Nilsson CI, Alibhai A, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008;43(4):1424-41.
478. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying patients with physician-diagnosed asthma in health administrative databases. Can Respir J. 2009;16(6):183-8.
479. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10 Stroke. 2005;36(8):1776–81.
480. Ronksley PE, Tonelli M, Quan H, Manns BJ, , , James MT, Clement FM, et al. Validating a case definition for chronic kidney disease using administrative data. Nephrol Dial Transplant. 2012;27(5):1826–31.
481. Lapointe-Shaw L, Georgie F, Carlone D, Cerocchi O, Chung H, Dewit Y, et al. Identifying cirrhosis, decompensated cirrhosis and hepatocellular carcinoma in health administrative data: A validation study. PLoS One. 2018;13(8):e0201120.
482. Zhang Q, Bush K, Nolan J, Schnier C, Sudlow C. Definitions of Chronic Obstructive Pulmonary Disease for UK Biobank Phase 1 Outcomes Adjudication. UK Biobank; 2008.
483. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. Diabetes Care. 2002;25(3):512–6.

484. Murray CJ, Kulkarni SC, Ezzati M. Understanding the coronary heart disease versus total cardiovascular mortality paradox: a method to enhance the comparability of cardiovascular death statistics in the United States. Circulation. 2006;113(17):2071-81.
485. Penberthy L, McClish D, Pugh A, Smith W, Manning C, Retchin S. Using hospital discharge files to enhance cancer surveillance. Am J Epidemiol. 2003;158(1):27-34.
486. Quan H, Khan N, Hemmelgarn BR, Tu K, Chen G, Campbell N, et al. Validation of a case definition to define hypertension using administrative data. Hypertension. 2009;54(6):1423–8.
487. Vosoughi K, Stovner LJ, Steiner TJ, Moradi-Lakeh M, Fereshtehnejad SM, Farzadfar F, et al. The burden of headache disorders in the Eastern Mediterranean Region, 1990-2016: findings from the Global Burden of Disease study 2016. J Headache Pain. 2019;20(1):40.
488. Noyes K, Liu H, Holloway R, Dick AW. Accuracy of Medicare claims data in identifying Parkinsonism cases: comparison with the Medicare current beneficiary survey. Mov Disord. 2007;22(4):509-14.
489. Stewart CC, Lu CY, Yoon TK, Coleman KJ, Crawford PM, Lakoma MD, et al. Impact of ICD-10-CM Transition on Mental Health Diagnoses Recording. EGEMS (Wash DC). 2019;7(1):14.