The prevalence, determinants and outcomes of multimorbidity and of resilience to multimorbidity

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List of abbreviations

ACDS	Aberdeen Child Development study
ACG	Adjusted Clinical Groups
ACONF	Aberdeen Children of the 1950s
AMND	Aberdeen Maternity and Neonatal Databank
ARI	Aberdeen Royal Infirmary
BMI	Body mass index
BMJ	British Medical Journal
CCA	Complete case analysis
CHI	Community Health Index
CHI	Community Healthcare Index
CI	Confidence Interval
CIRS	Cumulative Index Rating Scale
CIS	Continuous inpatient stay
DALYs	Disability Adjusted Life Years
DaSH	Data Safe Haven
GALI	Global Activity Limitation Indicator
GHQ	General Health Questionnaire
GP	General Practitioner
GROS	General Registry Office for Scotland
HR	Hazard Ratio
ICD	International Classification of Diseases
ICED	Index of Co-existing Diseases
ISD	Information Services Division
LTC	Long-term condition
MAR	Missing at random
MCAR	Missing completely at random
MI	Multiple imputation
MICE	Multiple Imputation by Chained Equations

MM	Multimorbidity
MNAR	Missing not at random
n/a	Not applicable
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NR	Not reported
OPCS-4	Office of Population Censuses and Surveys' Classification of Surgical Operations version-4
OR	Odds ratio
PAC	Privacy Advisory Committee
PQ	Postal Questionnaire
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOF	Quality Outcomes Framework
QOL	Quality of Life
RCT	Randomised controlled trial
RECORD	Reporting of studies Conducted using Observational Routinely-collected Data
RRMA	Remote, rural and metropolitan areas
SES	Socio-economic status
SF-36	Short-form 36
SIGN	Scottish Intercollegiate Guidelines Network
SIMD	Scottish Index of Multiple Deprivation
SMR	Scottish Morbidity Record
SNOMED-CT	Systematised Nomenclature of Medicine - Clinical Terms
SRH	Self-rated health
STROBE	Strengthening the reporting of observational studies in epidemiology
UK	United Kingdom

Declaration

I declare that this thesis was conceived, planned, conducted and written by myself. Where other sources of information have been used, these have been acknowledged. The thesis has not been submitted for any other higher degree.

Marjorie C Johnston

Additional Declaration

Subsequent to the successful examination of this thesis (23rd February 2018) and approval of minor corrections (18th May 2018), the Information Services Division (the national data processor responsible for linking the Aberdeen Children of the 1950s cohort (ACONF) to their administrative data and anonymisation) identified an error in their data-linkage process (14th June 2018). Specifically, hospital and mortality administrative data records (up to 30th September 2016) of members of the ACONF were allocated to the wrong individuals as the linkage key was scrambled. This means that conclusions regarding the associations between ACONF characteristics and exposures with the linked data outcomes as outlined in this thesis are incorrect. This affects parts of Chapter 6 (section 6.2), Chapter 8 (section 8.5), Chapter 9 (sections 9.6 and 9.8) and Chapter 10 (sections 10.3 to 10.6). This will also affect the interpretation of these sections. It is hoped that this error can be rectified and that a further analysis can be undertaken in the future. Consequently additional analyses may be available in the future by email contact with Dr Marjorie Johnston at Marjorie.johnston@abdn.ac.uk.

This event highlights challenges in maintaining data integrity in population data science. The requirement to protect individual privacy and confidentiality needs to be balanced against the need for data accuracy. As the field of population data science evolves, it is important to consider how to minimise the risk of incidences such as these. A crucial part of this will involve learning lessons from this current event.

This action was approved by:

Supervisors: Dr M Crilly, Professor C Black, Dr G Prescott, Professor S Mercer; Examiners: Professor B Guthrie, Dr S Fraser; Postgraduate coordinator: Dr K Kiezebrink; Director Institute of Applied Health Sciences: Professor A Lee; University of Aberdeen registrar: Mr R Findlay.

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Communications

Material from this thesis has been presented at a number of platforms which are listed below.

Journal article

Physical disease and resilient outcomes: a systematic review of resilience definitions and study methods. **Johnston M**, Porteous T, Crilly MA, Burton CD, Elliott A, Iversen L, McArdle K, Murray A, Phillips LH, Black C; Psychosomatics. 2015; 56(2):168-80

Conferences- oral presentation

-*World Congress of Public Health, Melbourne, April 2017.*
The influence of educational attainment on the association between social class at birth and multimorbidity in middle age in the Aberdeen Children of the 1950s birth cohort. **Johnston M**, Black C, Prescott G, Mercer S, Crilly, M.

-*European Public Health conference "Young Researcher's Forum", Vienna, November 2016.*
The influence of educational attainment on the association between social class at birth and multimorbidity in middle age in the Aberdeen Children of the 1950s birth cohort. **Johnston M**, Black C, Prescott G, Mercer S, Crilly, M.

-*Faculty of Public Health Scottish Conference, November 2015*
The influence of educational attainment on the association between social class at birth and multimorbidity in middle age in the Aberdeen Children of the 1950s birth cohort. **Johnston M**, Black C, Prescott G, Mercer S, Crilly, M.

-*Faculty of Public Health Scottish Conference, Aviemore, November 2014*
Physical disease and resilient outcomes: a systematic review of resilience definitions and study methods. **Johnston M**, Porteous T, Crilly MA, Burton CD, Elliott A, Iversen L, McArdle K, Murray A, Phillips LH, Black C.

Conferences- poster presentation

-*Society for Social Medicine Conference, Oxford, September 2014*
The role of physical disease in the development of resilient outcomes: a systematic review of resilience definitions, study methods and findings. **Johnston M**, Porteous T, Crilly MA, Burton CD, Elliott A, Iversen L, McArdle K, Murray A, Phillips LH, Black C.

Invited speaker

Multimorbidity: prevalence, risk factors and resilience in a large Scottish birth cohort. **Johnston, M.** Research Matters series, Department of Primary Care, University of Melbourne, December 2014

Prizes

-*World Congress of Public Health, Melbourne, April 2017.*
Winner of first prize (joint) for best oral presentation by an Early Career Researcher

-*European Public Health conference "Young Researcher's Forum", Vienna, November 2016.*
Winner of second prize for best oral presentation in the Forum

Thesis summary

Please see “additional declaration” on page *xvi* prior to reading this summary.

In this thesis I have studied multimorbidity and resilience to multimorbidity. The protocol was developed during the period 2013 to 2014. Multimorbidity is commonly defined as the co-existence of multiple health conditions within an individual. There is no consensus as to the precise definition of multimorbidity and the most appropriate way to measure it. Multimorbidity can be measured using simple counts of conditions or using weighted measures. Sources of data for measuring multimorbidity include medical case-note review, administrative databases and patient self-report. The variety of definitions and measures of multimorbidity available make describing the prevalence challenging. Prevalence figures range from under 10% to over 90%.

Previous research has found that increasing age and lower socio-economic (SES) status are among the important determinants of multimorbidity. Multimorbidity is associated with a range of negative outcomes including mortality, increased healthcare usage and poorer quality of life. There is a lack of large, long-term cohort studies in multimorbidity, limiting our understanding of the determinants and outcomes. The role of childhood SES status is an important gap. Educational attainment may mitigate its effect but this has not been studied.

Resilience describes the process of adapting to, or managing, sources of stress or trauma. Identifying individuals who are resilient to the effects of multimorbidity may be a way by which interventions could be developed to better enable individuals to manage disease. However, there has been little research in this area and it is limited by the lack of a consensus definition and measure of resilience in the context of disease.

Mental health is increasingly viewed as an important influence on the burden of multimorbidity but many commonly used measures do not include mental health conditions. Mental health conditions are likely to influence resilience to disease but this has not been studied.

The aim of this thesis was to define and measure the prevalence of multimorbidity and resilience to multimorbidity, to assess the role of mental health and childhood SES and to investigate the long-term outcomes, in order to inform Public Health research and action. The objectives were:

1. To determine how multimorbidity and resilience to multimorbidity should be defined and measured in Public Health research
2. To assess the prevalence of multimorbidity and resilience to multimorbidity using the measures identified in objective one
3. To assess the role of mental health conditions and childhood SES in the occurrence of multimorbidity and resilience to multimorbidity
4. To assess the impact of multimorbidity and resilience to multimorbidity on long-term outcomes

I used a combination of systematic reviews and analysis of two contrasting study populations to answer the objectives. The populations comprised the Diamond study and the Aberdeen Children of the 1950s (ACONF) cohort study.

In chapter 3 I present a systematic review which determined how multimorbidity should be defined and measured in this thesis. I concluded that multimorbidity is the occurrence of multiple diseases or conditions, and a cut-off of two or more is reasonable. Using disease counts (as opposed to weighted measures) is appropriate where a variety of determinants and outcomes are being used. Measuring multimorbidity from different perspectives is important.

I therefore measured multimorbidity by patient survey in primary care, person self-report and using secondary care administrative data. I used disease counts and set the cut-off at two or more. Primary care multimorbidity was measured in the Diamond study. The participants were asked to select from a list of 14 pre-selected conditions and these included two common mental health conditions (depression and anxiety). For person self-reported multimorbidity I included any condition an individual sees as being important to them. This was measured in the ACONF, where participants were asked to list up to six

"…long-term illnesses, health problems or disability which limit [their] daily activities or work [they] can do". I called this study population the "Original ACONF".

Secondary care multimorbidity was measured in the ACONF by linking these individuals to their secondary care administrative data record. I call this the Enhanced ACONF. I have used the conditions set out in a study by Barnett *et al*. Using Barnett *et al* in a secondary care population is a novel development and so I needed to adapt it from its primary care coding to that which can be used in secondary care. I describe the process of allocating International Classification of Diseases (ICD) codes to the Barnett measure in Chapter 4.

In Chapter 5 I present a systematic review determining how resilience should be defined and measured in this thesis. As a result I defined resilience as the ability to demonstrate healthy levels of function or wellbeing despite multimorbidity. I used the following self-reported measures: self-rated health (SRH), activity limitation and four items from the General Health Questionnaire (enjoyment, positive mood, negative mood and low self-esteem) to measure resilience.

In Chapter 6 I present the methodology for the analysis of the Diamond and the ACONF study populations. The Australian Diamond screening sample consists of 7,667 individuals aged between 18 and 75 selected from General Practices in Victoria, Australia during 2005. A range of self-reported demographic, health and wellbeing measures were sourced by questionnaire. This included self-report of 14 health conditions from which primary care multimorbidity was measured and measures of SRH and activity limitation from which resilience to primary care multimorbidity was measured.

The ACONF cohort is a longitudinal cohort based in the city of Aberdeen in the North-East of Scotland. The population consists of 12,150 individuals born in Aberdeen between 1950 and 1956. Early life data included contemporaneously measured occupational social class of the father at the birth of the participant and the results of cognition testing at age 7. Social class is a measure of SES. In 2001, 7,184 (74%) ACONF members responded to a postal questionnaire providing information on self-reported morbidities from which self-reported multimorbidity was measured. The questionnaire also provided information on

SRH, activity limitation and four questions from the General Health Questionnaire (GHQ) from which resilience to self-reported multimorbidity was measured. The questionnaire also provided self-reported highest educational attainment, information on the secondary school type (allowing assessment of whether the individual attended an elite or non-elite school) and adult health and demographic variables.

Members of the ACONF who were resident in Scotland were linked to their hospital records and mortality records (the "Enhanced ACONF"). This allowed assessment of secondary care multimorbidity measured using the Barnett conditions in 2001 (to be consistent with the timing of the questionnaire) and in 2016 (the end of the follow-up period). The administrative data were also used to assess the outcomes of hospital admission, mortality and later life secondary care multimorbidity in both the Original and Enhanced ACONF populations.

The analysis of the Diamond population was cross-sectional and the analysis of the ACONF consisted of both cross-sectional and longitudinal design. In Chapter 7 I present results for the Diamond study. Of 7,667 participants, 66% were female and the median age was 52 years. There were 2,922 individuals (38%) with primary care multimorbidity, the prevalence was similar between the genders and rose with increasing age. The prevalence decreased with higher levels of educational attainment ($p<0.05$) and was lower in those who were employed. The prevalence was higher in those who smoked compared to those who did not. The prevalence of no coexisting mental health condition decreased with the increasing number of physical conditions. For example it was 64% (95% CI 61% - 68%) in those with three conditions and 42% (95% CI 34% - 49%) in those with over five.

The prevalence of SRH resilience to primary care multimorbidity was 95%. This was higher in women compared to men, and was higher in those who had higher educational attainment and who were employed or studying. Resilience levels were lower in smokers compared to non-smokers. The prevalence of activity limitation resilience to primary care multimorbidity was 52%. This was significantly lower in men compared to women and in older age groups compared to young. The prevalence was higher in those with higher educational attainment and those who were employed. It was lower in smokers compared

to non-smokers. The prevalence of SRH resilience was higher in those with no mental health conditions compared to those with two. The prevalence of activity limitation resilience was not significantly associated with the number of mental health conditions.

In Chapter 8 I summarise the baseline characteristics of the Original and Enhanced ACONF study populations. There were 7,184 individuals in the Original ACONF, 52% were female and the mean age was 48 (SD 1.5). Compared to those not responding to the questionnaire, the responders were more likely to be female, have a higher social class at birth and higher mean cognition scores at age 7. For the Enhanced ACONF 2001 populations, of the 12,150 baseline cohort members, 9,547 (79%) were alive and resident in Scotland in September 2001. Of these, 8,438 (88%) were successfully linked to administrative data and form the study population. For the 2016 population, there were 8,411 participants alive and resident in Scotland at 30th September 2016. Of these 7,353 (87%) were successfully linked to administrative data and form the study population. Those without linked data were more likely to have been born into the highest or the lowest social class categories, but there was no difference by gender or by age 7 cognition score.

Of 8,438 individuals in the 2001 Enhanced population, 51% were male and the mean age was 48. Almost 65% of the population had responded to the postal questionnaire, meaning there was a large proportion of missing data for questionnaire variables including educational attainment and resilience measures. Of 7,353 individuals in the 2016 population, 50% were male and the mean age was 66. Almost 66% of the population had responded to the postal questionnaire.

In Chapter 9 I present results for the Original ACONF. The prevalence of self-reported multimorbidity was 5%, with no difference by age and little difference by gender. There was a statistically significant association between educational attainment, cognition score at age 7 and secondary school type with the presence of self-reported multimorbidity. Those with lower birth social class were more likely to have lower adult social class. I found that being born into a lower social class led to an increased likelihood of self-reported multimorbidity, however if an individual achieved a higher educational attainment this mediated the effect of social class. These findings were unaffected by taking into account

cognition scores at age 7 and whether the individual attended an elite or non-elite secondary school. There was no association between self-reported multimorbidity in 2001 and the presence of secondary care multimorbidity in 2016. There was also no association with mortality rate or hospital admissions.

I found that the prevalence of resilience to self-reported multimorbidity was similar for the SRH measure (60%) and the two of the GHQ measures (53% for enjoyment and 66% for positive mood state). The prevalence was lower in the remaining two GHQ measures (19% for negative mood state and 27% for low self-esteem). I found no association between social class at birth and each of the five resilience measures but confidence intervals were wide reflecting the lack of precision due to low power. For SRH resilience only, I found that the resilient group had a lower mortality rate than the expected group but the number of deaths were low.

In Chapter 10 I present results of the analysis of the Enhanced ACONF population. In 2001, the secondary care multimorbidity prevalence was 3% and in 2016 it was 10%. I found no association between the social class of an individual's father at the birth and the presence of secondary care multimorbidity in 2001 or in 2016. There was a cross-sectional association between deprivation (an area based measure of SES) and secondary care multimorbidity. There was a strong association between secondary care multimorbidity in 2001 and secondary care multimorbidity in 2016 and with the mortality rate. There was no association with the hospital admission rate. Analysis of resilience was limited by low power. There was a slightly lower mortality rate in those with SRH resilience. However, the number of deaths was small and death rate confidence intervals were very wide.

I finish the thesis with an overall discussion (Chapter 11). My thesis contributes to the evidence base for consensus definitions and measures of multimorbidity and resilience to multimorbidity. I adapted a commonly used multimorbidity measure for use in Scottish secondary care (and other systems using ICD coding). I found that mental health conditions played an important role and should be explicitly considered in studies of multimorbidity and resilience. A range of SES factors influence multimorbidity and resilience to multimorbidity and tackling these will be important to reduce health inequalities. The

measures of SRH and activity limitation are useful measures of resilience and warrant further investigation.

The approaches used in studying resilience in my thesis, despite being limited by power, can be used to inform methodology in future research with the aim of developing evidence based interventions to promote resilience. My own future research plans are to incorporate multimorbidity into models of ageing and investigate resilient ageing.

Part One: Introduction, aims and structure

1 Introduction

1.1 Overview

This thesis investigates multimorbidity and resilience to multimorbidity. In this introductory chapter I set the scene as it was when I designed my protocol between 2013 and 2014. I concentrate upon research conducted in countries defined by the United Nations as "developed economies" (for example, the United Kingdom (UK), United States, Australia, Canada and France).[1]

I begin by defining health and disease and describing healthcare systems. I go on to illustrate what is known about the definition, measurement and prevalence of multimorbidity. I then present evidence surrounding the determinants and key outcomes of multimorbidity with specific focus upon cohort studies of multimorbidity and the role of childhood socio-economic status (SES).

An important influence on the development of the aim and objectives in this thesis was a study of multimorbidity in Scottish primary care patients by Barnett *et al*.[2] This was published in 2012 and is a high profile study with a significant impact in the research community with regards to understanding the prevalence and determinants of multimorbidity. Given its profile and its influence upon my own thesis design, I describe the study features and findings.

Following this I illustrate what is known about resilience in the context of health and multimorbidity. I then describe the importance of mental health conditions with regards to multimorbidity and resilience. I go on to illustrate the management of multimorbidity and describe views on multimorbidity from the perspective of patients, caregivers, healthcare

workers, wider society and the political sphere. I conclude this chapter with a summary of the evidence and the key gaps in knowledge which will be addressed in this thesis.

1.2 Definition of health and disease

Health is often described using the World Health Organization (WHO) 1948 definition: "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*".[3] The definition was praised for being holistic and emphasising positive aspects of health and not just the negative. However it is also criticised for being absolute, as "complete" health across all these domains is unlikely to be achievable and so most individuals would be described as not being in good health.[4] Indeed there is no consensus as to what "complete" health actually is or on how to measure it.[4] Despite criticisms of the WHO definition, there is no single new definition of health to replace it. There are calls for definitions which are based on the concept of health being the ability to adapt to changing environments and which take into account the individual's own view on whether they are healthy.[4,5]

The WHO has been responsible for the global classification of diseases since 1948.[6] This is called the "International Classification of Diseases" (ICD) and is the international standard for reporting and diagnosing disease. It is also used to monitor disease prevalence and incidence trends.[6] There are other sources of disease definitions and classifications (for example individual countries may adopt different approaches) but the WHO system remains a dominant influence.

There are complexities over defining disease. What is defined as disease may be influenced by historical and cultural context, developing understanding of physiology and pathology, by researchers and healthcare providers, and by pharmaceutical companies.[7] For example, osteoporosis was originally viewed as an unavoidable part of normal ageing before being classed as a pathology in the early 1990s by the WHO.[8] What is defined as disease may also be driven by those with vested interests, for example pharmaceutical companies and healthcare providers, who benefit financially in being able to "treat" disease.[4] This may

include pressure to lower the threshold for intervention in factors such as cholesterol levels and blood pressure.[4]

Diseases are often defined as being physical conditions or mental health conditions. The former is often seen as being a result of organic dysfunction and the latter as a disorder of the mind.[9] Physical conditions include ischaemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD). Common mental health conditions are depression, anxiety, schizophrenia and bipolar disorder.

The distinction between physical and mental health conditions is reinforced by the separate categorisation of "mental and behavioural disorders" in the ICD[10] as well as the division between psychiatric and medical healthcare in most health services. This represents the philosophical concept of "Cartesian mind-body dualism", the view that the mind and body are separate.[11] However, the distinction between the two has been criticised for being overly simplistic in ignoring that some mental health conditions have an organic cause and that the mind and body are involved in the experience of all conditions.[9] For example, pain levels resulting from "physical illness" are affected by a wide variety of psychological response mechanisms and can vary between individuals. The presence of a mental health condition may lead to physical disease due to both maladaptive health risk behaviours and the physiological effects of the condition, whilst the impact of the burden of a physical disease may cause or worsen a mental health condition.[12,13]

The practice of medicine has been criticised for its dualistic approach and in particular its focus upon the biomedical model.[11] This "reductionist" approach involves targeting physical or chemical causes of disease or upon tackling visible lesions.[14] The wider psychological, social and environmental determinants of illness are ignored and illnesses resulting from these factors, in particular mental health conditions, were not seen as *a priori*ty or as health conditions in themselves.[11,15] Indeed, mental health conditions were not classified as diseases by the WHO until 1949.[7]

The classification of mental health problems as diseases has not solved the problem of mind-body dualism. This particularly relates to depression and anxiety which encompass a

range of different underlying pathologies and aetiologies. There is strong evidence that a large proportion of these illnesses arise due to wider psychological, social and environmental determinants. However, the development of treatment has predominantly revolved around pharmacological management.[16] There are also concerns that what is defined as depression or anxiety increasingly includes what might be viewed as normal human experience and represents medicalisation of personal emotions. For example, grief due to factors such as bereavement has been included in the American Psychiatric Association's classification system for mental disorders.[16]

There is much evidence to show that health is influenced by a wide range of risk and protective factors (determinants). The determinants of health are vast and interconnected. They include personal factors (such as age, gender and genetics), the physical environment (such as housing quality and climate), the social environment (such as social connections and status), the economic environment (such as personal income and economic policy) and the political environment.[17] Despite this, medical terminology is still predominantly focussed on the concept of "risk factors". These are frequently also limited to personal features and so-called "lifestyle factors". The latter encompass elements such as smoking, alcohol consumption, dietary patterns and exercise levels. These factors have been shown to be linked with poorer wider determinants of health (such as poorer social and economic status) and the use of the term "lifestyle" has been criticised for attaching blame to the individual themselves.[18]

A final concept for discussion in this section is the distinction between acute disease and chronic disease. Chronic diseases may be defined as those which are non-communicable, are of long duration and slow progression.[19] Examples are IHD and COPD.[19] Acute conditions are those which can be of a short duration such as myocardial infarction (MI) and pneumonia. But these terms are open to interpretation with regards to what duration means "chronic", the fact some acute conditions are manifestations of underlying chronic conditions (for example, MI as a result of IHD) and some communicable diseases such as Human Immunodeficiency Virus (HIV) have a chronic duration due to improved management. There is also debate over whether some conditions are risk factors for

disease or diseases themselves. For example, hypertension has been classed as both a risk factor for conditions such as IHD and a disease in itself.[20]

In the thesis I distinguish between physical conditions and mental health conditions to reflect that these are treated as being distinct in both the WHO disease classifications and across healthcare systems. I do not attempt to refine what is meant by "chronic" or "acute" disease, instead, I acknowledge that there is no consensus.

1.3 Design of healthcare systems

Most countries have systems in place for providing healthcare. These vary hugely in design, coverage and funding mechanisms. A healthcare system may be funded by taxation, by payment from the individual requiring care, by private healthcare insurance or social healthcare insurance. Commonly systems incorporate more than one of these.[21]

Here I briefly describe the concepts of "primary" and "secondary" care as these form important parts of the analysis in the thesis. There will be variations between healthcare systems as to which conditions are managed in primary care versus secondary care services and as to the scope of the care. The availability of services and the healthcare service funding mechanism will determine who is able to access care and which conditions may be managed. I discuss the systems relevant to the analysis in this thesis in later chapters.

Primary care broadly describes care by generalists and is usually conducted in a community setting. The delivery of care is part of the "General Practice" (or Family Medicine) model encompassing a multidisciplinary team including general medical practitioners, nurses, health visitors, pharmacists and others.[22]

Secondary care generally refers to care provided by specialists for a particular condition and normally in a hospital setting.[23] Secondary care in systems such as in the National Health Service (NHS) in Scotland and in the UK can usually only be accessed via referral from primary care, or by attendance at Accident and Emergency departments.[24] Conditions requiring admission or review in secondary care settings will likely be severe conditions

(including acute severe episodes of underlying chronic conditions) or require complex, specialised care (for example dialysis management for patients with chronic kidney disease).

Primary care systems therefore act as "first-contact care systems" and are often described as providing a gatekeeping role for secondary care services. However, primary care services also provide ongoing, comprehensive and coordinated care for a wide range of health conditions including chronic conditions such as chronic kidney disease. Their role incorporates promotion and prevention approaches alongside clinical care.[22]

1.4 Definition and measurement of multimorbidity

1.4.1 Definition of multimorbidity

Multimorbidity is commonly defined as the co-existence of multiple health conditions within an individual.[25,26] A related term, "comorbidity" describes the burden of illness co-existing with a particular index condition.[27]

There is a lack of consensus as to the precise definition of multimorbidity and the most appropriate way to measure it.[28] In research there is frequent over-lap with the term "comorbidity" despite increasing consensus that these are distinct terms and should be treated as such.[29,30] The definition of multimorbidity can vary in a number of ways, for example whether the minimum cut-off of the number of conditions equalling multimorbidity is set at two or more, or at a higher level.[31] An additional complexity is variation in the nature of health conditions included. Some define multimorbidity as being multiple "chronic diseases" and others do not specify.[32]

1.4.2 Measurement

The measurement of multimorbidity is closely related to its definition. There are a number of key methodological concepts in measuring multimorbidity: counts, weighting, data sources and the look-back period.

Disease counts

Disease counts are a simple sum of conditions from a defined list. There are a wide range of disease count measures available with varying numbers of included conditions.[26] Fortin *et al* in a review of prevalence studies of multimorbidity in 2012, found counts ranging from including five conditions to more than 185.[26] Some disease count measures only include what may be defined as chronic conditions and some include risk factors and acute conditions.[32,33]

Weighted measures

Weighted measures are those in which values are attached to included conditions based upon their association with a particular outcome.[34] Many tools used as weighted measures of multimorbidity were originally designed to measure comorbidity.[34] The Charlson comorbidity index is a commonly used measure. It consists of 17 conditions which have weights attached based on the relative risk of 1 year mortality in a cohort of breast cancer patients.[35] The conditions include diabetes, renal disease and Acquired Immunodeficiency Syndrome (AIDS). The latter was given the highest score (a value of 6). There have been updates and modifications of the Charlson comorbidity index to account for different population groups, outcomes and the changing management and prognosis of disease.[36] For example, the presence of HIV is frequently used instead of AIDS as the latter is very rare due to the availability of effective treatments.[37] Additionally due to improved management and survival it is probable that neither HIV nor AIDS should be allocated such a high score.[37]

The Charlson comorbidity index and other weighted measures such as the Cumulative Index Rating Scale, are based on diseases.[38,39] Others use different approaches. For example, the Chronic Disease Score is based on medical prescriptions and the Index of Coexisting Disease combines an assessment of disease severity with functional impairment.[38]

Data sources

There are a range of possible sources of data for measuring multimorbidity. These include medical case-note review, administrative databases and patient self-report. Case-note

review involves sourcing information about an individual's health conditions from the documentation which is made when they utilise health services.[27] Many early multimorbidity measures were developed and validated using information sourced from medical case-note review and this is often considered the gold-standard.[27] However, case-note review is resource intensive as it can be a lengthy process, particularly when the study population is large.[27]

Data from administrative databases are increasingly used in studies. Administrative data are defined as: "*information collected primarily for administrative (not research) purposes*".[40] These are often data from government and other national organisations. These type of data are also called "routine data" in that they are collected as part of an ongoing system. Non-routine data are those collected *ad hoc*, for example in surveys conducted in research.[41]

Administrative data in healthcare includes databases of reasons for hospital admissions. The conditions coded in these databases may be used to determine the presence of multimorbidity. The advantages of using administrative data include being able to achieve a large sample size at relatively low cost, better population coverage, the potential to gather a larger variety of heterogeneous data on individuals and the ability to follow-up over long periods of time.[42] Disadvantages of administrative data relate to its underlying quality and to its availability.[42] Research comparing multimorbidity measures derived from case-note review to those derived from administrative databases has produced evidence to support the use of administrative data as an alternative to case-note review.[27,43-45]

Patient self-report is a further data source. This can vary from patients selecting from a list of conditions set by clinicians or study teams to patients being asked to report any condition which they feel they have.[39,46,47] Research suggests that patient self-report captures a different construct of multimorbidity by providing information on conditions important to the individuals themselves.[47]

Look-back period for administrative data

Ascertaining the prevalence of morbidities in healthcare administrative databases requires setting an index date and a "look-back" period. Prevalence may be defined as the proportion of a population with the condition of interest.[48] The index date is that which is reported as the prevalence date. The look-back is the time period during which conditions may be sourced from healthcare records for inclusion in a measure of the prevalence of comorbidity or multimorbidity.[49] The reason for setting this period is that the record of the reasons for a single admission will likely miss conditions which are important but happen not to have been active during that admission.

The length of the look-back period has important implications. Including conditions based upon a short look-back time period (for example the previous six months) may under-estimate important ongoing conditions, such as previous stroke, which may have led to an admission more than six months previously. Having a very long look-back period (for example as far back as records are available) may over-estimate the degree of multimorbidity by including conditions which have now resolved or which no longer cause the individual any problems.[44,50]

"Look-back" overlaps with the concept of "period prevalence" in epidemiology. A point prevalence (assessing the prevalence at a single point in time) will likely under-estimate acute or episodic (not always active) conditions. A period prevalence, in which the proportion of those with the conditions is assessed over a defined time period, is recommended as being superior although there is no single recommended length for period prevalence estimates.[48]

1.5 Prevalence of multimorbidity

The variety of definitions and measures of multimorbidity available make describing the prevalence challenging. Additionally, the setting and patient population in which the research is conducted will influence the findings. The systematic review by Fortin and colleagues, which sourced studies describing the prevalence of multimorbidity, found wide

variation in prevalence estimates.[26] In studies in General Practice (from studies based in the UK, wider Europe, Canada and Australia) the prevalence ranged from just over 3% to almost 100%. In studies not restricted to healthcare populations, the prevalence ranged from 13% to 72%.[26] This included studies from Europe, Canada and the United States.

A 2014 systematic review by Violan *et al* identified 44 studies which examined the prevalence of multimorbidity and determining factors in primary care.[51] Prevalence estimates ranged from 13% to 95%. The authors found great heterogeneity in included studies with regards to multimorbidity definition and measurement, as well as the characteristics of the study populations and the data sources used to measure multimorbidity. The authors highlighted a need for consensus in the operational definition of multimorbidity. [51]

Despite challenges in measuring the prevalence, it is acknowledged that multimorbidity prevalence increases with age.[26,31] Globally, populations are ageing rapidly, with the WHO projecting that between 2015 and 2050 the proportion of the population aged over 60 years will almost double (from 12% to 22%).[52] Additionally the burden of chronic disease (for example diabetes and stroke) is rising and this is projected to continue without public health and other interventions.[53] However, it is important to be aware that multimorbidity also places a burden on younger populations. Barnett *et al* found that the absolute number of individuals with multimorbidity aged under 65 was greater than the number aged over 65.[2]

1.6 Determinants and outcomes of multimorbidity

1.6.1 Overview of the literature

There have been a number of systematic reviews of multimorbidity focussing on the determinants of multimorbidity and its outcomes.

Marengoni *et al*, in a systematic review of multimorbidity in older people, sourced only four papers examining risk factors for multimorbidity (and three were from the same population

cohort).[31] The risk factors were increasing age, lower education and a history of a higher number of previous diseases. In 12 cross-sectional studies they found evidence that multimorbidity was more common in older age, in women and in persons with lower SES.

The review found good evidence that multimorbidity is associated with poorer functional status.[31] There was mixed evidence as to the association between multimorbidity and mortality, although the majority of included studies did find that the coexistence of multiple diseases was associated with an increased risk of mortality.[31] Similarly, evidence was mixed regarding the association between multimorbidity and lower quality of life but the majority of studies did find an association.[31] The authors concluded there was a need for a life-course approach to examining determinants and outcomes of multimorbidity, including lifestyle and social determinants and taking into account factors such as resiliency.[31]

The systematic review by Violan *et al*, described in the previous section, also assessed the determinants of multimorbidity in included studies.[51] In concurrence with the review by Marengoni *et al*, there was evidence that multimorbidity was associated with older age, female gender and lower SES.[51] Additionally one included study found the presence of mental health disorders to be associated with a higher prevalence of physical condition multimorbidity. Almost 60% of the included studies were cross-sectional and the remainder were cohort studies.[51]

A systematic review by France *et al* in 2012 of prospective cohort studies in primary healthcare, sourced five eligible cohort studies. From these there was evidence that multimorbidity was associated with increased healthcare costs, inpatient admission, mortality, service use and reduced functional status.[54] The review found that psychological and social factors (including negative life events, a small social network and an external locus of control) were associated with multimorbidity. Additionally, certain combinations of conditions were associated with a higher risk of negative outcomes than others (for example chronic respiratory disease, congestive heart failure and diabetes were associated with greater physical decline). The authors commented that no study had studied socio-economic factors in detail and that whilst all studies defined multimorbidity as being two

or more conditions in a patient, there was no consensus approach towards the measurement tool used. The authors also found that methodological quality was variable and had concerns over the lack of use of conceptual frameworks, the sampling methodologies and the sample size.[54]

1.6.2 Findings of cohort studies

The authors of systematic reviews have commented on the lack of a life-course approach to multimorbidity research and the lack of large, long-term longitudinal cohort studies.[31,54] Life-course epidemiology may be defined as the study of life-long effects of factors from across the life-course and their influence on health or disease. This may include pre-natal factors such as exposure to maternal smoking in the womb, childhood factors such as the SES of the parents, and adult factors such as alcohol use, occupation and exposure to environmental adversity.[55]

Cohort studies are those in which the exposure (hypothesised determinant) is measured before the outcome has occurred and there is follow-up over time to assess the nature of the association between exposure and outcome. This type of study is deemed to be *longitudinal*. Cohort studies may be prospective (where the exposure data are collected at the time of occurrence and prior to the outcome occurring) or retrospective (where the exposure and outcome data are ascertained retrospectively). Retrospective designs may be time and cost efficient but are reliant upon the availability of high quality data.[56]

In order to investigate the availability of cohort studies in multimorbidity research I carried out a systematic search of the literature. The aim was to identify cohort studies assessing factors associated with multimorbidity or outcomes in multimorbidity in adult populations. The method is detailed in Appendix 1, section 13.1. The characteristics and findings of the 15 included studies are shown in Table 1.

Table 1: Introduction: Characteristics of included multimorbidity cohort studies

Study	Cohort type	Number- start of follow up	Number- end of follow up	Follow-up length	Exposure	Outcome	Summary of study findings*
Aarts 2012 [57]	Prospect.	1,823	1,184	6 years	3 groups: healthy, single morbidity and MM	Health related functioning (measured by SF-36)	MM associated with poorer physical functioning at all measurements. MM appeared to be unrelated to mental functioning.
Aarts 2011 [58]	Prospect.	1,763	1,123	12 years	MM	Cognition	MM clusters associated with cognition during a 12-year follow-up period. The disease combination malignancies and movement disorders MM also appeared to significantly affect cognition.
Ajmera 2012[59]	Prospect.	Not clear	8,963	3 years	MM	Hospitalisations which could have been avoided by timely, appropriate, and high-quality outpatient care.	MM (with or without mental illness) had an independent and significant association with avoidable hospitalisations. However, presence of mental illness alone was not associated with poor quality of care.
Demirchyan 2013 [60]	Retrospect.	725	725	22 years	SES, health behaviour, psychosocial (e.g. post-traumatic growth score, number of stressful life events).	Incident MM	Perceived low affordability of healthcare services, poor living standards during post-earthquake decade, and lower education were independent predictors of incident MM during period 1990–2012. Stressful life events and poor social support were psychosocial determinants of incident MM. Participants' baseline BMI was independently associated with incident MM.
Kuo 2013 [61]	Prospect.	959,990	903,376	6 years	MM	Annual healthcare costs	Low income earners had the highest prevalence of MM. After controlling for age and gender, an increasing number of MM conditions was associated with higher total healthcare costs.
(contin. overleaf)							

Study	Cohort type	Number- start of follow up	Number- end of follow up	Follow-up length	Exposure	Outcome	Summary of study findings*
Menotti 2001 [62]	Prospect.	2,285	Not clear	10 years	MM	Mortality	MM found to be associated with mortality
Nagel 2008 [63]	Retrospect.	13,781	13,781	Median 8.7 years	Educational attainment	MM	Educational level associated with MM. Increasing BMI most important additional predictor. Fully adjusted model, could not explain socio-economic inequalities in MM.
Payne 2013 [64]	Retrospect.	180,815	No reported loss to follow-up	1 year	MM	Hospital admission	Physical MM was strongly associated with unplanned admission to hospital, including admissions that were potentially preventable. The risk of admission was exacerbated by the coexistence of mental health conditions and socio -economic deprivation.
Quinones 2011 [65]	Prospect.	17,517	Not reported clearly. 9% missed at least one interview	Up to 11 years	MM	MM accumulation	1. MM accumulates over time 2. Black have higher initial levels of MM but slower accumulation than White 3. MM trajectory for Mexican Americans is lower than for White Americans 4. Including education in 2. Does not significantly change conclusion 5. Higher functional impairment, worse self-rated health, greater depressive symptoms, and higher BMI in the previous period are all associated with higher trajectories of MM (i.e., an upward shift of the MM trajectory)
Ruel 2013 [66]	Retrospect.	1,020	1,020	5 years	Foods, macro- and micro-nutrients	MM	High consumption of fruit and vegetables and grain products other than rice and wheat were associated with healthier stages in the evolution of MM.
Salisbury 2011 [67] **(contin. overleaf)**	Retrospect.	99,997	99,997	3 years	MM	Consultation rates and continuity of care	People with MM had higher consultation rates and less continuity of care compared with people without MM.

Study	Cohort type	Number- start of follow up	Number- end of follow up	Follow-up length	Exposure	Outcome	Summary of study findings*
Seeman 1989 [68]	Prospect.	4,174	2,539 for depression at 9 years. 3,938 for mortality at 17 years	9 years for depression and onset of multiple new conditions, 17 years for mortality	MM	Mortality, onset of multiple new conditions and depression	Age-adjusted analyses: baseline MM significantly associated with 17-year mortality, the development of multiple new conditions and occurrence of depression at 9-years. With adjustments for socio-demographic characteristics and health behaviours: all associations remain significant. The association with depressive symptoms, remains significant for the younger age group only, the association with mortality becomes non-significant in both age groups.
Vila-Rodriguez 2013 [69]	Prospect.	293	262	Median of 23.7 months	MM	Mortality	Participants who subsequently died had a greater baseline MM score (median=4) than those who were alive at follow-up (median=3); however, this difference was not statistically significant.
Woo 2013 [70]	Prospect.	4,000	3,401	4 years for non-mortality outcomes 9 years for mortality	Independent and combined effects of multi-morbidity, dependency, and frailty	Four health outcomes (mortality, decline in physical function, depression, and polypharmacy).	MM, dependency, and frailty may occur independent of each other, and also overlapped. All were significantly related with all health outcomes examined (mortality, decline in physical function, depression, and polypharmacy). MM is the overriding factor for polypharmacy.
Van den Akker 2001 [71]	Retrospect.	3,551	3,551	2 years	Six psychosocial concepts (coping styles, health locus of control, life events, long-term difficulties, type of living arrangement, and social network)	MM accumulation	After adjustment for basic socio-demographic variables, a high internal locus of control belief was found to be protective for the occurrence of morbidity, negative life events increased the risk. Characteristics specifically protective for the occurrence of MM were: a high internal locus of control belief, living as a couple or in a family as compared to living alone and a large social network.

* These are multimorbidity specific study conclusions Abbreviations: Prospect., prospective; Retrospect., retrospective; MM, Multimorbidity; SF-36, Short-Form 36; BMI, Body Mass Index; SES, socio-economic status

Nine studies were prospective[57,59,61,62,65,68-70,72] and six were retrospective.[60,63,64,66,67,71] The population size at the start of follow-up ranged from 293[69] to 959,990.[61] The studies with large sample sizes at baseline had tended to have short follow-up times and the studies with long follow-up tended to have small sample sizes. The study with the shortest length of follow-up time was Payne *et al* (1 year) and their population at baseline was 180,815.[64] The study with the longest follow-up time was Demirchyan *et al* (22 years) and their population at baseline was 725.[60]

Two studies (by Quinones *et al* and Seeman *et al*) examined multimorbidity as both an exposure and an outcome.[65,68] Six studies examined determinants of multimorbidity[60,63,65,66,68,71] and 11 studies considered multimorbidity as an exposure.[57,59,61,62,64,65,67-70,72]

Quinones *et al* examined multimorbidity as an exposure and multimorbidity accumulation by different racial and ethnic groups in the United States as the outcome.[65] There were differences between ethnic groups (for example black Americans had higher initial levels of multimorbidity but slower accumulation of conditions than white Americans).[65] The authors also observed that multimorbidity accumulation was higher when individuals had higher functional impairment, poorer self-rated health, a higher level of depressive symptoms and higher body mass index (BMI) at baseline.[65] Seeman *et al* found that multimorbidity at baseline was associated with the development of multiple new conditions (a higher degree of multimorbidity) at follow-up.[68]

With regards to determinants of multimorbidity, Demirchyan *et al* examined factors associated with multimorbidity in a cohort of survivors of an earthquake in Armenia.[60] The authors found poorer SES, higher BMI, stressful life events and poorer social support were associated with incident multimorbidity.[60] Nagel *et al* in a retrospective study, observed that educational attainment was significantly associated with multimorbidity.[63] Van den Akker *et al* concluded psychosocial factors such as coping styles and social network availability were associated with multimorbidity. [71] Ruel *et al* found that higher fruit, vegetable and grain consumption was associated with a lower risk of multimorbidity.[66]

In the cohort studies with multimorbidity as the exposure, the consensus was that multimorbidity is associated with poorer outcomes. For example Aarts *et al* (with two included studies) observed that multimorbidity was associated with poorer physical functioning and poorer cognition.[57,72] Other studies found multimorbidity was associated with potentially avoidable hospitalisations, higher healthcare costs and higher consultation rates.[59,61,64,67] Multimorbidity was associated with mortality in three studies[62,68,70] with one additional study by Vila-Rodriguez *et al* finding a non-significant association between a higher baseline multimorbidity score and mortality.[69] Payne *et al* concluded that the risk of hospital admission was higher in those with multimorbidity who also had co-existing mental health conditions and poorer SES.[64] Seeman *et al* found that multimorbidity was associated with the occurrence of depression at 9 year follow-up.[68]

1.6.3 Childhood socio-economic status and multimorbidity

A key theme emerging from the evidence described in the previous sections is that SES is an important determinant of multimorbidity. The SES is a description of an individuals combined social and economic status. There is much evidence supporting the fact that lower social and economic position in society leads to worse outcomes across most health conditions.[18] Health inequality describes *"differences in health status or in the distribution of health determinants between different population groups"*.[73] Some inequalities may be unavoidable (for example differences in health outcome due to age or genetic factors) whilst others may be deemed avoidable and unfair (for example differences in health outcome resulting from the environment in which an individual lives). Where the latter occurs it is described as an *inequity in health*.[73]

The SES of individuals is measured in a variety of ways including social class, occupation, education and income.[18] Social class based on occupation was a common measure in the UK during the 20th century with categories ranging from professional and managerial (for example doctors and dentists) through to unskilled (for example dock labourers).[74] There are also area based measures of deprivation which include composites of indicators such as income levels, housing quality, access to health services and crime levels. These

measures are frequently used as measures of inequality, an example being the Scottish Index of Multiple Deprivation (SIMD).[75]

Research has linked childhood socio-economic circumstances with poorer adult health and early mortality.[76,77] Many such studies rely on adult recall of childhood SES raising concerns as to accuracy and potential sources of bias. For example, Batty *et al* in a study of the Aberdeen Children of the 1950s (ACONF) cohort, found that agreement was moderate between contemporaneously measured childhood social class and adult recall of childhood social class, with disagreements mostly occurring due to participants reporting a higher social class than that which had been recorded at the time.[78] Using SES measured contemporaneously is therefore desirable.

Little research has examined the influence of childhood SES on adult multimorbidity. In order to investigate this gap further I conducted a systematic search of the literature with the aim to summarise the research regarding the association between childhood SES and multimorbidity in later life. The method for the review is in Appendix 1, section 13.2. Three studies were included and the findings are summarised in Table 2.[79-81]

Two of the studies were longitudinal and one was cross-sectional. Cornish *et al* examined 346 children from birth to age 18[79] and Neeleman *et al* examined 5,362 individuals up to age 43.[80] The remaining study by Tucker-Seeley *et al* was a cross-sectional analysis of 7,305 participants aged 50 and older.[81] In Cornish *et al* and Neeleman *et al* the SES was measured contemporaneously,[79,80] whilst Tucker-Seeley *et al* measured it retrospectively.[81]

Table 2: Introduction: Studies examining early life socio-economic status in association with multimorbidity

Study	Study aim	Population studied	Relevant socio-economic exposures	Outcome	Findings
Cornish 2013[79]	"We have investigated whether there is an association between socio-economic position measured during pregnancy and MM during childhood and adolescence"	Participants in ALSPAC were linked to the General Practice Research Database 20,248 pregnant women living in and around Bristol, UK with due dates April 1991 to December 1992. 346 children with complete data included. Follow-up to age 18 reported.	Measured contemporaneously during pregnancy and early childhood: 1. Social class (the lower of maternal or paternal social class) 2. Parental educational level 3. Housing tenure 4. Family adversity index (measure of social adversity) 5. Townsend score (based on address at study enrolment)	MM measured in three ways: 1. Count of the number of drugs prescribed 2. Count of chronic diseases 3. Person's predicted resource use score. Latter two derived using the Johns Hopkins ACG system. Measured during: 0 to 9 years and 10 to 18 years.	Non-statistically significant association between higher condition counts among children aged 0- 9 years and lower maternal education. Children whose mothers were better educated had higher rates of chronic illness between 10-18 years. Living in a more deprived area associated with a higher odds of chronic illness between 10-18 years.
Tucker-Seeley 2011[81]	"In this study we investigate the association among childhood financial hardship, lifetime earnings, and MM."	Cross-sectional analysis of 7,305 participants aged 50 and older from the 2004 Health and Retirement Study (United States) with linkage to Social Security Records.	1. Childhood financial hardship- retrospective recall (asked if ever had to move due to financial difficulties) 2. Average annual lifetime earnings Covariates: Included education	MM count of six chronic conditions reported in the 2004 Health and Retirement Survey (cancer, heart disease, lung disease, stroke, diabetes, and hypertension)	Childhood financial hardship and lifetime earnings associated with morbidity. Childhood financial hardship associated with higher number of conditions. Increase in lifetime earnings associated with a lower number of conditions.
Neeleman 2002[80]	"…we examined the hypothesis that personality attributes and early childhood environmental variables which are known overall prospective associations of adult psychiatric and somatic ill health, affect these two outcomes [adult psychiatric and somatic ill health] directly, and independently of each other."	MRC National Survey of Health and Development: 5,362 randomly selected births in England, Scotland and Wales, followed-up from 1 week in 1946 until the subject's 43rd year. 62% of original sample participated in home visit questionnaire at age 36 (t1) and 59% at second visit aged 43 (t2).	Paternal social class at age 15 measured contemporaneously from survey at age 15.	Somatic MM (from list of 20 chronic conditions) and psychiatric MM measured at t1 and t2.	Low paternal social class not directly linked with ill-health in adulthood- although it was linked via some of the temperamental and behavioural variables.

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; MM, multimorbidity; SES, socio-economic status; ACG, adjusted clinical groups; MRC, Medical Research Council

Multimorbidity was measured during childhood and adolescence in Cornish *et al* and in adulthood in Neeleman *et al* and Tucker Seeley *et al*.[79-81] Despite the variations across studies, there was evidence from all three that childhood socio-economic circumstances affected the development of multimorbidity. Childhood financial hardship was associated with a higher number of chronic conditions in the study by Tucker Seeley *et al*.[81] In the study by Neeleman *et al*, paternal social class was not directly associated with multimorbidity in adulthood, but was linked to multimorbidity via some temperamental and behavioural variables.[80]

Higher deprivation was associated with higher rates of chronic illness in those aged between 10 and 18 in the study by Cornish *et al*.[79] However, in this study, children whose mothers were better educated also had higher rates of chronic illness between 10 to 18 years. Education of the mother and deprivation are two different measures of SES but the authors cannot fully explain this contradictory finding other than it may reflect the nature of conditions more commonly seen in children. Asthma and eczema were amongst the most prevalent in the study and there is some evidence these are more commonly seen in healthcare in those whose parents are of higher SES.[79]

This review supports the fact that socio-economic position in early life is associated with multimorbidity. However, the review shows that no large study with long follow-up and SES measured contemporaneously at birth has examined the association between SES at birth and multimorbidity in later life.

1.7 The design and findings of the Barnett *et al* study

As described at the beginning of this chapter, the Barnett *et al* study is high profile.[2] In 2013, a survey of 50 multimorbidity researchers in The International Research Community on Multimorbidity voted the study by Barnett *et al* as the list of conditions which should be used in future studies on the operational definition of multimorbidity.[82] This online group is a community of researchers and healthcare professionals who have made leading

contributions to multimorbidity practice and research.[83] It is the main route of communication for the Special Interest Group on Multimorbidity in the North American Primary Care Research Group. The Barnett study is also highly cited (247 times by February 2014 after its publication in 2012). The paper is summarised in Table 3 and the complete list of the conditions included is in Appendix 2, Table 92.

Table 3: Summary of multimorbidity paper by Barnett el al, 2012 [2]

Summary variable	Data from paper
MM definition given	Those with two or more chronic morbidities
Stated aim	"We aimed to use a large, representative primary medical care electronic database to examine the distribution of multimorbidity in relation to age and socioeconomic deprivation, and the relation between comorbidity of physical and mental health disorders and deprivation."
Study design	Cross-sectional
Population description	1,751,841 patients (about a third of the Scottish population) from 314 Scottish medical practices. Men and women were equally represented, as were all deprivation deciles.
MM data source	Routine data- primary care and prescription data
MM measure used	Disease count
Rationale for MM measure	"We specifically sought to include morbidities recommended as core for any multimorbidity measure by a systematic review [Diederichs *et al*], diseases in the quality and outcomes framework (QOF) of the UK general practice contract, and long-term disorders identified as important by NHS Scotland. By clinical consensus, "identified those morbidities which were likely to be chronic (defined as having significant impact over at least the most recent year) and with significant impact on patients in terms of need for chronic treatment, reduced function, reduced quality of life, and risk of future morbidity and mortality" "Weighting is particularly useful if the purpose of measurement is to predict future outcome ...However, weighted measures are likely to be useful only for the specific outcome they are developed for. For example, back pain and osteoarthritis has major impact on quality of life and functional status but not on mortality...Weighted measures are therefore likely to be more appropriate than simple counts where the focus is on particular outcomes, but less appropriate when no-one outcome is being privileged. For our descriptive epidemiology purposes where we were primarily interested in implications for health care, research and education, we judged that an unweighted count was most appropriate"
Method for grouping conditions/codes for conditions	"When possible, we based our morbidity definitions on QOF business rules and Read code groups for long-term disorders (as defined by NHS Scotland). When coding definitions were unavailable or did not apply to the available routine data, the clinicians in our team agreed new definitions by discussion."
Prevalence of MM	23.2%
Summary of study findings	1. MM increased with age but absolute number with MM higher in those aged less than 65. 2. Onset of MM occurred 10-15 years earlier in people living in the most deprived areas compared to least deprived 3. The presence of a mental health disorder increased as the number of physical morbidities increased, and was much greater in more deprived than in less deprived.

Abbreviations: MM, Multimorbidity; QOF, Quality Outcomes Framework

The selection of morbidities was based upon conditions recommended by Diederichs *et al* in a systematic review of multimorbidity measures[38], the conditions which are part of the quality and outcomes framework (QOF) of the UK general practice contract and long-term conditions identified as having high prevalence in Scotland by NHS Scotland.[2] Clinical consensus was then used to identify conditions which were chronic and had a significant impact on patients (based on the need for chronic treatment, whether it reduced function and quality of life, and the risk of future morbidity and mortality). The authors used an unweighted count.

The prevalence of multimorbidity was 23%. The study found the onset of multimorbidity to be 10 to 15 years earlier in those living in more deprived areas and that those with an increasing number of physical disorders had an increasing likelihood of having a mental health condition.[2] This study has changed how we perceive multimorbidity by drawing attention to the importance of mental health conditions and to the association between multimorbidity and deprivation.

1.8 Resilience and multimorbidity

The systematic review by Marengoni *et al* called for investigation of the role of resilience in multimorbidity.[31] With growing interest in resilience in research and health policy, there is increasing consideration of promoting resilience as a way of improving health and health outcomes.[84,85]

1.8.1 Definition and measurement of resilience

There is no universally accepted definition of resilience.[84,86,87] Resilience research has its origins in the study of childhood development and early studies considered resilience as a psychological trait which a child may be born with.[84] Resilience was often measured on the basis of psychological measures such as high levels of self-esteem or autonomy.[86]

Over time there has been acknowledgement that resilience may not be a trait and instead derives from internal and external factors, and is a dynamic process which may vary at

different points across life.[84,86] The definition of resilience has therefore evolved. For example, a review by Windle in 2011, which combined stakeholder consultation with a summary of the literature, produced the following definition:

"Resilience is the process of effectively negotiating, adapting to, or managing significant sources of stress or trauma. Assets and resources within the individual, their life and environment facilitate this capacity for adaptation and 'bouncing back' in the face of adversity. Across the life course, the experience of resilience will vary."[84]

A range of related terminology is used in resilience research but authors such a Windle state these should not be treated as synonymous with resilience. This includes hardiness which describes the presence of stability in the face of stress, and thriving which indicates superior outcomes after adversity.[84,88]

1.8.2 Resilience and health

At the time of developing the protocol for this thesis there was no consensus on the definition or measurement of resilience to disease. Research of resilience in adult populations was also uncommon relative to the proportion of research in child populations.[84] Evidence suggests resilient individuals have better long-term outcomes, such a lower risk of negative psychological sequelae, fewer healthcare contacts and lower morbidity and mortality rates.[89-91] Additionally, the following factors have been found to be associated with resilience to disease: [92-95]

- Demographic variables (e.g. age, gender, ethnicity)
- Lifestyle and disease risk factors (e.g. use of alcohol, exercise levels)
- Socio-economic factors (e.g. social class, education, income)
- Clinical variables (e.g. comorbidity, disease specific factors such as severity)
- Psychological variables (e.g. cognition, sense of coherence and self-esteem)
- Social support (e.g. support from family members)

However, resilience research and the subsequent development of interventions to promote resilience to disease is hampered by the lack of a consensus definition and

measure in the context of disease.[96] There are few examples of well evaluated resilience interventions in the literature. A non-systematic review aiming to identify interventions promoting resilience in relation to health outcomes found very few relevant peer reviewed publications.[96] Of interventions sourced, many had not been evaluated, focussed upon children only or did not have physical health outcomes.[96]

1.8.3 Resilience and multimorbidity

To investigate existing quantitative research in resilience to multimorbidity, I conducted a systematic search of the literature. The method is described in Appendix 1, section 13.3. I found no relevant papers. Many papers were excluded because they did not describe "resilience" and instead described related concepts such as hardiness. Others focussed on individual physical diseases rather than multimorbidity or were qualitative. Out of the qualitative studies, there was one, by Ong *et al*, which focussed on resilience and multimorbidity. This consisted of in-depth interviews of 17 individuals who had multimorbidity but also felt they had maintained a sense of self over time in the face of adversity. The authors defined this as a resilient population.[97] The study found that preserving social roles (such as being a supportive grandparent) were important parts of maintaining resilience.[97]

Quantitative study is needed to build upon this qualitative research in order to define and measure resilience to multimorbidity and identify the determinants of resilience to multimorbidity.

1.9 Mental Health, resilience and multimorbidity

Whether or not making a distinction between "mental" and "physical" health conditions is correct, it is generally accepted that those conditions described as mental health conditions contribute heavily to morbidity and mortality, that they are affected by stigma leading to under-reporting, and that they are more likely to be subject to under-funding of services.[98] Depression is a leading cause of global disease burden according to the WHO.[99] The WHO assesses disease burden based upon an assessment of Disability Adjusted Life Years

(DALYs), which is a measure of the years of healthy life lost by individuals due to being in poor health or having a disability.[99] In the most recent assessment (2015) the 6th most common cause leading cause of disease burden in Europe was depressive disorders and the 11th most common was self-harm.[100]

A challenge when researching mental health conditions is accurately identifying those who have these conditions.[101,102] Using only medical records of mental health conditions has been shown to lead to lower estimates of the prevalence than surveys of individuals for example.[101] Reasons for not seeking help include perceived stigma (both from public and professionals and towards the self) and the fact that the symptom profile of conditions such as depression may mean an individual is less capable of seeking help.[103] Men are less likely to seek medical attention for symptoms of mental ill-health than women.[104,105] This is hypothesised to be partly due to gender stereotypes whereby men are expected to be "strong and stoical".[104,105] Whilst healthcare recorded prevalence of mental health conditions is lower in men, evidence shows that completed suicide rates in men are commonly much higher than in women.[104]

Mental ill-health has been highlighted by studies I have described earlier as an important negative influence on the burden of multimorbidity.[2,64] There is increasing awareness amongst researchers of the importance of considering mental health conditions along with physical health conditions when studying multimorbidity and a need for studies to continue to do so.[106,107] However, commonly used measures such as the Charlson comorbidity index do not contain mental health conditions.

Mental health is also hypothesised to influence resilience to disease but the pathways behind this are unclear. It may be that mental health conditions reduce resiliency due to their association with higher numbers of co-existing diseases. Alternatively measures of resilience may also be sensitive markers of mental ill-health.[108] Exploring this is limited due to uncertainty regarding the definition and measurement of resilience.

1.10 Management of multimorbidity

The clinical management of multimorbidity is complex and health services are not adequately designed to meet this challenge. In the UK and many other countries, secondary care services are frequently single speciality focussed and patients with more than one health condition may visit multiple secondary care specialists.[29] Practitioners in generalist settings such as primary care face challenges in managing patients with complex needs within resource constraints.[109,110]

A study in primary care found that individuals with multimorbidity were attending multiple specialities, receiving multiple medications (polypharmacy) and were at higher risk of having adverse drug reactions.[111] At the time of developing this thesis, there were no UK-wide guidelines for managing multimorbidity and available guidelines were of single disease focus. A review by Hughes *et al* examined five National Institute of Health and Clinical Excellence (NICE) guidelines for single diseases and found that these guidelines lead to a risk of polypharmacy in patients with more than one condition.[112]

A systematic review by Smith *et al* of interventions for patients with multimorbidity in primary care and community settings, concluded that few interventions existed.[29] Interventions which did exist included those focussing on targeting specific risk factors (for example improving management of hypertension), providing an enhanced multidisciplinary team (for example by adding a pharmacist) or improving areas where patients experience difficulties (for example improving functional ability).[29]

Non-clinical management is an important component of the management of illness.[113] Self-management of multimorbidity can include adopting healthy behaviours and maintaining medication adherence.[114] This was explored by a systematic review of qualitative studies conducted by Liddy *et al*.[115] The review included 23 studies and found evidence that for some individuals, developing multimorbidity may improve self-management compared to having a single disease as patients needed to learn to prioritise certain conditions. Additionally there was evidence of a resilient response, whereby the additional difficulty of having multiple conditions strengthened coping mechanisms. However, predominantly

patients reported difficulties in self-management arising from a large volume of (often contradictory) information provided by healthcare providers.[115]

1.11 Perspectives on multimorbidity

Multimorbidity has an impact at an individual level, on relatives and carers, on healthcare services and at a political and societal level. Here, I briefly introduce viewpoints on multimorbidity from these perspectives.

1.11.1 Patients, caregivers and healthcare professionals

The complexities in the clinical management of multimorbidity places a burden on patients and healthcare professionals. A questionnaire study by Mercer and Watt of primary care patients in Scotland found that patients in deprived areas were more likely to have multimorbidity and additional psychosocial distress. The study observed that there was insufficient time for practitioners to manage these issues which led to lower patient enablement and higher GP stress.[110] A related qualitative study of GPs and practice nurses in deprived areas in Scotland found that they struggled both personally and professionally to help those most in need. The study highlighted the need to change the system of care to effectively manage patients with multimorbidity in deprived areas.[109]

These findings were echoed in the review by Liddy *et al* in which patients reported struggling to self-manage due to an often single disease approach healthcare system providing a range of contradictory and confusing advice.[115] This review also highlighted that patients struggled with the impact of physical and emotional symptoms resulting from multiple diseases and that this had an impact on their ability to conduct daily activities. Depression and related issues such as sleep disturbance, worry and lack of energy were dominant features mentioned by participants.[115]

Family carers in a qualitative study by Ploeg *et al* described their experience as being stressful, exhausting and time consuming. This was partly related to the complexity of care needs due to multiple health conditions.[116]

1.11.2 Societal and political level

At a societal and political level multimorbidity has been of increasing focus.[117] For example, in Scotland in 2014 the Government developed an "Action Plan for Multimorbidity" for health and social care services.[118] This was in recognition that multimorbidity is common, the prevalence is rising as the population ages and that it is associated with higher levels of deprivation.[118] In 2015, a European Union forum discussed the challenge of multimorbidity with speakers including European policymakers, researchers and campaigners. The event was viewed as an important step forward in the recognition at a political and societal level of the challenge of multimorbidity and the need to improve prevention and management.[119]

Research into multimorbidity is increasingly common.[117] In 2012 the British Medical Journal (BMJ) published an editorial calling for urgent shift in research and healthcare practice away from single diseases to multimorbidity.[120] In 2015 the UK National institute for Health Research published a themed call for research into multimorbidity in older people.[121]

1.12 Summary, key evidence gaps and next steps

In this chapter I have demonstrated the Public Health challenge of multimorbidity. It is common, determined by a range of individual and societal factors, leads to poor outcomes and places a burden on individuals, their carers, practitioners and health services. The prevalence of multimorbidity is likely to continue to rise in the future with demographic and disease prevalence changes.

For effective Public Health action, there is a need to address gaps in our knowledge and understanding. The first is regarding what the most appropriate definition and measurement approach is for multimorbidity. Related to that is assessing the burden of multimorbidity and doing so from more than one perspective (i.e. from the perspective of individuals themselves and from that of healthcare services). Acknowledging the resource implications of measuring multimorbidity in a large population, there is a need for

measures derived using administrative data so as to be a useful method for population health research.

Understanding the role of resilience in multimorbidity could lead to the development of interventions to improve the experience and outcomes of individuals with multimorbidity. The first step is to clarify how it should be defined and measured in the context of disease and then apply this to study populations.

The potentially important role mental health conditions play in the prevalence and outcomes of multimorbidity and resilience was highlighted, but also recognised as a significant research gap. Whilst SES was evidenced as an important determinant of multimorbidity, there is a key gap in our knowledge regarding the role of childhood SES on multimorbidity. With multimorbidity being recognised as an emerging health service and Public Health priority, there is a need to better understand the long-term outcomes in those with multimorbidity. Methodologically, there is a clear need for large, cohort based studies of multimorbidity with long-term follow-up from childhood into adult life.

2 Aim and structure of thesis

2.1 Overview

In this chapter I present the aim and objectives for my thesis. I then describe the structure of the thesis in relation to those objectives.

2.2 Aim

To define and measure the prevalence of multimorbidity and resilience to multimorbidity, to assess the role of mental health and childhood socio-economic status (SES) and to investigate the long-term outcomes, in order to inform Public Health research and action.

2.3 Objectives

1. To determine how multimorbidity and resilience to multimorbidity should be defined and measured in Public Health research
2. To assess the prevalence of multimorbidity and resilience to multimorbidity using the measures identified in objective one
3. To assess the role of mental health conditions and childhood socio-economic status (SES) in the occurrence of multimorbidity and resilience to multimorbidity
4. To assess the impact of multimorbidity and resilience to multimorbidity on long-term outcomes

2.4 Structure of thesis

I use a combination of systematic reviews and analysis of two contrasting study populations to answer the objectives. The thesis comprises of four parts as described below.

2.4.1 Part one: Introduction, aims and structure

Part one encompasses the Introduction chapter and this current chapter (Chapters 1 and 2).

2.4.2 Part two: Determining the definition and measurement of multimorbidity and of resilience to multimorbidity

Part two addresses the first objective and comprises of three chapters. In Chapter 3 I present a systematic review with the aim to determine how multimorbidity should be defined and measured in this thesis. In Chapter 4 I show how I developed a novel administrative data measure of multimorbidity which I use in part three. In Chapter 5 I present a systematic review determining how resilience should be defined and measured in this thesis. By the end of part two, I have identified the definition and measures of multimorbidity and resilience to be used in Part three.

2.4.3 Part three: studying the prevalence, determinants and outcomes of multimorbidity and resilience to multimorbidity

In part three I address objectives two to four using two study populations. In Chapter 6 I provide the Methodology for the analysis conducted, including a description of the populations. The populations comprise the Diamond study and the Aberdeen Children of the 1950s (ACONF) cohort study. The ACONF will be analysed in two parts (the "Original ACONF" and the "Enhanced ACONF") which will be explained in detail in Chapter 6.

In Chapter 7 I present results for the Diamond study and in Chapter 8 I show the study population characteristics of the ACONF populations. I present the findings of analysis of the Original ACONF in Chapter 9 and in Chapter 10 I present the findings for the Enhanced ACONF.

Each study population contributes uniquely to the objectives. The strengths and limitations of these are detailed in the relevant chapters.

2.4.4 Part four: Discussion and recommendations

At the end of all chapters (except those in Part one and the Methodology in Chapter 6) I provide a detailed discussion and conclusions. Therefore in this part, which encompasses Chapter 11, I summarise key findings, the strengths and limitations of the thesis, new developments in the literature, and recommendations for future Public Health research and action.

Part two: Determining the definition and measurement of multimorbidity and of resilience to multimorbidity

3 Developing consensus definition and measurement of multimorbidity

3.1 Overview

In this Chapter I present a systematic review of systematic reviews of multimorbidity definitions and measures. I supplement the findings of that review with that of my cohort studies review (described previously in Chapter one). I finish the chapter with an overall discussion of findings and my recommendation as to how multimorbidity should be defined and measured.

3.2 Defining and measuring multimorbidity: a systematic review of systematic reviews

3.2.1 Background

This review was first conducted on literature published to November 2013 and informed the methodological approach in this thesis. In preparing the review for publication I updated the literature search to February 2017. The findings of the update did not alter the conclusions and so I have presented the updated review here. I led the design of the protocol and the data extraction database, and finalised these in discussion with my co-authors. I conducted the search, I was primary reviewer in selecting the papers to include and I was primary data extractor for all included reviews.

The aim of this systematic review was to seek consensus on the most appropriate ways to define and measure multimorbidity by pooling the findings of systematic reviews which had examined multimorbidity definitions and measures.

3.2.2 Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 checklist guided method development and reporting of findings.[122] Medline, Embase, PubMed and the Cochrane database of systematic reviews were searched from database inception to 13th February 2017. The search strategy was comparable across all databases. There was no MeSH term for multimorbidity. The search terms relating to "multimorbidity" and its measures were drawn from a previous systematic review of the multimorbidity literature.[39] These were combined by the Boolean operator "AND" with "review" as a title word. The terms were searched in the title only, as an initial trial search found that widening this to the abstract or full text significantly reduced the ability to detect relevant reviews. The search strategy is in Appendix 1, Table 90.

Systematic reviews of the multimorbidity literature which examined multimorbidity definitions and/or measures as a central focus of the review were included. Whilst comorbidity is now commonly accepted to be distinct from multimorbidity, the terms have been used synonymously in the past. Reviews of comorbidity where no specific index disease was considered were therefore eligible. Systematic reviews which did not have the primary aim to summarise multimorbidity definitions and measures were excluded. Reviews which were "narrative" or "semi-structured" or which otherwise were not systematic reviews were excluded.

Title, abstract and full-text screening for eligible studies was carried out independently by myself and one other (Professor Stewart Mercer). Disagreement was resolved by a third researcher (Professor Corri Black). Primary data extraction was carried out by myself with four others acting as independent second reviewers (Professor Mercer, Professor Black, Dr Mike Crilly and Dr Gordon Prescott). Data extraction included: the review characteristics, the definition and measures of multimorbidity presented in the review and the rationale

behind any recommended measures of multimorbidity (if given). Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal checklists were used to assess the quality of included reviews ("low quality", "acceptable" or "high quality"). The results were combined narratively.[123]

3.2.3 Results

Figure 1 summarises the results of the search. Out of 1,051 articles sourced during the search, there were 432 duplicates. Following screening of titles, abstracts and full texts, six reviews were included.[34,38,39,124-126] The characteristics of these reviews, including their stated aims, are presented in Table 4. The Le Reste and Willadsen reviews focused on the definition of multimorbidity, whilst the remaining four focussed on measures. The number of studies included by the reviews ranged from 39 to 194. Five reviews were of "acceptable quality".[38,39,124-126] De Groot was "low quality" as they did not report the literature search strategy, the results of the literature search and the identification of papers clearly.[34]

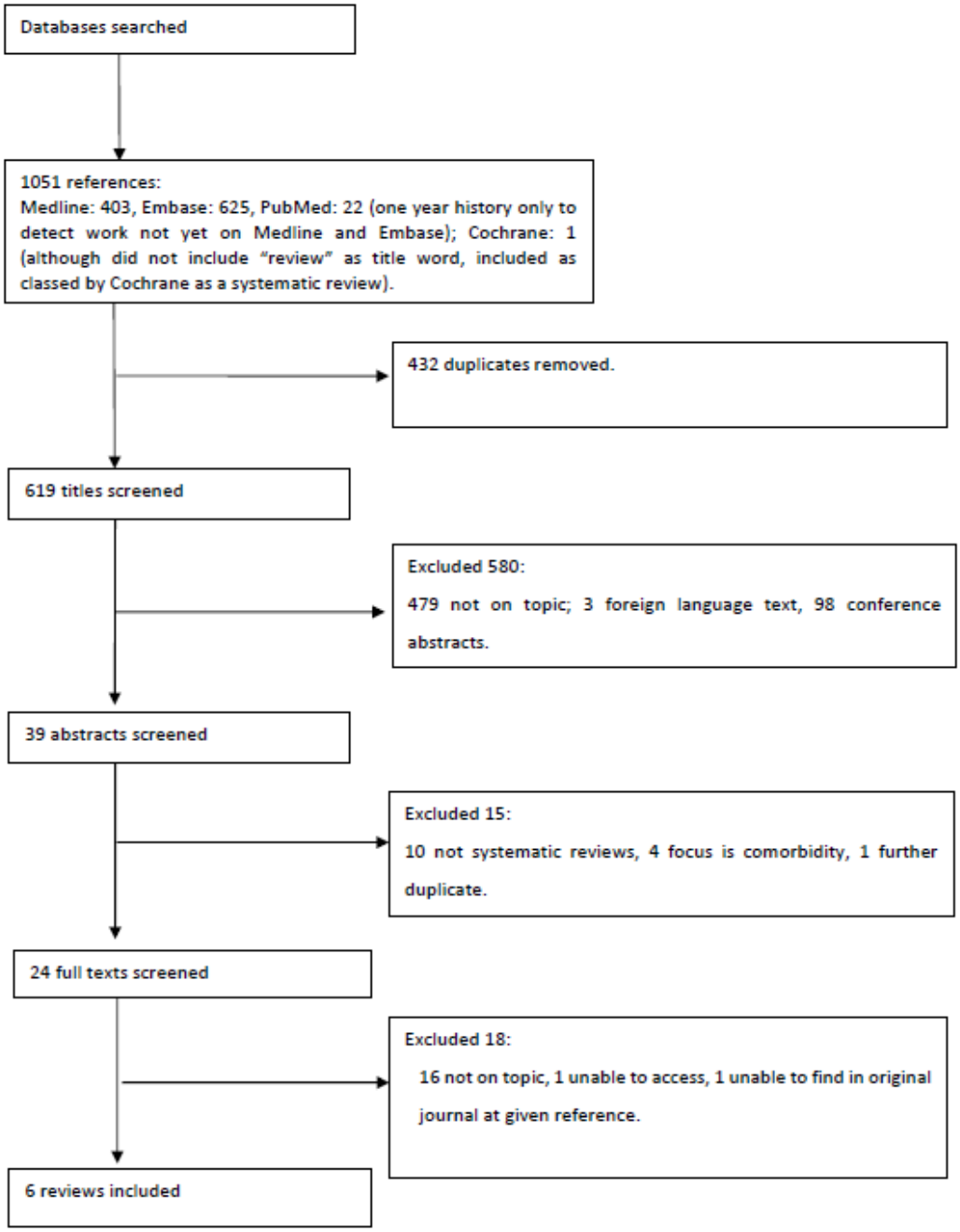


Figure 1: Systematic review of multimorbidity reviews: flow-chart of search strategy

Table 4: Systematic review of multimorbidity reviews: characteristics of included reviews

Study	Stated Aim	Databases and search dates	Total titles screened	Total texts included	Quality assessment*
De Groot 2003[34]	'Which methods are available for measuring comorbidity that can be used in RCTs and prognostic studies'	Medline: January 1966- September 2000. Embase: January 1988 to September 2000.	Not reported	Not reported	Low quality
Diederichs 2001[38]	'Multimorbidity, defined as the coexistence of 2 or more chronic diseases, is a common phenomenon especially in older people. Numerous efforts to establish a standardized instrument to assess the level of multimorbidity have failed until now, and indices are primarily characterized by their high heterogeneity. Thus, the objective is to provide a comprehensive overview on existing instruments on the basis of a systematic literature review.'	Medline: January 1, 1960 to August 31, 2009	1,120	39	Acceptable
Huntley 2012[39]	'The aims of this review were (1) to identify and describe measures of multimorbidity that are most suitable for use in research in primary care and community populations, taking into account the data and resources they require, and (2) to investigate the validity of these measures in terms of whether they have demonstrated anticipated associations with patient characteristics, process measures, and health outcomes.'	Medline and Embase: database inception to December 2009	11,191	194	Acceptable
Le Reste 2013[124]	'What are the criteria for multimorbidity found in the scientific medical literature and what definition could be produced with these criteria?'	PubMed, Embase and Cochrane: January 1, 1990 to December 31, 2010.	416	54	Acceptable
Yurkovich 2015[125]	'To conduct a systematic review of studies reporting on the development or validation of comorbidity indices using administrative health data and compare their ability to predict outcomes related to comorbidity (i.e., construct validity).'	Medline and Embase: 1946 to September 2012	955	76	Acceptable
Willadsen 2016[126]	'Objective is to explore how multimorbidity is defined in the scientific literature, with a focus on the roles of diseases, risk factors, and symptoms in the definitions.'	PubMed, Medline and Embase: inception to October, 4, 2013. Cochrane database: inception to October,10, 2013	943	163	Acceptable

Abbreviations: SIGN, Scottish Intercollegiate Guidelines Network; RCT, randomised controlled trial
* Based upon SIGN categories

Definitions

The multimorbidity definitions used in the included reviews are summarised in Table 5. As described above, Le Reste and Willadsen were the only papers focused on reviewing definitions[124,126] and so the definitions provided by the other four were the author's own.

Table 5: Systematic review of multimorbidity reviews: multimorbidity definitions from included reviews

Review reference	Definition given *a priori** or as a result of evidence review	Definition
De Groot 2003[34]	*a priori*	'the co-occurrence of multiple chronic or acute diseases and medical conditions in one person'
Diederichs 2001[38]	*a priori*	'Multimorbidity describes "the coexistence of two or more chronic diseases" in the same individual.'
Huntley 2012[39]	*a priori*	'The co-occurrence of multiple diseases or medical conditions within 1 person.'
Le Reste 2013[124]	Review of evidence	'Multimorbidity is defined as any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor. Any biopsychosocial factor, any somatic risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity). Multimorbidity may modify the health outcomes and lead to an increased disability or a decreased quality of life or frailty.'
Yurkovich 2015[125]	*a priori*	This review used the definition of comorbidity: 'Comorbidity may be defined as the total burden of illnesses unrelated to the principal diagnosis'
Willadsen 2016[126]	Review of evidence	Provides no single definition. Conclusion: -Existing definitions (consisting mainly of diseases) are 'more usable for epidemiologists than for clinicians and patients'. -Recommends definition by Le Reste (above)

* *a priori* indicates this is the authors own definition

Le Reste produced a new multimorbidity definition as a result of their review:

"…any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor".[124]

Willadsen found that more than a third of studies used a cut-off of two or more conditions to define multimorbidity, another third did not specify any cut-off and the remainder had

varying cut-offs. The authors found that less than a third of their included studies used an existing definition of multimorbidity. Additionally, definitions varied according to whether or not they specified a duration of condition (e.g. "occurrence in the last 5 years" or having lasted "for at least 3 months") and whether or not they specified the severity of the condition. The authors state that consideration of whether included diseases clustered together was considered in only "a few" articles and there was little consideration of complications of diseases. The authors concluded that the majority of existing definitions are "*more usable for epidemiologists than for clinicians and patients*" and recommended the Le Reste definition due to its comprehensive nature for including more than just disease.[126]

In the remaining reviews, De Groot and Yurkovich primarily used the term "comorbidity".[34,125] The consensus amongst all four was that multimorbidity is the occurrence of multiple diseases or conditions. Diederichs specified that multimorbidity is *two or more* chronic conditions.[38]

Measures

Commonly used measures

Le Reste did not focus on multimorbidity measures.[124] The measures covered by the remaining reviews are in Table 6. Whilst the stated aim of Willadsen was to "*explore how multimorbidity is defined in the scientific literature*", there was overlap between definitions and measures.[126]

The measures included by reviews encompassed disease counts and weighted indices such as the Charlson Index, the Cumulative Illness Rating Scale (CIRS), the Index of Coexistent Disease (ICED), the Adjusted Clinical Groups (ACG) System and the Duke Severity of Illness.

Table 6: Systematic review of multimorbidity reviews: Multimorbidity measures, conditions and data sources recommended by each review

Study	Measures included	MM measure recommended	Rationale for MM measure	Specific conditions recommended	MM data sources recommended?
De Groot 2003[34]	Disease counts and 12 weighted measures (Burden of disease index, Charlson, CIRS, Cornoni-Huntley index, Duke Severity of Illness, Hallstrom index, Hurwitz index, ICED, Incalzi index, Kaplan index, Lui index. Shwartz index)	Concludes Charlson, CIRS, ICED and Kaplan are valid and reliable methods to measure comorbidity in clinical research.	Validity and reliability	None	No specific recommendation. - Commonly used methods to obtain data in included studies: 'interviews, questionnaires, physical examinations, medical chart reviews and coded databases'.
Diederichs 2001[38]	Weighted indices: Charlson, Comorbidity Symptom Scale, Seattle Index of Comorbidity, Medication-Based Disease Burden Index, KoMo Score, ICED, Functional Comorbidity Index, Incalzi Index, Kaplan Index, Physiologic Index of Comorbidity, Geriatric Index of Comorbidity, Self-Administered Comorbidity Questionnaire, Shwartz Index and CDS	Recommends disease count of 11 conditions. Found most studies did not specify criteria for selection of diseases. If criteria given: high prevalence of the disease, using other indices as a reference point for the selection of disease, conditions associated with increased mortality risk, conditions associated with impact on function and health and the need for management.	Disease count based on conditions which are 20 most frequently listed diagnoses for people aged > 65 years in three data sources in Germany (inpatient sector, the outpatient sector and mortality statistics).	Cancer, diabetes, depression, hypertension, MI, chronic ischaemic heart disease, heart arrhythmias, heart insufficiency, stroke, COPD, arthritis.	No specific recommendation. - Included studies used: patient self-report, physician reports, clinical examinations, medical records, and administrative data. - Gives advice on self-report: 'use disease specifications that can be distinguishable by lay persons [in order to increase validity of self-report].
Huntley 2012[39] (contin. overleaf)	Disease counts and weighted measures. Most common measures (n studies): disease count (98), Charlson (38), ACG System (25), CIRS (10), Duke Severity of Illness (6).	1. Care utilisation: the ACG, Charlson, or disease counts 2. Costs: The ACG 3. Mortality: Charlson 4. Quality of life: Disease counts or Charlson index 5. Others: disease or medication counts	Recommendations based upon purpose of study and evidence base behind measures used for that purpose.	None	No specific recommendation. - Commonly used measures: interviews, questionnaires, physical examinations, medical chart reviews, and coded databases.

Study	Measures included	MM measure recommended	Rationale for MM measure	Specific conditions recommended	MM data sources recommended?
Yurkovich 2015[125]	Administrative data measures (n studies): Charlson and its adaptations (35); Elixhauser (2); Fleming *et al*. index (1); Abildstrom *et al*. index (1) Medication-based indices: CDS (9), Rx-Risk (3) and Medication Based Disease Burden Index (2)	Diagnosis-based measures, (particularly Elixhauser and the Romano adaptation of the Charlson) resulted in higher ability to predict mortality outcomes. Medication-based indices, (such as the Chronic Disease Score) demonstrated better performance for predicting health care utilization.	Recommends selection of measure to be based on 'type of data available, the study population, and the specific outcome of interest in the study.'	None	Review was limited to administrative data indices only but authors commented on included studies which compared data sources (all were Charlson studies). Two studies found self-report and administrative data had similar ability to 'predict various outcomes'. One review and 2 studies found poor agreement between case note review and administrative data
Willadsen 2016[126]	Charlson, Clinical Classification Software, CIRS, ACG, Aggregated Diagnosis Groups, Medication based, Expanded Diagnosis Clusters, Resource Utilization Bands, The Functional Comorbidity Index, ICED, QoF, The Registration Network Family Practices	Does not recommend a single measure. Authors state the importance of including risk factors and symptoms and severity as well as diseases if want a clinically relevant definition (and thus measure)	N/A	None	No specific recommendation. The included studies used data from administrative data and self-report

Abbreviations: MM, multimorbidity; CIRS, Cumulative illness rating scale; ICED, Index of Coexistent disease; CDS, Chronic Disease Score; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; ACG, Adjusted Clinical Groups; QoF, Quality Outcomes Framework; N/A, not applicable; Rx Risk, Prescription Risk

Yurkovich and Huntley examined the frequency of measures. Yurkovich categorised measures as "administrative data" (the most common being Charlson) and "medication-based" (the most common being the Chronic Disease Score).[125] Huntley categorised the most common measures as: disease counts, the Charlson index and variations, the ACG system, the CIRS and the Duke Severity Illness Check-list System.[39] Huntley found disease counts being used in 98 studies and the number of disease "items" included within counts

ranged from 9 to 35.[39] These items varied between measures from being individual diseases to categories of conditions. Willadsen found that measures contained conditions ranging in number from 4 to 147.[126]

Recommended measures

Yurkovich reviewed studies reporting on the development, validation and predictive ability of comorbidity indices.[125] Validity describes whether an instrument is able to measure what it is intended to measure.[127] Yurkovich defined a validation study as one which evaluates the ability of the index to predict a specific outcome. This is called construct validity.[127] The authors found that diagnosis based measures such as the Elixhauser index and the Romano adaptation of the Charlson index were best able to predict mortality outcomes whilst the medication based Chronic Disease Score, was best able to predict health care use.[125] Huntley also investigated the construct validity of measures of multimorbidity.[39] They recommended that researchers select a measure for a study based upon the measure validated for use in that scenario, for example, the Charlson index for predicting mortality. The authors also stated that simple counts of diseases or medications perform almost as well as complex measures in predicting most outcomes.[39]

De Groot assessed the content, criterion and construct validity of measures. Content validity describes whether the measure includes all relevant items and the authors assessed this by describing the characteristics of the measure.[34] Criterion validity assesses whether the measure correlates with another measure, ideally a "gold-standard".[127] De Groot state that as there is no gold-standard they included studies in which measures were compared to other measures for their predictive ability. They concluded that the Charlson, CIRS, ICED and Kaplan indices are valid methods for use in clinical research but that other measures (such as disease counts) were more difficult to assess due to limited data.[34]

Willadsen did not recommend a single measure and instead, as described previously, stated the importance of including risk factors, symptoms and severity of diseases.[126] Diederichs also did not recommend a single measure. They found studies of disease counts often did not specify the criteria for the selection of diseases, but if criteria were given these were:

high prevalence of the disease, using other indices as a reference point for the selection of disease, or high impact conditions in terms of increased mortality risk, an impact on function and health and the need for management. They recommended 11 conditions selected on the basis of being the most common causes of inpatient and outpatient attendance as well as death in people aged over 64 in Germany. The conditions included cancer, depression, myocardial infarction and hypertension.[38]

Data sources

All five reviews found patient self-report, physician reports, clinical examinations, medical record reviews and administrative data ('coded databases' or 'routine data') were common sources of multimorbidity data amongst their included studies.[34,38,39,125,126] No review studied whether any source was superior, although Yurkovich found evidence that the Charlson index derived from self-report and that derived from administrative data had similar abilities to "*predict various outcomes*".[125] De Groot stated that medical chart reviews are preferable for use in smaller studies as they likely yield the most complete data but that this is likely impractical in larger studies and so administrative databases can be used.[34] Similarly, Huntley noted that administrative data have the advantage of ease of use but may be limited by data quality issues.[39]

3.2.4 Conclusion

This review pooled the findings of six systematic reviews. There was heterogeneity of multimorbidity definitions and measures but there were a number of commonalities. Most of the reviews defined multimorbidity as the occurrence of multiple diseases or conditions. Where a cut-off was set, the majority set this at two or more. Common measures included the Charlson comorbidity index, CIRS, ICED, Kaplan, the ACG system and disease counts, with advice that measures be selected based upon the purpose of a particular study.[34,39] Disease counts may be more appropriate where no weighted measure exists for an outcome. No reviews made recommendations about the most appropriate data sources to use when measuring multimorbidity.

3.3 Defining and measuring multimorbidity: an overview of multimorbidity cohort studies

This review formed part of the Introduction in order to inform the evidence base regarding the size, follow-up time and findings of multimorbidity cohort studies. In Appendix 1 I described the literature review strategy in detail and the details of included texts were summarised in Chapter one, Table 1. Here, I summarise how each study defines and measures multimorbidity.

I included any cohort study in which multimorbidity was either the main exposure or outcome variable. There were 15 studies included overall.[57,59-72] The multimorbidity definition and measures used by each study are shown in Table 7 alongside the study size at baseline and follow-up period.

The prevalence of multimorbidity ranged from 10%[62] to 80%.[59] With regards to the definition, there was general agreement that multimorbidity was the co-existence of multiple conditions within an individual. Most authors operationalised it as being two or more conditions.[57,59,60,63,66-68,70,71] Two papers operationalised it as a continuous variable.[65,69]

Most studies (13 in total) used a disease count. Kuo *et al*, 2013 used a medication group count based upon medication groups within the Johns Hopkins ACG System.[61] Salisbury *et al* used a disease count as well as the ACG system.[67] There was insufficient discussion of the rationale behind the choice of multimorbidity measures by studies to assess why these measures were chosen. No study compared measures. Five studies limited the multimorbidity measure to only include chronic conditions[59,63,67,70,72] whilst others included acute conditions, risk factors or prescriptions.

Table 7: Review of multimorbidity cohort studies: multimorbidity definition, data source, measure and prevalence in included studies

Study	Population at baseline Follow-up time	MM definition given	MM data source used	MM measure used*	Rationale for MM measure	Prevalence MM at baseline**
Aarts 2012 [57]	1,823 6 years	The co-occurrence of two or more chronic diseases within one person	Routine data- primary care electronic medical records	Disease count. MM operationalised as two or more diseases: malignancies, movement disorders, chronic respiratory diseases, cardiovascular, endocrine, neurological disturbances, psychological disorders.	Based on medical literature and clinical experience.	35.5%
Aarts 2011 [58]	1,763 12 years	The occurrence of multiple medical conditions within one person	Routine data- primary care electronic medical records	Disease count. Does not specify how MM operationalised. 96 chronic medical conditions. Single morbidities combined into clusters of conditions	Based on medical literature and clinical experience. Also chronic conditions with high prevalence and/or potential to impact brain functioning	55.2%
Ajmera 2012[59]	Not clear at baseline (8,963 at end of follow-up) 3 years	The concurrent presence of multiple chronic conditions	Self-report	Disease count MM operationalised as 2 or more chronic conditions. Seven conditions: arthritis, cancer diabetes, heart diseases, hypertension, respiratory, osteoporosis.	Based on published studies establishing clinical burden (morbidity and mortality), economic burden (cost and), and high prevalence	80.3%
Demirchyan 2013 [60]	725 22 years	Co-occurrence of two or more health problems	Self-report	Disease count. MM operationalised as two or more diseases. Respondents provided with predetermined list of non-communicable conditions (both physical and mental) and the option “other”.	None given	17.0%
Kuo 2013 [61] (contin. overleaf)	959,990 6 years	Co-occurrence of two or more conditions within a specified period of time; or coexistence of multiple illnesses	Routine data- the National Health Insurance claims data (Taiwan)	Medication group count (Rx-MG) MM based upon 2 or more Rx-MG assignments	Based on literature backing use of prescription measures for cost outcomes.	79.3%

Study	Population at baseline Follow-up time	MM definition given	MM data source used	MM measure used*	Rationale for MM measure	Prevalence MM at baseline**
Menotti 2001 [62]	2285 10 years	Combination of several diseases, without a single focal disease as reference.	Unclear ? Clinician assessment	Disease count. Does not specify how MM operationalised. Conditions: CHD, heart failure, stroke, intermittent claudication, COPD, diabetes and cancer.	Talks about impact of "major chronic diseases" upon outcomes. However, not explicit as to rationale	2 diseases: 10.3-15.8%; 3 or more: 2.5-7.5%
Nagel 2008 [63]	13,781 Median 8.7 years	Two or more concurrent chronic conditions	Self-report of physician diagnosed chronic conditions.	Disease count MM operationalised as 2 or more chronic conditions	None given. Authors used pre-existing study and just appeared to use all available data	67.4%
Payne 2013 [64]	180,815 1 year	The presence of more than 1 long-term disorder	Routine data-Primary care electronic medical records	Disease count Used list of 40 conditions from Barnett *et al* paper (2012).	Based on conditions used in another paper (Barnett *et al*, 2012)	Not explicitly reported: 48.3% based on MM as ≥ 2 physical conditions
Quinones 2011 [65]	17,517 Up to 11 years	Coexisting diseases that occur without one central or index disease	Self-reported Appears to be some attempt to validate through discussion with clinician.	Disease count Multimorbidity treated as a continuous measure. Validated this by calculating a weighted index based upon each diseases mortality prediction. Found the count and this weighted index had good correlation	None given. Authors used pre-existing study and appeared to use all available data	Average 2.08 diseases per respondent
Ruel 2013 [66] (contin. overleaf)	1,020 5 years	The presence of two or more medical conditions in an individual	Combined clinical assessment for some and self-report for other conditions	Disease count MM operationalised as 2 or more diseases Included: anaemia, hypertension, hypercholesterolemia, diabetes, arthritis, hepatitis, CHD, asthma, stroke, fracture and cancer.	None given	14%.

Study	Population at baseline Follow-up time	MM definition given	MM data source used	MM measure used*	Rationale for MM measure	Prevalence MM at baseline**
Salisbury 2011 [67]	99,997 3 years	Multiple coexisting chronic medical conditions	Routine data-primary care electronic medical records	Disease count. MM operationalised as 2 or more chronic conditions. Two approaches: 1. Any of 17 "important chronic conditions for which care is incentivised under QOF" 2. Using the ACG system which had a much wider list of chronic conditions.	Data availability and clinical experience. Chronic conditions were chosen based on clinical experience and conditions which last more than 6 months or require ongoing disease or risk management or have significant risk of recurrence	QOF : 16%. ACG: 58%
Seeman 1989 [68]	4, 174 9 to 17 years	Coexistence of two or more chronic conditions and/or symptoms	Self-report	Disease count MM operationalised as 2 or more conditions. 22 conditions including chronic conditions and symptoms	None given. Authors used pre-existing study and appeared to use all available data	Those aged 38-59: 43%, those aged over 60: 56%
Vila-Rodriguez 2013 [69]	293 Median of 23.7 months	Not given	Combined clinical assessment and self-report	Disease count Multimorbidity a continuous variable. 12 conditions including psychiatric illness and blood borne viruses	None given	Not stated. Median number conditions was 3
Woo 2013 [70]	4,000 4 to 9 years	Coexistence of more than one chronic medical condition	Self-report of doctor diagnosed disease	Disease count MM operationalised as 2 or more chronic conditions. Does not describe which conditions in MM measure	None given	24.7%
van den Akker 2001 [71]	3,551 2 years	Suffering from multiple diseases	Routine data-primary care electronic medical records	Disease count MM operationalised as 2 or more active conditions	Only active disease Did not include symptoms, pregnancy and delivery without pathology, test results not leading to a diagnosis, variation of normal function, superficial injuries, and risk factors. Total of 335 diagnostic categories included in the analysis.	57.1%

* Where feasible the list of conditions included is given ** Only multimorbidity prevalence at baseline is provided for clarity as some studied reported prevalence at follow-up differently and some did not measure it. Where multimorbidity was treated as a continuous variable, there was no overall prevalence calculated.
Abbreviations: MM, Multimorbidity; QOF, Quality Outcomes Framework; ACG, Adjusted Clinical Groups; CHD, Coronary Heart Disease; COPD, Chronic Obstructive Pulmonary Disease

The study by Menotti *et al* was unclear regarding the data source used.[62] Of the remainder, six used routine (administrative) data to measure multimorbidity[57,61,64,67,71,72] and eight used patient self-report or a combination of self-report with clinician assessment.[59,60,63,65,66,68-70]

Of the routine data studies five used primary care records (the two studies by Aarts *et al* used the same data)[57,64,67,71,72] whilst Kuo *et al* used insurance claims data.[61] The population at baseline in these six studies ranged from 1,763 in Aarts *et al* [72] to 959,990 in Kuo *et al*.[61] In all the studies using non-routine data the list of conditions was generated prior to the research (i.e. participants were not asked to self-report on *any* condition they may have). The study by Ajmera *et al* was unclear regarding the study population at baseline (there were 8,963 by the end of follow-up). Of the remaining seven, the study populations size at baseline ranged from 293[69] to 17,517.[65]

3.4 Discussion

Both literature reviews found heterogeneity in multimorbidity definitions and measures. However, there were a number of important commonalities. These are summarised in this section along with a comparison to other published literature and a discussion of the strengths and limitations of my approach. I finish this section with the recommended definition and measures to be used in the study of multimorbidity in the thesis.

3.4.1 Multimorbidity definition

There is overlap between the definition and measurement of multimorbidity particularly when multimorbidity is defined and measured on the basis of a count of conditions. In studies using weighted measures the definition and measurement of multimorbidity may be more distinct. In both reviews, the consensus was multimorbidity is the occurrence of multiple diseases or conditions, and the most common cut-off given was two or more. This cut-off was also used by Barnett *et al* as described in the Introduction.[2]

In the review of systematic reviews, Willadsen highlighted that many definitions and measures seem to be tailored towards use in research rather than being clinically relevant.[126] The definition by Le Reste is more likely to capture this complexity but the multi-faceted nature of the definition may make it difficult to operationalise in practice. Le Reste and colleagues have commenced research into developing approaches to measuring multimorbidity in this way.[128] An alternative approach is to examine multimorbidity from different perspectives such as that from self-report. For example Bayliss *et al* found that patient self-report was better able to capture the biopsychosocial factors relating to multimorbidity.[47]

The wide prevalence ranges due to differing definitions (and measures) can be seen in the studies from my review of cohort studies where the prevalence ranged from 10% to 80%. This finding agrees with that of Fortin *et al*, who in their systematic review of prevalence studies of multimorbidity found marked variation between prevalence estimates due to varying study design.[26] Marengoni *et al*, in their systematic review of ageing studies in multimorbidity, also commented that a wide range of prevalence in included studies can be linked to different definitions and measures being used.[31]

3.4.2 Multimorbidity measures

In both literature reviews there was evidence of disease counts and weighted measures being used, and no single measure was recommended as being superior. Of note, I have used the term "disease counts" as this is the common phrase used in the literature, but acknowledge these measures can include a wider spectrum of health conditions (for example risk factors for disease and categories of disease).

The review of systematic reviews highlighted that weighted measures, if used for appropriate outcomes, can assist in predicting patient outcome and future healthcare usage and can also provide an assessment of the burden of multimorbidity experienced by the patient, their carers or health and social care services.[129] For example, the Charlson comorbidity index has good evidence for predicting mortality.[39,125]

I also found evidence that disease counts may perform almost as well as weighted measures in predicting the majority of outcomes.[39] Disease counts may therefore be more appropriate for scenarios where multiple outcomes are being considered or in which no single weighted measure has been validated.[39] This was the justification given by Barnett for their approach.[2] Counts may also be a more intuitive summary of multimorbidity burden in patients, for example when showing the link between multimorbidity and SES or between physical and mental health.[2]

Diederichs stressed the importance of specifying the criteria for selecting conditions to include in a count. The evidence from both my reviews supports choosing conditions based upon the purpose of the work being conducted. Some conditions, for example depression, may have greater impact upon patients in terms of quality of life or function.[130] Other conditions such as heart disease may impact more upon health services in terms of number of admissions or treatment costs.[26,38] In the published literature the rationale for selecting conditions (if given) includes it being of high prevalence [2,26,38,58,59] or of high burden (morbidity, mortality, long duration, impact on patient or cost).[2,26,38,59,61,67]

Not all disease counts will be from a researcher developed list. Asking individuals which conditions are important to them is an alternate source of information. For example a study by Hansen *et al* found that when comparing patient self-report to clinician report certain conditions such as diabetes (which have established clinical guidelines and clear diagnosis pathways) had good agreement but conditions with more complex diagnosis or which are associated with stigma (such as haemorrhoids) had poorer agreement.[131]

3.4.3 Data source

No systematic review recommended a particular data source to measure multimorbidity and in my review of cohort studies I found both administrative and non-administrative data being used. In the wider literature, a number of studies and reviews have compared data sources for comorbidity and multimorbidity measures, often with conflicting findings.[27,45] For example, Needham in their review of the Charlson comorbidity index in administrative databases found the Charlson index derived using administrative data compared

favourably to that from medical chart review in predicting mortality.[45] However, a systematic review by Leal and Laupland found that for infectious diseases, the Charlson from administrative data underperformed compared to that of case-note review.[27] I conducted and published research which found that Charlson comorbidity scores derived from case-note review had similar predictive ability for mortality as those sourced from administrative data in a renal population.[43]

The availability of data and the resource implications will additionally affect the choice of data used. For example, whilst case-note review is viewed as being more complete than administrative data it is more resource intensive.[27,45] Given the resource constraints of collecting data and the relative resource advantages of using routine data, it is not unexpected that in my review of cohort studies, the smallest studies used non-routine data and the largest studies used routine data.

3.4.4 Strengths and limitations

My review of systematic reviews provides a high level summary of both the definition and measurement of multimorbidity in relevant systematic reviews. This was the first to focus on those reviews which primarily aimed to examine multimorbidity definitions or measures. This is important given the heterogeneity in definitions and measures available and the associated complexity in developing consensus.

I acknowledge that reviews such as that by Fortin *et al* (of prevalence studies of multimorbidity)[26] and Marengoni *et al* (of ageing and multimorbidity)[31] discuss recommended definitions and measures at the end of their reviews, but I have not included these in the review as their primary aim did not meet our inclusion criteria. However I do draw upon these and other relevant studies and reviews in this discussion.

By also reviewing cohort studies of multimorbidity I have widened the evidence base. The findings complement those of my review of systematic reviews and confirm the issue caused by a lack of a consensus definition and measure.

A limitation of both my literature reviews is that search terms were limited to the title only for practical reasons which means some relevant reviews could be missed. I conducted a test search for my review of systematic reviews, including these terms in the abstract or full text which revealed no additional reviews in the first 100 titles screened.

One of the included systematic reviews (examining measures of multimorbidity) was classed as low quality.[34] However, as there were four other reviews examining multimorbidity measures this should reduce the likelihood that this affected the findings. I did not quality assess the studies in my review of cohort studies as the primary purpose of that review had been to assess the availability of multimorbidity cohort studies.

3.4.5 Recommendations for multimorbidity definition and measure

A key recommendation is that researchers be explicit about the definitions and measure(s) they are using and give a rationale for their choice. This will enable comparison of findings across different settings as well as progress the evidence base regarding the most appropriate definitions and measures for particular scenarios.

Overall, a definition of multiple co-existing conditions is reasonable and researchers wishing to set a cut-off would be consistent with others by using a cut-off of two or more. In studies of outcomes, a weighted measure validated for the outcome being considered is advised. However, where evidence is weak or where multiple outcomes or populations are being considered, the use of disease counts is appropriate. There is precedence for the inclusion of conditions other than solely chronic disease in a multimorbidity measure.

In this chapter I have found that multimorbidity measurement is rarely the measurement of the incidence or prevalence of active conditions. For example, in disease counts, conditions may be included if they have *ever* been present. In other measures, conditions are weighted to better predict future outcome. Multimorbidity measurement may therefore be an assessment of burden rather than true "prevalence" as used by epidemiologists. For example, Fortin *et al*, in their study of the impact of multimorbidity on quality of life, found that for some conditions such as those from cardiac and respiratory

systems, the combined effect was greater than the sum of the whole regarding the impact on quality of life.[132]

Conditions which are not currently active may still impact on patients, on patient use of services and on outcomes. For example, they may make individuals more vulnerable to developing other conditions (such as depression as a result of a physical disease)[2] or impact on an individual's ability to cope with future disease.[89-91] Thus in this chapter I also conclude that multimorbidity measurement is more an indication of the composite burden of multiple health conditions rather than "prevalence". In my thesis I use the term "prevalence" for ease of interpretation.

There is no recommended disease count. As I described in chapter one, the paper by Barnett el al is one of the most high-profile disease count measures in the multimorbidity research field. The selection of conditions was not based upon a formal framework and instead was a combination of those recommended by Diederichs (as described in Table 6) along with diseases as part of the QOF General Practice contract and those set as important long-term conditions by NHS Scotland. This was combined with clinical consensus to identify important chronic and high-burden morbidities. Whilst such consensus approaches may be critiqued for being subjective, the process was clearly defined and the authors used reasonable underlying data sources for selecting conditions. An advantage of using the Barnett measure is that this paper has a high profile within the multimorbidity community. This can allow comparisons between studies and analysis of changing trends over time.

In addition to this, self-report is one route by which to capture the burden of multimorbidity from an individual's perspective and should also be studied when considering the Public Health impact of multimorbidity.

3.4.6 Implications for thesis methodology

In this thesis I define multimorbidity as the co-existence of two or more health conditions in an individual. I measure multimorbidity using disease counts, reflecting that I am studying prevalence and a variety of determinants and outcomes. The results of this chapter describe the value which can be drawn from assessing the prevalence of

multimorbidity from different perspectives. In the thesis, multimorbidity is therefore measured by patient survey in primary care, person self-report and using secondary care administrative data. As described in Chapter 2, I am using two study populations: the Diamond study and the Aberdeen Children of the 1950s (ACONF) cohort study. The ACONF consists of the Original ACONF and an Enhanced ACONF (described in Chapter 6).

Primary care multimorbidity is measured in the Diamond study. The participants were asked to select from a list of 14 pre-selected conditions. For person self-reported multimorbidity I include any condition an individual sees as being important to them. This is measured in the Original ACONF, where participants were asked to list up to six "…long-term illnesses, health problems or disability which limit [their] daily activities or work [they] can do".

Secondary care multimorbidity is measured in the Enhanced ACONF by linking these individuals to their secondary care administrative data record. I use the conditions set out by Barnett *et al*. Using Barnett *et al* in a secondary care population is a novel development and so I create a novel adaption from its primary care coding to that which can be used in secondary care. In the next Chapter I describe this process.

4 Adapting the Barnett multimorbidity measure for use in Scottish secondary care administrative data

4.1 Overview

In this thesis I use Scottish healthcare administrative data to measure multimorbidity in the ACONF. I also measure the hospital admission rate and the mortality rate. The latter is drawn from Scottish mortality records. I start the chapter by giving background to Scottish administrative data systems. Following this I describe the steps I took to adapt the Barnett measure for use in the thesis.

4.2 Background: Scottish health and mortality administrative data

4.2.1 Available data

Since 1948, the United Kingdom has had a free at the point of use nationally funded universal care system- the National Health Service (NHS).[133] This covers all primary and secondary care with variations geographically regarding the payment of certain services such as prescriptions and dental care. In Scotland, the NHS is a devolved matter and is therefore the responsibility of the Scottish Government.[134] NHS care is delivered by 14 regional Health Boards. Aberdeen is based in the NHS Grampian Health Board.[135]

In the 1960s, a system was developed to hold all hospital discharge records and death records centrally in Scotland. Work in the 1980s began bringing together these records into datasets in which patients were linked to their own records. In healthcare, records are held and analysed by the Information Services Division (ISD).[136] Mortality records are held by the National Records of Scotland.[137]

Coding is the process by which a range of clinical events are translated into codes which enables analysis both for operational and epidemiological purposes.[138] There are nationally

agreed coding systems in place in Scotland, varying depending on the form of data considered. These are:

- International Classification of Disease (ICD) for diagnoses recorded in secondary care
- Read Coded Clinical Terms (Read codes) - a coded thesaurus of clinical terms, used in Scottish primary care health systems.
- Office of Population Censuses and Surveys' Classification of Surgical Operations version-4 (OPCS-4) for procedures and interventions in secondary care.
- Clinical Imaging Procedure codes [138]

The Systematised Nomenclature of Medicine - Clinical Terms (SNOMED-CT) is a system combining the above codes which will ultimately replace these.[138]

4.2.2 Scottish morbidity records

Scottish Morbidity Records (SMRs) are hospital patient records pertaining to different types of care in Scotland. The datasets used in this thesis to code multimorbidity are the SMR01, the SMR04 and the SMR06. SMR01 relates to non-obstetric and non-psychiatric inpatients and day cases (general acute), SMR04 relates to psychiatric inpatients and SMR06 is the Scottish cancer registry.[139] The SMR06 was specifically developed to record data on malignant cancer diagnoses, including personal and demographic information and detailed diagnosis information (for example site and histology of the tumour).

For SMR01 and SMR04, the record is generated after a completed episode of care. The entire admission of a patient is called the Continuous Inpatient Stay (CIS) and includes all movement from the first admission through to the final discharge. It is made up of one or more episodes, with episodes being generated when a patient is discharged from hospital or when they are transferred to a different hospital, specialty or to the care of a different consultant.

Each episode of care within the CIS is coded separately (ISD; email communication; July 2014). A range of data are collected during a CIS, including demographic details, diagnoses

(coded using ICD) and procedures (coded using OPCS-4).[140] The ICD is now in its 10th revision (ICD-10).[6] ICD-10 contains significantly more codes and categories than the 9th revision (ICD-9), allowing the more detailed recording of conditions.[141] The ICD-9 was in place in most countries around the world from the 1980s and was replaced by ICD-10 in 1992 and adopted for use by ISD in 1996.[138] Data used in this thesis are coded using both ICD-9 and ICD-10 depending on the date of multimorbidity measurement.

Coders work using the Patient Management System which contains discharge letters, GP referral letters, and results of laboratory and radiological tests. A team of coders allocate codes to discharges within six weeks of discharge. The majority of the information for these codes will be drawn from the "Immediate Discharge Letter" (IDL) which is normally written by a junior doctor. The full case-note for the patient will be not routinely be accessed and will only be requested if a coder is unable to apply codes based upon the information available. If the Consultant alters the final diagnosis in the final discharge letter (FDL) there is no mechanism in place to ensure any codes already entered for that patient are updated. (Dyllis Bruce, Aberdeen Royal Infirmary coding manager; oral communication; April 2014).

Six codes are listed, with the first being the main diagnosis ("main condition"). Subsequent codes will either be other diagnoses occurring during that episode or comorbidities, and so may or may not be active conditions during that episode. There is no mechanism to state whether a particular code on discharge refers to a new diagnosis or a pre-existing diagnosis- other than the fact the first code must be the main reason for the episode of care.

ISD have provided a list of important conditions to code for as comorbidities but coders can also use their discretion as to what they include. [142] Comorbidity information may come from past medical history documented on the discharge letter or more commonly from the GP referral letter.

4.2.3 Changes in coding practice over time

The guidance given to coders changes over time and may influence the range of diseases recorded. For example, from 1st October 2007 coders were given a list of 25 important "comorbidities" which should be recorded subsequent to the "main diagnosis" if space

permits. This list included Diabetes Mellitus and hypertension which had previously been under-recorded in hospital administrative data.[142] This may therefore lead to an apparent higher prevalence of certain conditions from 2007. There are also regular updates and advice given to coders as to which codes to use in specific scenarios.[143]

4.2.4 Validation and quality assurance of the Scottish Morbidity Records

In Scotland, ISD support the coding process and provide training, support, validation and quality assurance checks of data. The most recent quality assurance report for SMR01 (2014 to 2015) involved a random sample of hospitals from all mainland Health Boards (plus NHS Orkney) and a random selection of inpatient and day case records for assessment.[136] The accuracy rate of coding for the "Main Condition" was found to be 89% (not statistically significantly different from the ISD recommended minimum standard of 90%).[136] These checks were undertaken in comparison with the data in the IDL primarily, or in the FDL if that was available.

Checks were also conducted on the accuracy of supplementary coding (i.e. those codes being entered after the "main diagnosis") for the list of important comorbidities as described in the previous section. The report found that almost half of common conditions which were present in the case-notes for the patient were not being coded as they were not in the IDL or FDL. Overall the accuracy rate for selected common chronic conditions was 80%.[136]

4.2.5 Linking individuals to healthcare and mortality records

A single individual may generate administrative data across a number of databases. It is important to be able to link (match) people correctly to their own data. This can be made more straightforward by the presence of unique identifiers such as the Community Health Index (CHI) in NHS Scotland. The CHI number is a unique 10 digit identifier allocated to a patient on first registration with the NHS system (e.g. at birth or when registering with a GP). In 2005 work was conducted to improve the use of CHI in all clinical communications and this reached over 97% by 2010. The use of CHI on all clinical communications is now

mandatory. If a patient presents for treatment with no CHI number then one will be allocated.[144]

Where there are not unique identifiers matching is more difficult. Up to 3% of true links may be missed by matching on each of a range of key identifying information (such as surname and date of birth). Improving the likelihood of true matches by including more variables means more true links will be missed.[145]

When linking individuals to records, ISD Scotland use a combination of probability and deterministic matching to link records.[146] Deterministic matching is based upon a criterion being met (for example the pair of records being considered match a unique identifier) and if they do not match then it is a non-link.[147] This is used primarily now due to the availability of CHI.

Probability matching was more common prior to the existence of CHI. This is calculated on the basis that every time identifying information matches between two records, the probability that this is the same individual increases and that every time the information does not match this decreases the probability.[147] The distribution of probability scores differs by the nature of the records being linked (for example due to differing availability of identifiers). Therefore the level at which matched records are said to be truly linked is set after clerical checking of a sample of pairs.[145]

4.2.6 Administrative data in this thesis

In this thesis I measure multimorbidity and hospital admission rates using the SMR01, SMR04, SMR06 and I measure the mortality rate based upon the date of death from mortality records. To do so, the ACONF cohort were linked to their healthcare and mortality records. The cohort had previously been linked to Scottish administrative data for research purposes but there was no record of the CHI numbers. Therefore the cohort needed to be "CHI seeded" (the process of matching CHIs to persons) for linkage to be undertaken.[148] Once CHIs were available, ISD could link ACONF members to their records. The details and results of this process are in Chapter 6, the methodology.

4.3 Method

The definition of conditions in Barnett *et al* was based upon either the presence of Read codes specified for that condition or the presence of certain prescriptions. Read codes are not directly comparable to ICD codes. As secondary care data in Scotland is coded using the ICD, the first step was to source these codes for each of the Barnett conditions. The selection of codes was undertaken in a two-stage manner.

Firstly, ISD were approached for any documents which recommended codes to map to conditions. Secondly, I conducted a literature review to search for papers describing ICD codes for multimorbidity or comorbidity coding. The aim of the literature review was to find out which coding algorithms were most commonly used and/or validated. Synonyms for administrative data, coding and multimorbidity were entered into the search engines Medline, Embase and PubMed from database inception to March 2014. The literature search terms are in Appendix 1, Table 91. I screened titles, abstracts and full texts for studies which either developed algorithms for applying ICD codes to conditions, or which validated indices of ICD codes.

After this process I allocated ICD-10 and ICD-9 codes to each of the Barnett conditions.

4.4 Results

4.4.1 Data from ISD

ISD provides regular guidance to coding staff across NHS Scotland as to which codes should be used for which conditions.[143] As described above, in 2007 coders were given a list of 25 "comorbidities" which should be recorded in the space subsequent to the "main diagnosis" if space permits. This list contains ICD-10 codes for each of the 25 conditions.[142]

Additionally, ISD had a document with ICD-10 codes allocated to a range of "long-term conditions".[149] The list was developed by ISD in order to assess the prevalence of these conditions in Scotland. The conditions were selected by using the most common conditions

appearing in the Quality Outcome Framework (part of the UK General Practice contract), using national health survey data and in discussion with ISD colleagues. There were 26 conditions in total, including cancer, rheumatoid arthritis and diabetes.[149] ISD also highlighted the availability of an online ICD-10 tool which can be searched by condition name[10] and their own mapping service for converting ICD-10 to ICD-9 codes.

4.4.2 Literature review

After searching the coding literature, duplicates were removed and the resulting 775 papers were screened by title and abstract. Two systematic reviews[27,150] and eight individual studies[151-158] were included after full text screening.

The Deyo modification of the Charlson index, the Elixhuaser method and the Quan adaption of the Charlson and Elixhuaser were the most commonly cited in studies found in the literature search. The systematic review by Sharabiani at al found the Deyo variant of Charlson was the most commonly used, followed by the Elixhauser measure.[150]

Quan *et al* used the Deyo modification of the Charlson index and the Elixhauser list.[157] These measures had ICD-9 codes and the authors updated these to ICD-10 codes. The authors assessed the performance of the new algorithms, finding the ICD-9 and the new ICD-10 versions worked similarly. Additionally, ISD had used Quan *et al* to inform the development of the coding in the documents described above (supplemented by clinical advice). As Quan *et al* (from now to be called "Quan") was a widely used source, and it contains the two most commonly used comorbidity measures, the paper was selected for use in this work.

4.4.3 Allocation of codes

Using the results of my search of the ISD data sources and the relevant literature I took the following steps to develop my ICD Barnett measure. I firstly concentrated upon ICD-10 codes for each condition. I used Quan as the primary source. Where there were gaps, there was comparison to recommendations from ISD and these codes were used if available. Where neither Quan nor ISD had codes for a condition, I used the online ICD-10 tool.[10] The

summary of the findings of the process for selecting the ICD-10 codes for the Barnett conditions is in Appendix 2, Table 93. Fifteen conditions were sourced using the online tool. These included visual problems (glaucoma and blindness), learning disability, constipation, anxiety, irritable bowel syndrome and migraine.

The next step was to map these ICD-10 codes to corresponding ICD-9 codes. Not all conditions were available with ICD-9 codes in the Quan paper and there was no easily accessible online tool to find these. Therefore I approached ISD to utilise the mapping service. An ISD analyst generated the ICD-9 codes using my list of ICD-10 codes. I then compared the results against a sample of ICD-9 codes in Quan ("diabetes" and "rheumatoid arthritis") and these were found to match. A summary of all the Barnett conditions and the corresponding ICD-9 and ICD-10 codes is in Table 8.

Table 8: List of Barnett condition categories with corresponding ICD-10 and ICD-9 codes

Condition category	ICD-10 codes*	ICD-9 codes
Hypertension	I10.x; I11.x – I13.x; I15.x (no I14)	401, 402, 403, 404, 405
Coronary heart disease	I20.x-I25.x	410-414, 4230+410, 4259, 4295+410, 4296+410
Diabetes	E10.x -E14.x	250
Thyroid disorders	E00.x-E07.x	240, 241, 242, 243, 244, 245, 246
Hearing loss	H90.x-H91.x, H93.1	3880, 3882, 3883, 389
COPD	J40.x- J44.x	4168, 4169, 490- 496, 500, 501, 502, 503, 504, 505, 5064, 5081, 5088
RA, Inflammatory polyarthropathies Connective tissue	M05.x-M14.x, M30.x-M36.x	1361, 446, 4476, 710, 712, 713, 714, 7160, 7161, 7162, 7164, 7165, 7166, 7168, 7169, 7192, 7193, 7200, 725, 7293
Alcohol problems	F10.x; G62.1; I42.6; K29.2; K70.0; K70.3; K70.9; T51.x; Z50.2; Z71.4; Z72.1	291, 303, 3050, 4255, 3575, 2652, 5353, 5710, 5712, 5713, 980
Substance misuse	F11.x-F16.x; F18.x- F19.x	292, 2940, 304, 3052-3059
Stroke, TIA	G45.x; G46.x; H34.0; I60.x–I69.x	430-438, 3623
Chronic kidney disease	I12.0; I13.1; N17.x-N19.x; N25.0; Z49.0 – Z49.2; Z94.0; Z99.2	403, 404, 5822, 585, 586, 5880, V560, V568, V420, V451
Diverticular disease	K57.x	5620, 5621
Atrial fibrillation	I48.x	427.31
Peripheral vascular disease	I70- I71.x; I73.1; I73.8; I73.9; I77.1; I79.0; I79.2; K55.1; K55.8; K55.9; Z95.8; Z95.9	440, 441, 4431, 4438, 4439, 4471, 5571, 5579, V434
Heart failure	I11.0; I13.0; I13.2; I42.x - I43.x; I50.x	3989, 402, 404, 4254-4255, 4257-4259, 428, 7798
Prostate disorders	N40.x – N42.x	600, 601, 602
Glaucoma	H40-42	365
Dementia	F00.x - F03.x; G30.x	290, 2941, 3310, 3312
IBD	K50.x- K51.x	555 , 556
Blindness & low vision	H25.x-H26.x; H28.x; H53.x-H54.x	366, 368, 369
Chronic sinusitis	J32.x	473
Learning disability	F81.9	3159
Anorexia, bulimia	F50.x	3071, 3075
Bronchiectasis	J47.x	494.0
Parkinson's disease	G20.x- G22.x	332
Multiple sclerosis	G35.x	340
Viral Hepatitis	B15.x-B19.x	070
Chronic liver disease	I85, I86.4, I98.2, K70 - K76, Z94.4	4560, 4561, 4562, 4568, 570, 571, 572, 5730, 5733, 5734, 5738, 5739
Depression	F32.x, F33.x F34.1 F41.2, F43.2	2963, 2980, 3090, 3092, 3098, 3099, 311, 3004
Painful conditions**	F45.4; F45.5; H57.1; H92.0; K14.6; K08.8; M25.5; M54x; N64.4; M75.8; M79.6; N23.x; R07.0- R07.4; R10x; R52.x	7890, 7841, 7865, 3887, 3798, 7194, 7295, 3078, 7236, 7248, 7234, 7231, 7241-7243, 7245, 5296, 5258, 7880
Asthma	J45.x- J46.x	493
Treated dyspepsia	K30.x	5368
Treated constipation	K59.0	5640
Epilepsy	G40.x- G41.x	345
Anxiety, neurotic stress related & somatoform disorders	F40.x - F41.x	3000, 3002, 3004, 3005
Irritable bowel syndrome	K58.x	5641
Cancer	C00.x-C97.x	140 - 208
Schizophrenia, non-organic psychosis, bipolar	F20.x- F29.x; F30.2; F31.x	295, 297, 298.3, 298.4, 298.9
Psoriasis or eczema	L20.x-L30.x; L40.x	690-691, 6920-6926, 6928-6929, 693, 6943, 6958, 6960, 6961
Migraine	G43.x	346

*".x" means all digits following decimal place included **Abdomen, back, breast, chest, ear, eye, joint, limb, back, pelvic, psychogenic, throat, tongue, tooth, kidney, non-specified. Abbreviations: ICD, International Classification of Diseases; RA, Rheumatoid Arthritis'; COPD, Chronic obstructive pulmonary disease; TIA, , transient ischaemic attack; IBD, inflammatory bowel disease

4.5 Discussion

4.5.1 Summary and interpretation of findings

In this chapter I have developed ICD codes for Barnett conditions in order to measure multimorbidity in Scottish secondary care. All research is affected by the underlying quality of data used. Scottish secondary care administrative data undergoes quality checks as I described above. It is reassuring that the accuracy of coding was almost 90% when the "main diagnosis" codes were compared to the IDL (or FDL where available).[136] However, the IDL may be written by a doctor not involved with the care of the patient. I described how the FDL (which will be written by the consultant looking after the patient) is often not available to coders by the time of coding. The impact of this potential source of error has not been checked. Additionally, the ISD quality assurance report found that for those conditions which coders are to commonly look for in sources outside of the IDL, the accuracy rate was lower (80%).[136]

The date a condition is first recorded in secondary care administrative data is not necessarily the date of onset. It may have been previously diagnosed in primary care for example. In Scotland, linkage between primary and secondary care data is currently not possible. It is also not possible to link the ACONF to their primary care record. A further issue of which to be aware is that codes subsequent to the first code do not necessarily refer to conditions active during a particular admission. Coding data should therefore not be used to measure the incidence of a certain condition at a specific time point. This provides support for using a look-back period (rather than a snapshot of data).

As I described in Chapter 1, there is no consensus on look-back period length. For the thesis I adopt the approach I took in previous comorbidity research (where I compared Charlson comorbidity scores derived from case-note review to those sourced from administrative data).[43] I set the look-back at five years based on evidence that it is of sufficient length to ascertain chronic disease status and to model outcomes of mortality and admission.[49,50]

Despite this, it is important to acknowledge that a look-back period may miss important conditions. These issues are ones which all researchers of multimorbidity and comorbidity face.

It is tempting to choose multiple look-back periods to test but this is not the aim of my PhD. This is particularly important because I aim to look at the determinants and outcomes of multimorbidity. Post-hoc changing of the look-back period in order to fit a desired result is methodologically unadvised.

I plan to use all coding (not just the "main diagnosis") in order to provide the most comprehensive assessment of multimorbidity burden. I can justify this as I am using a look-back period and because by not doing this I would miss important conditions which may not be part of an admission.

4.5.2 Strengths and limitations of my approach

In 2014 when I conducted this work, I was the first to apply ICD coding to all of the conditions in the high-profile Barnett multimorbidity measure. I ensured that the codes I used were drawn from commonly used existing sources where possible. I explicitly considered using the codes for conditions which are used by those coding data in Scotland where available. I systematically searched the literature for validated coding algorithms and also took into account the most commonly used algorithms. I used expertise from ISD to convert ICD-10 codes to ICD-9.

Where codes were not sourced by the above means I used the ICD-10 data dictionary. An alternative approach would have been to search for validated algorithms for each of these conditions individually. However, the ICD-10 coding manual has excellent search functions and I have also been explicit as to which codes were sourced this way. Of note, many of the conditions sourced this way (including constipation and migraine) may be more likely to be seen in primary care.

5 Developing consensus definition and measurement of resilience to disease

5.1 Structure of chapter

In this chapter I present a systematic review which I designed, personally undertook and subsequently published, of resilience definitions and measures in the context of disease.[159] Using the findings of the review I then select measures of resilience for use in my thesis. I finish with an integrated discussion of the findings from this chapter.

5.2 Literature review: "Physical disease and resilient outcomes: a systematic review of resilience definitions and study methods"

5.2.1 Introduction

As described in the Introduction chapter, research into resilience to disease is hampered by the lack of a consensus definition and measure. The aim of this systematic review was to identify a consensus definition and measure by summarising the definitions of disease resilience and the approaches taken to study resilience in studies examining physical disease and resilient outcomes. I did not limit the review to multimorbidity as there have been so few studies in this area.

5.2.2 Method

I used the PRISMA 2009 checklist to guide the method development and reporting of findings.[122] I searched Medline, Embase, PsychInfo, PubMed and the Cochrane database of systematic reviews from database inception to 17th March 2013. The search strategy was comparable across all databases. I combined "resilience" with a range of disease terminology, as well as multimorbidity, and searched for these in the title or abstract, as well as using MeSH terms where available. The search strategy is in Appendix 1, section 13.6.

Studies in which physical disease was assessed for its association with resilient outcomes were included. Peer reviewed quantitative studies with 100 or more participants were eligible. The sample size restriction was applied for pragmatic reasons as my early work demonstrated that studies of physical disease and resilient outcomes often involved complex analyses with multiple variables and analyses with smaller populations were often under-powered. Studies examining only mental health conditions and resilience at a family or community level were excluded, as were studies not in the English language. Study authors were contacted for papers not accessible.

Title, abstract and full-text screening were carried out independently by two reviewers (myself and Dr Terry Porteous) and any disagreement was resolved by a third reviewer (Professor Corri Black). I screened the references of included articles for relevance.

Primary data extraction was carried out by myself and Dr Porteous with three others acting as independent second reviewers (Dr Chris Burton, Dr Alison Elliott and Dr Lisa Iversen). The data extraction form was prepared by myself and finalised with discussion with the other reviewers. Data extraction included: the study characteristics, the theoretical definition of resilience given by the authors and the measures of resilience used. Any disagreement between the reviewers following this process was resolved by Professor Black. I used SIGN critical appraisal checklists to assess the quality of included studies.[123] The quality of the study was not used as an exclusion criterion but as a guide to inform interpretation of the findings. The results were combined using a narrative approach.

5.2.3 Results

Summary of study characteristics

Of 2,280 articles, 12 met the study criteria (Figure 2).[160-171] Study characteristics are reported in Table 9. Hardy (2004) analysed a sub-set of the population from a previous study (Hardy (2002)) however both are reported here as the study aims, exposures and outcomes differed.[164,165] Seven studies were cross-sectional and five were longitudinal. Six were from North America, four were from Europe, and two were from Asia. Sample size at analysis ranged from 145 to 3,347. The average age was 70 or over for five of the studies.[163-

[165,167,168] Two out the 10 studies included only women.[166,169] There was a greater proportion of women compared to men in the remaining eight.[160-162,164,165,167,168,171] Five out of the seven studies reporting ethnicity had predominantly white ethnicity.[162-165,171]

One study was of high quality,[170] nine studies were of moderate quality[160-166,168,169] and two were low quality.[167,171] Lundman *et al* was deemed low quality because the resilience scale they used was not validated, there was a lack of information about sample selection and the statistical analysis was univariate.[167] Yi-Frazier was assessed to be low quality because of a lack of information regarding sample selection and they used a convenience sample which may introduce bias.[171]

There was complete agreement between the two reviewers for data regarding the theoretical definition of resilience and the resilience measurement. Arbitration by the third reviewer was required for the quality assessment in five studies.

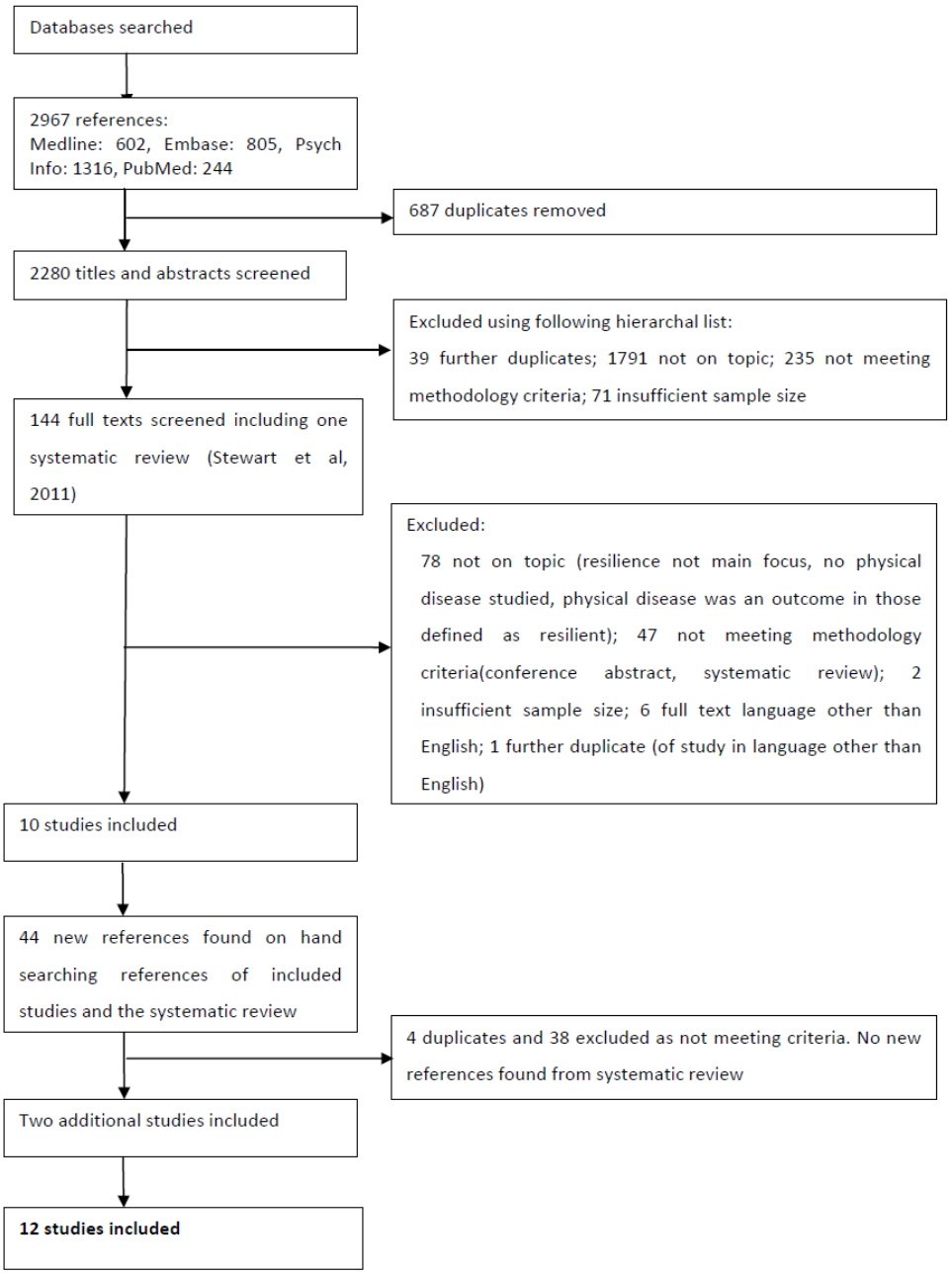


Figure 2: Systematic review of resilience to physical disease: flow-chart of search strategy

Table 9: Systematic review of resilience to physical disease: baseline characteristics of included studies

Study reference	Stated study aim	Study design	Study setting location	Study population	Population characteristics: age, % F, ethnic group	Quality assessment
Bonanno 2007[160]	" to address this deficit [previous research too focussed on person-centred variables] by examining other factors that may inform resilience to PTEs, including demographics, social and material resources, and additional life stressors "	Cross-sectional	Community North America	2752	Age over 18; 54% F; mixed ethnicity	Moderate
Bonanno 2008[161]	"To examine trajectories of psychological functioning…on a sample of hospitalized survivors of the 2003 severe acute respiratory syndrome (SARS) epidemic"	Longitudinal	Hospital Hong Kong	Analysis on 890 with sufficient follow up data	Mean age 42; 61% F; ethnicity not reported	Moderate
Costanzo 2009[162]	"To examine psychosocial impairment, resilience or thriving among cancer survivors in the general population by comparing them to individuals without a cancer history."	Longitudinal cohort nested in survey	Community North America	NR in detail. 1,194 analysed	Mean age 63; 63% F; predominantly white ethnicity	Moderate
Glymour 2008[163]	Does not succinctly state aim. "We hypothesize that stroke survivors with more extensive social ties and greater emotional and instrumental social support immediately after stroke will experience greater improvements in cognitive function over 6 months of follow-up and achieve a higher level of cognitive functioning 6 months after stroke."	Longitudinal cohort	Hospital North America	272 at baseline, 25 lost to follow-up	Mean age 70; 49% F; predominantly white ethnicity	Moderate
Hardy 2002[164]	"to identify the life events that older persons experience as most stressful, to determine how often each type of event is identified as most stressful (particularly among those with a recent serious illness), to evaluate the perceived consequences of these events for the lives of older persons, and to evaluate the relationship between demographic factors and measures of health and functional status and these perceived consequences."	Cross-sectional	Community North America	754	Median age 78; 65% F; predominantly white	Moderate
Hardy 2004[165] (contin. overleaf)	"To assess resilience of community-dwelling older persons using a new scale based on response to a stressful life event and to identify the demographic, clinical, functional, and psychosocial factors associated with high resilience."	Cross-sectional	Community North America	546 analysed of the 754 individuals available in the study (due to missing data)	All aged 70 and over (38% over 74); 64% F; predominantly white ethnicity	Moderate

Study reference	Stated study aim	Study design	Study setting location	Study population	Population characteristics: age, % F, ethnic group	Quality assessment
Lam 2010[166]	Does not succinctly state aim. From background: “The distinct trajectories of psychological distress over the first year of the diagnosis with breast cancer and its determinants have not been explored.”	Longitudinal	Hospital China	405 available at baseline and 285 without missing data over follow-up	Mean age 51; 100% F; ethnicity not reported	Moderate
Lundman 2012[167]	“The aim of this study was to elucidate relationships among inner strength and objective physical status, diagnosed diseases, living arrangements, and self-reported social relationships in people aged 85 years and older”	Cross-sectional	Community Europe	185	Age over 85; 64% F; ethnicity not reported	Low quality
Perna 2012[168]	“This study aims to investigate the association between resilience and health behaviours (such as physical activity and consumption of fruit and vegetables) in elderly individuals.”	Cross-sectional	Community Europe	3347	Median age 72; 53% F; ethnicity not reported	Moderate
Scali 2012[169]	“This retrospective epidemiological study aims to evaluate resilience in a high-risk women sample... taking into account life-time history of trauma (distinguishing personal from non-personal events), socio-demographic characteristics and lifetime mental health."	Cross-sectional	Outpatients Europe	238 analysed out of 324 participating	Median age reported by resilience category: low (53), intermediate (54) and high (52); 100% F; ethnicity not reported	Moderate
Taylor 2011[170]	“We explore the physical, psychological, and social factors associated with reporting a good QOL in the context of poor seizure control and socioeconomic disadvantage (‘‘resilient’’ outcome) and the factors associated with reporting a poor QOL in the context of good seizure control and socioeconomic advantage (‘‘vulnerable’’ outcome).”	Longitudinal cohort based upon RCT	Outpatients UK	1611; analysis on 617 with sufficient follow up data	Mean age 38; 46% F; ethnicity not reported	High quality
Yi-Frazier 2010[171]	"To explore whether varying levels of resilience resources differentiated the coping profiles of patients with diabetes."	Cross-sectional	Community and hospital North America	145	Median age 49; 57% F, predominantly white	Low quality

Abbreviations: F, female; PTE, potentially traumatic event; QOL, quality of life; NR, not reported; RCT, randomised controlled trial; UK, United Kingdom

Summary of study approach

There were two general approaches taken in the included studies (Table 10):

1. Physical disease was an adversity leading to resilience
2. Physical disease was a variable modifying the relationship between a different adversity and resilience

Although I have categorised the studies in two ways, there were also areas of overlap (for example where one disease is the adversity and a further disease influences whether there is resilience to that adversity).[169]

In six studies the disease of interest was considered to be the "adverse event".[161-163,166,170,171] In five of these, all study participants were selected on the basis of having the physical disease being studied and so these studies did not examine whether physical disease led to *increased* or *decreased* resilience.[161,163,166,170,171] For example, in Yi-Frazier, all participants had diabetes and the authors studied whether those with better levels of "resilience resources" were better able to cope with disease. In the remaining study, Costanzo compared cancer survivors to those without a cancer history.[162] The study found cancer survivors had impairment relative to the comparison group in mental health, mood, and some aspects of psychological well-being, but they showed resilient social well-being, spirituality, and personal growth.[162]

In the remaining six studies physical disease was studied for its association with resilient outcomes in populations exposed to adverse events such as bereavement or illness. The nature of the physical diseases and the adversities considered varied.

Table 10: Systematic review of resilience to physical disease: summary of study approach

1.Studies in which resilience is assessed in those exposed to a physical disease adversity

Study	Physical disease adverse event	Impact of physical disease upon resilience
Bonanno 2008[161]	SARS	All participants had disease*
Costanzo 2009[162]	Any cancer except skin	Exposed group (cancer survivors) and non-exposed group. • Cancer survivors demonstrated impairment relative to the comparison group in mental health, mood, and some aspects of psychological well-being. • Survivors exhibited resilient social well-being, spirituality, and personal growth.
Glymour 2008[163]	Stroke	All participants had disease*
Lam 2010[166]	Surgery for breast cancer	All participants had disease*
Taylor 2011[170]	Epilepsy	All participants had disease*
Yi-Frazier 2010[171]	Diabetes	All participants had disease*

2.Studies in which the physical disease and other variables are assessed for their association with resilience

Study	Adverse event population exposed to (if described)	Physical disease	Impact of physical disease upon resilience
Bonanno 2007[160]	World Trade Centre September 11 terrorist attacks.	Physician diagnosed chronic disease (exact nature not described)	Statistically significant association of lower resilience with increasing number chronic diseases.
Hardy 2002[164]	Personal illness or injury, death of a family member or friend, illness or injury of a family member or friend, and nonmedical events.	13 self-reported physician-diagnosed chronic conditions, dichotomised into ≥2 or <2.	Not associated with resilience.
Hardy 2004[165]	As for Hardy 2002	As for Hardy 2002	Not associated with resilience.
Lundman 2012[167]	Does not include	Range of diseases considered.	Resilience included in inner strength score. Conditions significantly associated with inner strength: • COPD, heart failure, osteoporosis Conditions not significantly associated: • Cerebrovascular disease, cataract
Perna 2012[168]	None.	Disease (present/absent): Diabetes mellitus, MI, stroke	Higher prevalence of high resilience in those without disease compared to those with disease.
Scali 2012[169]	Recent breast cancer, lifetime psychiatric diagnoses, lifetime traumatic event (includes cancer disease, death of close relative and life-threatening illness)	Breast cancer	Women scoring at an intermediary level of resilience significantly more likely than those with low resilience to have been exposed to a recent breast cancer.

Abbreviations: SARS, Severe Acute Respiratory Syndrome; NR, not reported; PTE, potentially traumatic event; QOL, quality of life; F, female; COPD, Chronic Obstructive Pulmonary Disease; MI, myocardial infarction
*All selected on basis of having the disease so no assessment of whether having it led to increased resilience.

Five of these studies included more than one physical disease.[160,164,165,167,168] Both studies by Hardy used a count of 13 chronic conditions which they dichotomised as less than two and more than two. This is therefore a multimorbidity measure although the authors do not describe it as such. Both studies found no association between multimorbidity and resilience in individuals exposed to adversities including death and illness in close family members and friends.[164,165] Bonanno (2007) categorised chronic diseases as "0", "1 to 2" and "3 or more" and found an association between an increasing number of diseases and lower resilience to the effects of being in the World Trade Centre September 11th terrorist attack. As for the studies by Hardy, the authors did not describe this as multimorbidity.[160]

Scali found women scoring at an intermediary level of resilience were significantly more likely than those with low resilience to have been exposed to a recent breast cancer,[169] whilst Perna found a greater prevalence of "high resilience" in those without disease compared to those with disease.[168]

Resilience definitions

A theoretical definition of resilience was provided by 11 out of 12 studies (Table 11).[160-162,164-171] Glymour did not provide a definition but implied that *cognitive resilience* is maintenance of cognitive function and absence of dementia.[163] The following component parts of the definition were common to most of the other 11 studies:

1. An adversity must be experienced in order to demonstrate resilience (all studies)[160-162,164-171]
2. Resilience is the ability to maintain healthy levels of function over time despite adversity or to return to normal function after adversity (eight out of 11 studies) [160-162,166-169,171]
3. Resilience is a dynamic concept as opposed to a fixed personality trait (10 out of 11 studies)[160-162,164-167,169-171]

Table 11: Systematic review of resilience to physical disease: Resilience definitions and resilience measurement in all included studies

Study	Theoretical definition of resilience	Resilience measurement
Bonanno 2007[160]	"the ability of adults in otherwise normal circumstances who are exposed to an isolated and potentially highly disruptive event such as the death of a close relation or a violent or life-threatening situation to maintain relatively stable, healthy levels of psychological and physical functioning . . . as well as the capacity for generative experiences and positive emotions."	Resilience based upon outcomes Outcome categories defined based upon PTSD symptoms (assessed using the National Women's Study PTSD module) six months following September 11 terrorist attack. Three outcome categories 1) resilient: 1 or 0 PTSD symptoms; 2) mild-moderate trauma: >=2 PTSD symptoms; 3) probable PTSD: defined using standard Diagnostic and Statistical Manual of Mental Disorders criteria.
Bonanno 2008[161]	Provides same definition as Bonanno 2007 above	Resilience based upon outcomes Psychological functioning (MCS) was measured using the SF-12. Authors defined their four trajectories of psychological functioning as: 1. Resilient group - high mean score for psychological functioning on the SF-12 MCS that changed little over time (i.e. slope that was essentially zero) 2. Chronic dysfunction group - low mean SF-12 MCS score that changed little over time (i.e. slope that was essentially zero) 3. Recovered group - initial low mean SF-12 MCS score followed by steep positive increase/slope 4. Delayed dysfunction group - initial high mean SF-12 MCS score followed by steep negative increase/slope
Costanzo 2009[162]	" Carver describes survival with impairment as continuing compromised functioning, but he distinguishes this pattern from resilience, defined as a return to normal or baseline functioning, which is then further distinguished from thriving, described as exceeding one's original level of functioning."	Resilience based upon outcomes Range of measures of 'functioning' were compared pre- and post-diagnosis: mental health, mood, psychological well-being, social wellbeing and spirituality/ religiosity. Results were interpreted as: "Impairment indicates a decline, resilience indicates no change, and thriving indicates improvement in functioning from Wave 1 (pre-diagnosis) to Wave 2 (post-diagnosis)."
Glymour 2008[163]	NR. Implied definition of cognitive resilience is maintenance of cognitive function and absence of dementia	Resilience based upon outcomes Resilience appears to be based upon improvement in cognitive function baseline and 6 months after stroke
Hardy 2002[164]	"Resilience has been viewed as the process by which individuals survive or even thrive under adversity, incorporating both the internal traits, such as hardiness or high self-efficacy, and the external factors, such as social support, that promote coping."	Resilience measured using a resilience scale/questionnaire Authors do not set out to measure resilience and instead interpret their findings using resilience theory in their discussion. Questions assessing the consequences of stressful life events were adapted from the Resilience Module of the Asset and Health Dynamics Among the Oldest Old study. Authors interpreted individuals who had positive responses to the negative event as responding "resiliently".
Hardy 2004[165] (contin. overleaf)	Same text as Hardy 2002.	Resilience measured using a resilience scale/questionnaire A new resilience scale was developed (authors do not specify if they developed this scale). This 6-item scale measured response to a stressful event. Three groups examined: low, intermediate and high level resilience groups based on tertiles of scores on resilience scale.

Study	Theoretical definition of resilience	Resilience measurement
Lam 2010[166]	“Resilience is considered to be the most common outcome following exposure to potential trauma. Bonanno (2005) proposed four distinct patterns of adjustment in response to potential trauma: (1) chronic disruption of normal functioning, (2) recovery with a relatively mild and short-lived disruption of functioning, (3) delayed disruption of functioning, and (4) resilience with little or no disruption of functioning.” References the same work as Bonanno 2008 and therefore has a similar operationalised definition and the same resilience groups.	Resilience based upon outcomes Psychological distress measured using CHQ-12 at four time points (5 days, 1 month, 4 months and 8 months) post-surgery for breast cancer. Authors defined four trajectories of psychological distress as: 1. Resilient: relatively stable levels of low distress across assessment points 2. Chronic distress: stable high levels of distress at each measurement 3. Recovered: initial elevated distress which gradually declined 4. Delayed recovery: initially relatively low distress which elevated before reducing again.
Lundman 2012[167]	"Resilience has been referred to as a kind of plasticity that influences the ability to recover and achieve psychosocial balance after adverse experiences and as the ability to bounce back in the face of adversity. Resilience in older people has been described as the ability to achieve, retain, or regain physical or emotional health after illnesses or losses."	Resilience measured using a resilience scale/questionnaire This study treated resilience as a component part of "inner strength". Inner strength was a sum score created from factor analysis of 4 assessment scales - the Resilience Scale (Wagnild and Young), the Sense of Coherence Scale, Purpose in Life Scale and the Self-Transcendence Scale
Perna 2012[168]	“Resilience is generally understood as the ability to adapt successfully to stressful situations (Luthar *et al*. 2000; Schumacher *et al*. 2004).” "In our study, resilience is conceptualized as protective personality factor, referring to the ability to adapt successfully to stressful experiences."	Resilience measured using a resilience scale/questionnaire Used a short version of the resilience scale developed by Wagnild and Young. Groups defined based on the resilience score: resilient/high resilience=scores in upper third of scores; non-resilient/low resilience scores=scores in middle or lower third of scores
Scali 2012[169]	"Resilience has been defined as the capacity of individuals to cope with traumatic events, namely the capacity to ‘‘maintain relatively stable, healthy levels of psychological and physical functioning as well as the capacity for generative experiences and positive emotions’’ (Bonanno 2004)."	Resilience measured using a resilience scale/questionnaire Used Connor Davidson resilience scale CD-RISC 10, an abridgment of CD-RISC (a 25-item scale) Three groups examined: low, intermediate and high level resilience groups based on tertiles of scores
Taylor 2011[170]	"Resilience can be conceptualized as the process of achieving unexpected positive outcomes in adverse conditions, as opposed to an individual trait"	Resilience based upon outcomes Four groups identified based upon seizure control and socio-economic status: 1. Resilient=good QOL despite poor seizure control and socio-economic disadvantage 2. Vulnerable= poor QOL despite good seizure control and socio-economic advantage 3. Expected good= good QOL with good seizure control and socio-economic advantage 4. Expected poor= poor QOL with poor seizure control and socio-economic disadvantage
Yi-Frazier 2010[171]	"...resilience, defined as an individual’s capacity to maintain psychological and physical well-being in the face of adversity"	Resilience measured using a resilience scale/questionnaire A resilience factor score was derived using four scales, used to measure: optimism, self-esteem, self-efficacy and self-mastery. Three groups identified: low, moderate and high resilience based upon the lower, middle and upper tertiles of the resilience factor score.

**R*esilience based upon outcomes or measured using resilience scale/questionnaire. *Abbreviations:* PTSD, post-traumatic stress disorder; NR, not reported; QOL, quality of life; HIV, Human Immunodeficiency Virus; SF-12, Short Form 12; CHQ-12, Chinese Health Questionnaire

All 11 studies described adversity in their theoretical definition. This was variously described as "adverse events" or "adversity",[162,164,165,167,170,171] "a potentially highly disruptive event",[160,161] "potential trauma",[166] "stressful situations"[168] and "traumatic events"[169]. Lundman and Perna did not identify an adversity in their study design, although they do discuss it in their theoretical definitions of resilience.[167,168]

Many studies referred to previous work by Bonanno and colleagues[160,161,166,169,171] and defined resilience as maintaining healthy levels of function over time despite adversity. Others similarly defined resilience as returning to normal function after adversity[162], retaining normal function[167] or adapting successfully to stressful situations.[168] The high quality paper by Taylor defined resilience as positive outcomes in adverse conditions.[170] In contrast to this, two studies included the concept of thriving under adversity.[164,165]

Perna was the only study which stated it was studying resilience as a protective personality factor. This was their justification for not including an adversity in their study design.[168] The remaining definitions treat resilience as a dynamic process, for example Bonanno 2007 and Bonanno 2008 describe the ability to maintain stable functioning following adversity as evidencing resilience.[160,161]

Resilience measures

There were two approaches taken when measuring or identifying resilience in the included studies (Table 11):

1. Measuring it using a new or established "resilience scale"[164,165,167-169,171]
2. Identifying it based upon outcomes observed in study participants [160-163,166,170]

Six studies identified resilience using new[165,167] or established[164,168,169,171] resilience scales. In these studies participants completed questionnaires from which were derived scores indicating levels of resilience. Most studies then defined categories of resilience on the basis of scores.[165,168,169,171] For example Scali used an abridged form of the Connor Davidson resilience scale which was split into low, intermediate and high resilience groups based upon tertiles of scores.[169]

The remaining six studies identified resilience based upon outcomes observed in study participants.[160-163,166,170] For example, outcome categories for Bonanno (2007) were based upon the severity of the outcome, with the resilient group being those with the absence of, or only one, post-traumatic stress disorder symptom.[160] Costanzo defined the resilient group as those in which there was no change in functioning before and after the adverse event.[162] Two studies examined how individuals responded psychologically to an adversity (severe acute respiratory syndrome[10] and breast cancer[15]) and the way which these responses changed over time. In these studies the resilient group were defined as those who demonstrated high psychological functioning following the adversity which changed little over time.[161,166]

The high quality study by Taylor identified resilience as being those who had experienced the adverse event (epilepsy) together with additional disadvantage (poor seizure control and socio-economic disadvantage) whilst still maintaining a good outcome (good quality of life). The authors distinguished this from an "expected good" outcome (those who experienced epilepsy but no additional disadvantage and demonstrated good quality of life).[170] The authors also describe a "vulnerable" group who were individuals who had poor quality of life despite good seizure control and socio-economic advantage, and an "expected poor" group who were those who experienced both the adversity and additional disadvantage and had poor quality of life. In other studies, the terminology for describing the "non-resilient" group varied (for example "chronic dysfunction" and "impairment") [160,162] and there was often more than one "non-resilient" category.

5.2.4 Conclusion and implications for resilience measurement in this thesis

The component parts of the resilience definition shared by most studies were: an adversity must be experienced in order to demonstrate resilience, resilience is the ability to maintain healthy levels of function over time despite adversity or to return to normal function after adversity and resilience is a dynamic concept as opposed to a fixed personality trait. I found that disease may be an adversity which leads to resilience and/ or may be a factor influencing whether resilience is observed after a different adversity.

The concept of resilience being dynamic is of importance. Resilience may be demonstrated in the face of one adversity but not another. Resilience may be found in only one "domain", for example physical wellbeing but not in another, for example mental wellbeing.

In my review, resilience was measured either using a "resilience scale" or by identifying it based upon outcomes observed in study participants. The former treats resilience as a personality trait which is contrary to the consensus over it being an adaptive process which can change over time and which is related to both internal (e.g. psychological) and external (e.g. social support) factors.[84] Assessing outcomes is therefore more consistent with the findings of the review.

Given resilience is a dynamic process and may not be present in all life domains, the measure chosen should be appropriate to the scenario. Example measures are good levels of wellbeing despite disease or the lack of hospital admissions despite disease. What is important when measuring resilience is to be explicit about the nature of the "domain" of resilience being measured. For example, "wellbeing resilience" may be present without "hospital admission resilience" but in a study concerned with identifying individuals who feel good levels of wellbeing despite disease, the wellbeing resilience measure would be the focus.

There were varying approaches taken towards categorising the individuals not defined as resilient. I chose to adapt that used by Taylor as it was a high quality study with intuitive categorisation. As I was focussing on the individuals who have experienced the adversity (multimorbidity) the non-resilient group will be those with a poor outcome and multimorbidity and will be called the "expected poor" group.

The majority of studies were cross-sectional indicating resilience may be measured by a cross-sectional approach. I found some studies had used multimorbidity measures (counts) but had not explicitly defined these as such.

In conclusion, I define resilience in the context of this thesis as the ability to demonstrate healthy levels of function or wellbeing despite multimorbidity. Those not showing a healthy response will be defined as being in an "expected poor" group. I will measure resilience in more than one domain and for the purposes of this thesis I will measure it on the basis of self-reported measures. Each of these will measure a "domain" of resilience. This approach is outlined in Table 12.

Table 12: Categorisation of resilient and expected poor groups in those with multimorbidity

Self-report category	Resilient categorisation in population with multimorbidity
Positive self-reported experience	Resilient
Negative self-reported experience	Expected poor

The study populations used in this thesis (Diamond and ACONF) were both selected on the basis that they enabled assessment of multimorbidity as well as having self-reported health measures which enable the assessment of resilience. I have selected the following measures from the study populations (Table 13):

Table 13: Summary of resilience measures and population in which they are available

Measure	Study population for which measure is available
Self-rated health	ACONF and Diamond
Self-reported activity limitation due to health	ACONF and Diamond
General Health Questionnaire	ACONF

Abbreviations: ACONF, Aberdeen Children of the 1950s

In the next section I describe these measures and the evidence supporting their use as measures of health and wellbeing. I will then describe how they will be used a measures of resilience to multimorbidity in my thesis.

5.3 Description of resilience measures in this thesis

5.3.1 Self-rated health

Self-rated health (SRH) is generally a single item indicator asking an individual to rate their own health.[172-174] In ACONF participants were asked "Over the last 12 months your health on the whole has been: poor, fair, good or excellent?". In Diamond participants were asked: "In general, would you say your health is: poor, fair, good, very good or excellent?".

Self-rated health may be measured in various ways. For example, a study by El-Gabalawy *et al* distinguished between self-rated physical health and self-rated mental health[175] whilst others use measures in which participants were asked to rate their health on scales (such as between one and five).[92,175] Commonly responses range from "excellent" through to "poor".[93,94,176-178]

The exact wording of the SRH question asked may also vary.[179] For example, some measures provide a time reference point ("how would you rate your health at the present time" or "how would you rate it over the past 12 months") and some may provide a comparative reference point ("how would you rate your health in relation to your previous health" or "how would you rate your health in relation to your same-aged peers").[173] These different SRH measures may not be directly comparable.[179]

Evidence supports SRH measures being reliable and valid measures of individual and population level health and they have been found to be powerful predictors of future morbidity and mortality.[172-174] Mavaddat *et al*, in their systematic review and meta-analysis of self-rated health measures in cardiovascular disease, found an association between SRH and fatal and non-fatal events.[174] Idler and Benyamini in their review of 27 community studies found global SRH to be an independent predictor of SRH in nearly all studies.[180]

SRH is known to be a useful predictor of future health status. Reasons why this could be are hypothesised to be:

1. Individuals are taking into account more than solely existing disease but a combination of this, their medical history, their family history and symptoms of as yet undiagnosed disease[174,180]
2. SRH reflects both internal resources (such as self-efficacy) and external resources (such as social support), both of which my allow an individual to cope better with existing disease, both in terms of self-management and healthcare usage.[85,174,180,181]

There is evidence that poor SRH and poor mental health are related but the direction of association is debated. A study by El-Gabalawy *et al* found that individuals suffering from co-occurring anxiety and a physical health condition had poorer physical or mental SRH than individuals suffering from either a physical condition or anxiety alone.[175] Molarius and Janson found a difference by age. In the middle aged, depression was the only chronic disease strongly related to poor SRH. In the elderly, the contribution of all chronic diseases was large.[94]

Nutzel *et al* found in a population of patients with multimorbidity that depressive symptoms were independently associated with lower SRH.[95] Gerber *et al* found that anxiety and depression were strongly associated with poor SRH even when adjusting for confounders including physical comorbidity.[92] In a study of Paget's disease patients by Gold *et al*, a multivariate model showed that an increasing number of comorbid conditions, alongside the presence of depression, significantly predicted poorer SRH.[93]

There is precedence for using SRH as a measure of resilience. Cairns *et al* examined area level health resilience (examining deprived areas which had better than expected health) and used a composite morbidity score which included SRH and a self-report of long-term illnesses. No detail is given as to how the SRH method was scored prior to being included in the composite measure. The authors defined the resilient areas as those who fell into the highest scoring quartile of the composite morbidity score.[182]

A further study by Cairns, examined the SRH measure as an outcome.[183] The measure was: "Over the past 12 months would you say your health has on the whole been: good, fairly good or not good?". This was converted into a binary measure (good combined with fairly

good) and the authors identified resilient areas as those with good/fairly good health despite long-standing deprivation.[183]

5.3.2 Activity limitation due to health

Both the ACONF and Diamond ask respondents: "Do you have any long-term illness/health problem/disability which limits daily activities?" However, understanding how this measure has been used in the literature was difficult due to the lack of a common nomenclature for it. Some studies call it a measure of disability whilst others call similar measures "activity limitation indicators."[184,185] For example, McDaid *et al* used the measure: "Is your daily activity limited by a long-term illness, health problem or disability?" and called this a disability measure.[185] The authors conducted a cross-sectional analysis of 6,159 adults and related the impact of multimorbidity to this outcome as well as to SRH and quality of life. The authors found that those with multimorbidity had the highest risk of disability, low SRH and poor quality of life.[185] I searched citing articles of this study but was unable to find any further research describing this measure as a "disability measure".

A more commonly used term is the "Global Activity Limitation Indicator" (GALI). This has emerged as a common measure of Healthy Life Expectancy in the European Union.[186,187] GALIs range from questions to individuals about the presence of a long-term condition or disability which limits activities (with yes/no as a response) to questions specifically asking about the effect of that condition on a range of activities (for example the ability to work or to carry out leisure activities).[184] The commonly reported GALI measurement asks individuals "For at least the past six months, to what extent have you been limited because of a health problem in activities people usually do?" The responses normally range from "not at all" to "severely limited".[186]

To further support the use of this term, I found studies which specifically distinguished between the GALI and measures of disability. For example, a study of over 27,000 individuals across 11 European countries found the GALI was associated with subjective and objective measures of disability.[187] A Spanish study found that the GALI measure was

strongly correlated with the functional disability scale (which asked questions regarding limitations in using a telephone, buying food and so on).[188]

Evidence supports the fact that GALI measures predict outcomes. A study of over 8,000 respondents to a health survey in Belgium, which compared a GALI measure to a SRH measure, found that both measures independently predicted mortality.[189] In order to assess the literature base for resilience and these measures I combined the search terms "resilience" with "Global Activity Limitation Indicator". I was unable to find any relevant studies. When I widened the search to include "self-reported disability" I did not find any relevant studies.

5.3.3 General health questionnaire

The General Health Questionnaire (GHQ) was developed as a screening tool for detecting those at risk of having or developing psychiatric disorders. The original GHQ contains 60 questions but a 12-item version (GHQ-12) is commonly used.[190,191] The questions relate to depression and anxiety symptoms and ask respondents to indicate the degree to which they had experienced these. Six of the questions are about positive mood states (e.g. being able to enjoy daily activities) with four answer options: "much less than usual", "less so than usual", "about same as usual" or "more so than usual". Six questions concern negative mood states (e.g. feeling unhappy or depressed) with four answer options: "not at all", "no more than usual", "rather more than usual" or "much more than usual".[192]

Four questions from the GHQ were included in the ACONF postal survey. Two of these questions are positively framed and two are negatively framed (Table 14). Evidence suggests the ambiguous wording of the negatively phrased items in the GHQ leads to response bias.[192] For example, those wanting to indicate the absence of a negative mood state may choose either "not at all" or "no more than usual".[192]

Studies evaluating GHQ-12 have found it is valid and reliable at detecting psychiatric disorders in patient settings and there is evidence to show it works well in general populations.[191,193] The scoring of the GHQ may take a number of forms: the ordinal Likert

method (0-1-2-3), the original GHQ dichotomous system (0-0-1-1) and a corrected GHQ system (positively phrased items are scored 0-0-1-1 and negatively phrased items are scored 0-1-1-1).[190,191,193,194]

Table 14: Resilience: General Health Questionnaire items included in ACONF postal questionnaire

General Health Questionnaire item	Options for answer	Positive or negatively phrased
1. In the past few weeks have you been able to enjoy your normal day to day activities?	1 More so than usual 2 About same as usual 3 Less so than usual 4 Much less than usual	Positive
2. In the past few weeks have you been feeling reasonably happy, all things considered?		
3. In the past few weeks have you been feeling unhappy and depressed?	1 Not at all 2 No more than usual 3 Rather more than usual 4 Much more than usual	Negative
4. In the past few weeks have you been losing confidence in yourself?		

The original GHQ dichotomous system may remove the ambiguity effect in the negatively phrased items but will be less well able to detect patients with chronic mental illness.[191,192] The corrected system was developed to allow for this latter issue.[193] Studies comparing the different scoring methods have found conflicting results in different population groups as to which method is superior.[191,193] There is no single recommended system.

There is precedence for using the GHQ as a measure of resilience. A study by Netuveli *et al* using data from a large household survey, operationalised resilience as GHQ-12 scores which increased after exposure to adversity (for example bereavement) and returned to the pre-adversity level within a year.[195] I was unable to find any studies using individual GHQ questions or measuring resilience cross-sectionally using the GHQ.

5.3.4 Categorisation of resilience measures

Following my assessment of the literature surrounding the chosen measures and my systematic review I now categorise each for use in the analysis stages. In my systematic

review I found there is no single approach to measuring resilience and so it is crucial that the approach taken is described sufficiently to enable reproducibility.

I define resilience in the context of this thesis as the ability to demonstrate healthy levels of function or wellbeing despite multimorbidity. Those not showing a healthy response will be defined as being in an "expected poor" group. Thus I categorised the measures based on this. I also ensured I labelled each measure on the basis of what "domain" of resilience it measures. For example, the SRH measures are described as representing "overall health and wellbeing" and the activity limitation question represents "activity limitation". The measures are set out in Table 15.

The Diamond and ACONF SRH measures for use in this PhD were categorised with those responding "poor" being the expected poor group and all other responses being in the resilient group. For the activity limitation due to health measure, those responding "no" were resilient and those responding "yes" were categorised as expected poor.

GHQ items may be combined into a single composite measure, however due to conflicting evidence about the scoring of the GHQ, I decided not to do this. Based upon my summary of the literature earlier, I decided to use the corrected GHQ scoring method. For the two positively phrased GHQ questions the resilient group was defined as those with multimorbidity who respond "more so than usual" or "about same as usual" to these questions. For the two negatively phrased GHQ questions, the resilient group was those who responded "not at all" to these items.

I am not measuring "activity limitation" in the Original ACONF self-reported multimorbidity population because the wording of the multimorbidity questions overlaps with the wording of the activity limitation question. For the multimorbidity measure, individuals are asked to list up to six "…long-term illnesses, health problems or disability which limit [their] daily activities or work [they] can do"). However, I do use it in the Enhanced ACONF multimorbidity population.

Table 15: Resilience measures used in the analysis in Diamond and ACONF cohorts

Cohort	Question	Those with multimorbidity		Domain measured
		Resilient group	***Expected poor***	
Diamond	In general, would you say your health is; 5 response options… (SRH)	Respond: Fair, good, very good or excellent despite multimorbidity	Respond: poor and have multimorbidity	Overall health and wellbeing
	Do you have any long-term illness/health problem/disability which limits daily activities?	Respond: No despite multimorbidity	Respond: yes and have multimorbidity	Activity limitation
ACONF 2001 populations*	Over last 12 months your health on the whole has been; 4 response options... (SRH)	Respond: Fair, good or excellent despite multimorbidity	Respond: poor and have multimorbidity	Overall health and wellbeing
	In the past few weeks have you been able to enjoy your normal day to day activities? (Positive GHQ 1)	Respond: more so or same as usual despite multimorbidity	Respond: less so or much less than usual and have multimorbidity	Ability to experience enjoyment
	In the past few weeks have you been feeling reasonably happy, all things considered? (Positive GHQ 2)			Mood state (positive)
	In the past few weeks have you been feeling unhappy and depressed? (Negative GHQ 1)	Respond: not at all despite multimorbidity	Respond: No more, rather more or much more than usual and have multimorbidity	Mood state (negative)
	In the past few weeks have you been losing confidence in yourself? (Negative GHQ 2)			Self-esteem
	Do you have any long-term illness/health problem/disability which limits daily activities?**	Respond: No despite secondary care multimorbidity	Respond: yes and have secondary care multimorbidity	Activity limitation

Abbreviations: ACONF, Aberdeen Children of the 1950s; SRH, self-rated health; GHQ, General Health Questionnaire
*Multimorbidity is measured in the Original ACONF (self-reported multimorbidity) and in the Enhanced ACONF (secondary care multimorbidity)
** Measured in secondary care multimorbidity population only

5.4 Discussion

5.4.1 Findings of the systematic review of resilience

My systematic review found consensus that an adversity must be experienced in order to demonstrate resilience, that resilience is the ability to maintain healthy levels of function over time despite adversity or to return to normal function after adversity and that

resilience is a dynamic concept as opposed to a fixed personality trait. Resilience may be measured using a "resilience scale" or by identifying it based upon outcomes observed in study participants. Given the dynamic nature of resilience, my findings suggest researchers should use outcome measures and be clear as to which domain of resilience is being measured.

The findings of the systematic review are in agreement with Windle's definition (as outlined in Chapter 1) and also with others including those in the developmental, the psychobiology and the neurobiology literature.[84,196-198] This provides support for the fact that the definition of resilience in the context of physical disease is no different from when it is used in other contexts.

I found three studies which analysed disease as a count but none described it as a multimorbidity measure. This highlights the issue of the lack of consensus on the definition of multimorbidity as well as the need to conduct research into multimorbidity and resilience.

It is noteworthy that many studies of physical disease refer to resilience in terms of returning to or maintaining normal function.[162,166,167,171] This shows a resilient outcome need not be an exceptional outcome, particularly if function prior to the adverse event was not at a high level. Indeed, for those whose baseline functioning was low prior to the adverse event, the measurement of good function post-event may evidence thriving not resilience. Thriving is commonly defined as not solely returning to a normal level of function (as for resilience) but achieving a higher level of functioning.[87,199] The concept of thriving is therefore different and its place in the resilience spectrum should be considered further and clarified.

I established that physical disease may be considered as an adversity after which an individual may or may not demonstrate a resilient outcome. My work also found that physical disease may act as a variable which promotes or reduces resilience following an adverse event. The promotion of resilience may be an example of a "steeling effect", whereby a negative experience strengthens resilience to another stress.[196] In addition to

this, there was a large degree of variability between studies. The nature of the adversity experienced, the characteristics of the disease, the timing and the nature of the measurement of resilience as well as the individual's socio-contextual and personality risk and protective factors are all likely to affect the resilient outcome.[85,196,200]

The characteristics of the resilience measurement scales were not well described by studies but all included a range of psychometric properties. A recent methodological review of resilience measurement scales concluded many were lacking conceptual adequacy by focussing on psychometric properties and failing to examine resilience across multiple levels.[201] The review included scales used by studies in this review, including the Wagnild and Young Resilience Scale,[167,168] and the Connor Davidson resilience scale.[160,163,166,169]

It is therefore important to measure resilience as a dynamic process. This can be achieved by using measures of experience or outcome. Three of the studies in my review which examined resilience measures used composite health indicators such as the short-form 12 questionnaire[161,162,166] and three did not.[160,163,170] Composite measures may capture a wider spectrum of the resilience experience. Self-reported measures, even if not composite, are also likely to capture a wide spectrum of resilience. These are viewed as being reliable and valid measures of individual and population level health and have been found to be powerful predictors of future morbidity and mortality.[172,173] In my thesis I am using more than one measure of resilience in order to encompass more than one life-course domain.

5.4.2 Strengths and limitations of the systematic review of resilience

There are few systematic reviews in the resilience literature and no previous reviews had summarised the literature surrounding the definition and measurement of resilience in studies of physical disease and resilient outcomes. My review therefore addressed an important research gap regarding how resilience is defined and measured in the context of disease.

In the literature, the term “resilience” has been used inter-changeably with psychological terms such as hardiness, mastery and thriving.[84,85,87] However, as described previously, there is debate as to whether these terms represent component parts of resilience rather than being synonymous with resilience.[84] I therefore did not include these concepts as search terms.

Given the heterogeneity of resilience definitions and measures in the context of disease, this review had to have strict inclusion and exclusion criteria. This included focussing on physical conditions. This was not to downplay the role of mental health conditions in resilience. Rather it allowed a more focussed search enabling the conclusions made by this review. A definition and measure of resilience in the context of disease should be expected to apply to all health conditions including mental health conditions.

The sample size restriction was applied for pragmatic reasons as my early work demonstrated that studies of physical disease and resilient outcomes often involved complex analyses with multiple variables. Therefore analyses of populations under 100 participants were often under-powered. This was further validated by the classification of the two studies with the smallest sample sizes in this review as being “low quality”. The limitation to adults only is reasonable given that the burden of disease is known to increase with age.[2]

Despite these restrictions there were still large differences across studies with regards to study design and quality. As a result, the reviewers encountered challenges in these areas with reaching agreement. Of particular note, the inclusion of the study by Glymour was subject to some debate due to its focus upon “cognitive resilience” which is generally treated as a component part of cognitive reserve and thus could be seen as a more specialised form of resilience than this review aimed to cover.[163]

5.4.3 Measures of resilience in this thesis

I have described the measures of resilience I am using in my thesis and the way in which I will categorise these. All measures are self-reported and will be assessed cross-sectionally. There is precedence for both these factors as shown in my systematic review.

A complexity of reviewing the literature regarding the activity limitation indicator in this thesis was the lack of a consensus nomenclature for the measure. I decided to call it an activity limitation indicator as this is more specific than calling it a measure of "disability". Only four of the GHQ items were included in the ACONF. However, this was based on the fact that previous research had found that including four items from the GHQ was sufficient to rank individuals according to mental distress.[194]

I found evidence of use of the SRH and GHQ in studies of resilience however I was unable to find any studies using activity limitation indicators. The WHO describe resilience (in the context of ageing) as being the existence of higher levels of functioning despite poorer levels of physical or mental health.[52] In this context I can justify using the activity limitation measure in a population with multimorbidity.

5.4.4 Strengths and limitations of my approach in this chapter

A strength of my approach is that I undertook a systematic review of the literature in order to improve the consensus over the definition and measurement of resilience to disease. This provides a robust under-pinning to my subsequent methods. Using a single measure of resilience is not advised given that my review highlights that resilience is a dynamic process (not a personality trait) and may be apparent in some "domains" and not in others. A strength of my work is therefore that I am using more than one indicator to measure resilience.

It may seem that the choice of resilience measurement indicators is arbitrary. However, my review confirms that there is no single "resilience measurement" tool which is recommended. Therefore, as I have adopted the approach of describing resilience as being healthy levels of function or wellbeing despite adversity, my approach is valid. What is also

key is that the adversity is defined and the “domain” of resilience being measured is defined as I have done.

As my approach is novel and the literature base regarding using these measures in resilience to disease research is small, I used my own judgement to select the “cut-offs” in the resilience measure responses as to which equal resilience. I have been explicit over my approach which allows reproducibility by others and is key when working with novel measures and attempting to develop consensus.

Part three: studying the prevalence, determinants and outcomes of multimorbidity and resilience to multimorbidity

6 Methodology for objectives two to four

Please see "additional declaration" on page *xvi* for information regarding section 6.2.2.

6.1 Background and structure of chapter

This chapter describes the study design and methodology for the analysis conducted in this thesis. This refers to objectives two, three and four. The study populations are the Diamond and ACONF. A detailed description of the study populations follows next, followed by an overview of the methodological and statistical approaches.

6.2 The Cohorts

6.2.1 Diamond study population

The Diamond screening sample consists of 7,667 individuals aged between 18 and 75 selected from General Practices in Victoria, Australia during 2005 (Figure 3).[202,203] The screening sample was created as part of the Diamond longitudinal study (which is limited to those with depression symptoms in general practice).[202] I am using the screening sample in this thesis.

Victoria is a state located in the South-east of Australia. It is the most densely populated state in Australia with the majority of the population situated in, or near, the city of Melbourne. In 2005, the population of Victoria stood at just over 5 million.[204] Around 70% of Victorians were born in Australia, with people born in the United Kingdom, New Zealand, Italy, China and Vietnam making up the majority of those not born in Australia.[205]

Healthcare in Australia is delivered via a combination of public and private mechanisms. Public sector services in Victoria are managed by the Victorian government. Private sector services are provided by a range of private providers.[206] Medicare is the universal public health insurance scheme in Australia. It is partly funded by taxpayers who pay a levy on their taxable income. The level paid is dependent on income with some not needing to pay.[207] Medicare gives individuals access to free or subsidised public healthcare. Individuals can also choose to take private health insurance to access private services including general practice, often which have less waiting times for service.[206]

In 2004/05 there were 5,537 practicing GPs in Victoria.[208] There is no information available on the total number of practices at the time, but the study team estimate it this to be at least 1,000.

Construction of the sample population

The Diamond study was developed by a multi-disciplinary team based at the Primary Care Research Unit at the University of Melbourne. It was funded by the National Health and Medical Research Council and the Victorian Centre for Excellence in Depression and Related Disorders.[202]

Participant selection was through General Practice. The sample size estimation for the Diamond longitudinal study (calculated based upon the number of individuals with depression symptoms required to answer key hypotheses and an estimate that there would be 30% attrition over 12 months) was 900. A pilot study was conducted by the study team in two practices in order to inform the required number of patients to be invited to participate in the study. This showed a 50% survey return rate with 10% of respondents having depression symptoms. Therefore it was estimated that around 18,000 patients would need to be invited.[202]

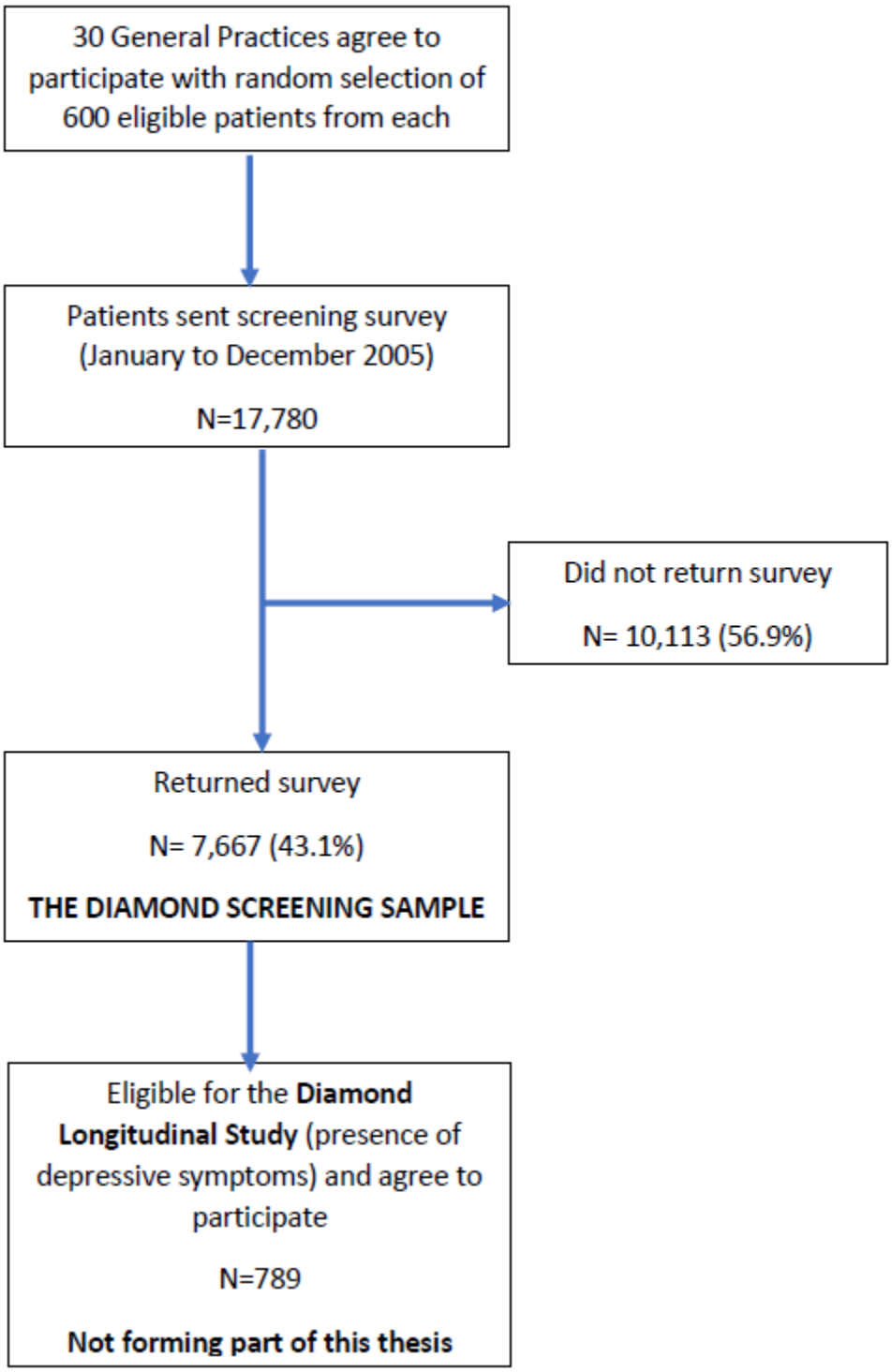


Figure 3: Methodology: Flow diagram of structure of Diamond cohort

The urban-rural distribution of General Practices in Victoria was used as the basis of selecting practices in order to recruit a population representative of the urban-rural distribution of the wider population. The Australian rural, remote and metropolitan areas (RRMA) classification describes the urban rural nature of the Australian population and ranges from the most metropolitan to most rural.[209] The distribution of the population at the time of the survey is shown in Table 16 (source: email correspondence with Diamond study team, June 2017) and shows that the majority of the population live in an urban area.

Table 16: Methodology: Diamond: Remote rural and metropolitan areas (RRMA) classification of Australian population

Remote, rural and metropolitan areas (RRMA) classification	Proportion of Australian population in 2003/04 (%)
1 – Capital cities and metropolitan areas	64
2- Other metropolitan and urban centre population > 100,000	8
3- Large urban area, urban centre population 25,000 to 99,999	6
4- Small rural area, urban centre population 10,000 to 24,999	7
5- Other rural area, urban centre population less than 10,000	13
6 and 7- Very remote areas	Not included in the study due to extreme remoteness

The Australian Health Insurance Commission provided a randomly selected sample of 200 General Practitioners (GPs) from 30 General Practices stratified on the basis of remote and rural geography. GP eligibility criteria were:

- Had seen at least 600 patients aged between 18 and 75 in the previous year
- Were able to provide an electronic list of patient details
- No other GP in the practice was already in the study[202]

GPs were recruited until 30 agreed to participate. Each of the 30 practices received $350AUD whilst each GP received $50AUD. Practice staff, with the support of a research assistant, searched GP electronic records to randomly select 600 eligible patients from each practice. Patient inclusion criteria were:

- Aged between 18-75 years
- Had seen the study GP in the previous year
- Could read English
- Were not terminally ill
- Did not reside in a nursing home[176]

A screening survey was prepared to collect a wide variety of demographic, socio-economic and clinical factors. The scales used to collect information were selected by the study team on the basis of their suitability for use in postal surveys.[210] For example, self-rated health (SRH) was measured using the general health question of the Short-Form 12 Health Questionnaire. In addition, a list of 12 physical conditions were selected on the basis of being commonly seen in Australian General Practice and having been identified as National health priority areas.[211,212] The two commonest mental health conditions seen in General Practice (depression and anxiety) were also selected.[211,212]

During the year 2005, selected patients were sent information about the study as well as the screening survey, a resource card containing information of mental health and related services, and a pre-paid reply envelope. There was one reminder sent at two weeks. For security, the identifiable details of patients were not held by researchers, who instead held a de-identified record of age and gender. The overall survey response rate was 43%. The details of non-response characteristics are in Chapter 7.

Details of key Diamond variables

The variables included:

- Age at completion of survey
- Gender
- Educational attainment
- Employment status
- Alcohol consumption
- Smoking status

- Presence of any long-term illness/health problem/ disability which limits daily activities
- Presence of physical conditions or mental health conditions
- Self-rated health

All Diamond variables were categorised in the same way as the original study team had done. The exceptions were the multimorbidity and resilience variables which I derived for analysis in the thesis (these are described below and in Chapters 3 and 5).

Educational attainment

Compulsory education in Australia commences at the age of five in primary school and children attend secondary school from age 12 ("year 7"). Secondary school runs to year 10 with "senior secondary school" including two additional years. Following secondary school, individuals can study for additional certificates or diplomas, or they can go on to study for a bachelor degree or higher.[213] The educational attainment categories in the Diamond cohort, from highest to lowest were:

- Bachelor Degree or higher
- Certificate / Diploma
- Completed year 12
- Completed year 10
- Left school before year 10

Employment status

Individuals were asked to indicate their employment status from the following list of options:

- Employed
- Unemployed
- Unable to work
- Home duties/unpaid work/maternity leave
- Student only

Alcohol consumption

Alcohol consumption was measured using the validated "FAST" screening tool.[214] Participants were asked four questions on the frequency of heavy drinking, amnesia due to alcohol, inability to do daily activities and whether friends or healthcare workers are concerned about their drinking. Each of these are scored (from 0 to 4) and those with a score of three are more are deemed to be drinking at hazardous levels. Consistent with previous Diamond research, I have used the presence of hazardous alcohol consumption as a marker of alcohol consumption. Alcohol is a significant determinant of morbidity and mortality.[215]

Smoking status

Tobacco smoking was based upon self-reported number of cigarettes smoked. The responses were categorised as: never smoked, ex-smoker, occasional smoker and regular smoker. Tobacco smoking is a significant determinant of ill health and premature death.[216]

Morbidity

Morbidity was captured in two ways. Firstly, respondents were asked: "Do you have any long-term illness/health problem/disability which limits daily activities?". Response options were "yes" or "no". For the purposes of this thesis, this question was classed as "activity limitation" resilience.

Respondents were also asked to tick any of the following listed 12 chronic physical conditions that they had experienced in the past 12 months:

- Stroke
- Emphysema
- Cancer
- Heart Disease
- Diabetes
- Chronic Sinusitis
- Dermatitis
- Asthma
- Lipid Disorder
- Hypertension
- Arthritis
- Back Problems

They were also asked to self-report on two common mental health conditions: depression and anxiety.

Primary care multimorbidity

I derived the primary care multimorbidity variable from the morbidity information above (the 12 physical conditions and the two mental health conditions). Multimorbidity was the presence of two or more health conditions, consistent with the definition pre-set for this thesis. In addition to this standard measure of multimorbidity I will use a measure consisting of only physical conditions (physical condition multimorbidity) to demonstrate the impact of mental health conditions.

Self-rated health

The second measure of resilience in the Diamond cohort uses the self-rated health (SRH) measure. The participants rated their health by answering: "In general would you say your health is: Excellent, Very good, Good, Fair or Poor?".

6.2.2 ACONF Study population

The ACONF cohort is a longitudinal cohort based in the city of Aberdeen in the North-East of Scotland, with ongoing follow-up from the 1950s. In 2016, Aberdeen had an estimated population of just under 230,000 people and had the fourth densest population by council area in Scotland.[217] Aberdeen was traditionally a city whose economy relied on farming and fishing.[218] In 1969, North Sea oil fields were discovered leading to an economic boom and

prosperity for many (but not all) residents.[218] The impact of this upon my findings is discussed in more detail in Chapter 8.

Aberdeen in the 1950s would have been predominantly made up of "white Scottish" or "white British" individuals. Even though the city itself became more ethnically diverse over time, particularly due to the impact of the oil and gas industry, the population of Aberdeen is still relatively homogenous. In 2001, the census shows that 96% of the Grampian area were white Scottish or white British.[219]

Construction of the sample population

Entire ACONF

The ACONF is a large subset of another study, the Aberdeen Child Development study (ACDS).[218] The ACDS consisted of 15,000 children born in 1950-56 who were in primary school in Aberdeen in December 1962. The children were administered a number of tests in 1962 and 1964 (including a survey of demographic information). The study also made use of information routinely collected on school children at the time and retrospectively collected data on school cognition tests which were undertaken at ages 7, 9 and 11 years.[218,220,221]

In 1999, work was commenced to revitalise the ACDS and this follow-up was called the Aberdeen Children of the 1950s study. The study team were a collaborative group of researchers from the London School of Hygiene and Tropical Medicine and the Universities of Aberdeen, Glasgow and Bristol. The team was led by David Leon and funded by the UK Medical Research Council.[220]

The ACONF consists of individuals from the ACDS who were born in Aberdeen and so could be linked to obstetric records from the Aberdeen Maternity and Neonatal databank (AMND). This amounted to 12,150 individuals. The AMND is a unique database of all obstetric events occurring in Aberdeen City from 1950 onwards.[222] This gave information on the participant's birth characteristics and the occupation of the father at the time of birth.[218]

Work was carried out to trace the core population and started with extracting names and dates of birth from the original 1962 ACDS manual and sending this information to the General Registry Office for Scotland (GROS). GROS used the NHS Central Register to ascertain residence area and vital status of individuals in the UK.[218]

Original ACONF

The tracing of ACONF, conducted during 1999 to 2001, identified 11,282 individuals as alive and resident in the UK (excluding those in the armed forces or an institution or resident in the Western Isles of Scotland or in Northern Ireland). This amounted to 93% of the 12,150 members of ACONF. In 2001 these individuals were sent a postal questionnaire. The questionnaire assessed factors such as self-reported health, wellbeing, function, occupation, education and income.[220] Questionnaires to Scottish based residents were sent by the Information Services Division (ISD) Scotland. Local Health Authorities sent questionnaires to those resident in England and Wales.[218]

The responders to this questionnaire form the population I have called the "Original ACONF" in my thesis and I study self-reported multimorbidity using the questionnaire data. A summary of the process is in Figure 4.

The questionnaire was designed by the study team using a process of team discussion combined with individual experience with other cohorts and the use of previously validated questions if possible (source: ACONF study coordinator). The questionnaire was piloted on colleagues and then on a sample of 45. Participants were not sent incentives to complete the questionnaire. One reminder was sent. The basic questionnaire amounted to 21 pages (A4). This questionnaire was completed by men. Women were given a questionnaire which contained an extra two and a half pages specific to women's health (for example menstrual history). The majority of questions were close ended (for example smoking status). A further number were open (for example listing health conditions).

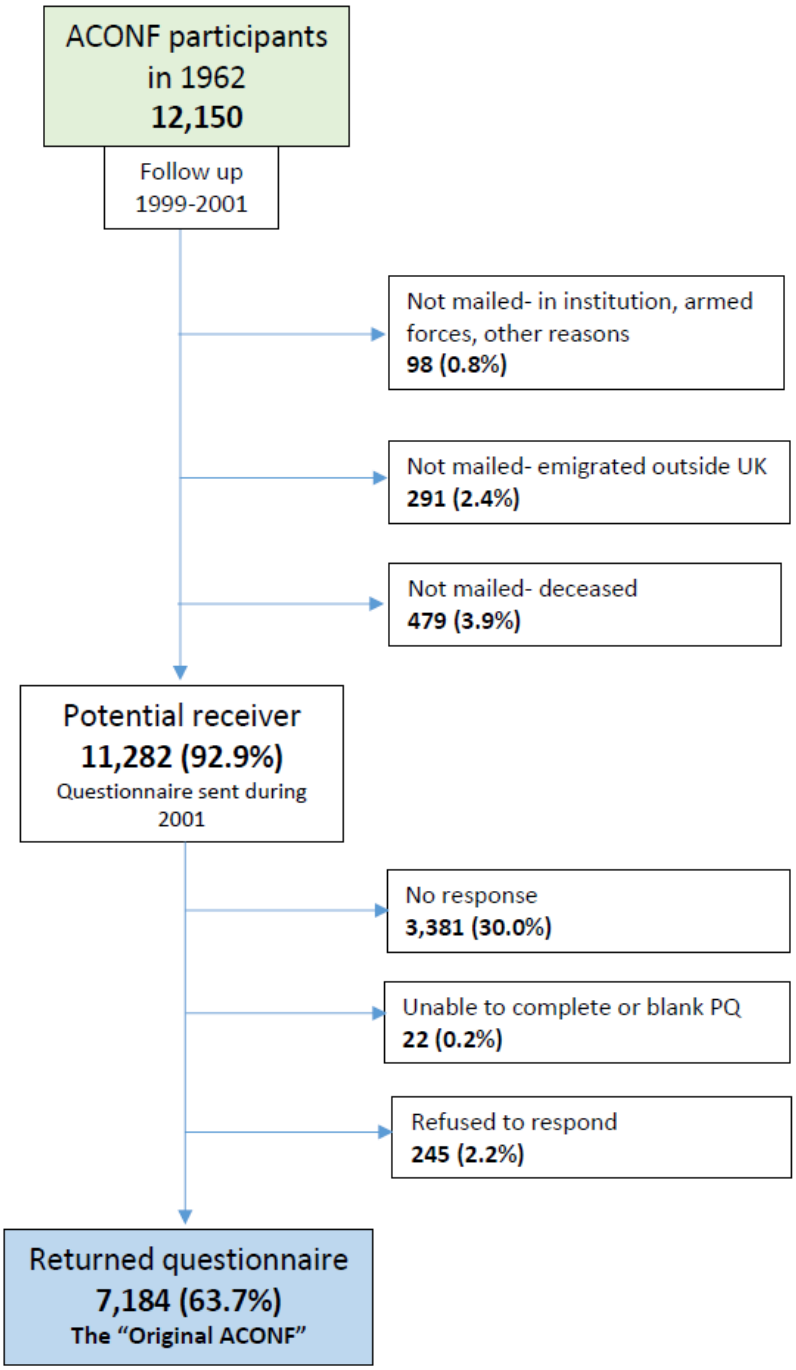


Figure 4: Methodology: Profile of ACONF from 1962 through to postal questionnaire
Abbreviations: ACONF, Aberdeen Children of the 1950s; PQ, postal questionnaire

Data extraction from the questionnaire was carried out by an external data entry company using double data extraction. The data were returned to the study team and were stored on the University of Aberdeen server. All data entries were checked for inconsistences against the questionnaires by the study team. Where required, the team re-contacted the respondent to check they had provided the correct information and if they replied this would be corrected.

Enhanced ACONF

I gained permission to link the ACONF to Scottish secondary care administrative data and mortality data (described in the "permissions" section later). I have described administrative data collection and the Scottish linking process in Chapter 4. This linked population are termed the "Enhanced ACONF" in my thesis.

ISD CHI seeded the ACONF participants resulting in 89% matched to their unique identifier. Following this, ACONF participants were linked to their SMR01 (non-obstetric and non-psychiatric inpatients and day cases), SMR04 (psychiatric inpatients), SMR06 (the cancer registry) and mortality records. The linkage date was from 1981 to 30th September 2016.

I measured Barnett secondary care multimorbidity in the Enhanced ACONF in 2001, so as to be comparable with the date of the questionnaire, and in 2016, the latest date of follow-up available. I set the index date (the date at which the look-back period for the measurement of multimorbidity was set) as 30th September in the study year.

Status of ACONF

I distinguish between the "Original" and "Enhanced" ACONF populations in the thesis on the basis of the measurement of multimorbidity- whereby multimorbidity is measured from the postal questionnaire in the former and from additional linkage to administrative data in the latter. I have named them separately to aid interpretation, however the Original ACONF do also have linked administrative data for the assessment of outcomes.

The status of the ACONF at any particular time period is important because it gives information on which individuals have left Scotland or died outside Scotland. Only those with an admission or death in Scotland may be linked to administrative data. Therefore individuals without Scottish admissions or deaths may in fact no longer be resident in Scotland rather than having not experienced the event.

The status of the ACONF for the questionnaire was ascertained over the period of January 1999 to May 2001, as outlined in Figure 4.

In addition to the questionnaire status I was given a further updated status as of 1st October 2013. There were no other full status checks conducted. The status of the populations for the Enhanced ACONF analysis was therefore developed as follows. For the September 2001 population I used the postal questionnaire status figures as a baseline and incorporated all Scottish recorded deaths to 30th September 2001. For the September 2016 population I used the October 2013 status as a baseline and incorporated all Scottish recorded deaths from 2nd October 2013 to 30th September 2016. I also took into account Scottish hospital admissions between 2nd October 2013 and 30th September 2016. If an individual coded as being outside Scotland in the October 2013 status had an admission I made the assumption they were once again a Scottish resident.

The status of participants as of September 2001 is shown in Table 17. Of the 12,150 baseline cohort members, 9,547 (79%) were alive and resident in Scotland in September 2001. Of these, 8,438 (88%) were successfully CHI seeded. Just over 6% of the population were known to have died, 11% were elsewhere in the UK and 5% had embarked or had a status unknown. The proportions were comparable between men and women.

The status of the population on 1st September 2016 is shown in Table 18. There were 8,411 participants alive and resident in Scotland at 30th September 2016 (70% of 12,150 baseline cohort members) and 17% were known to have died, 9% were elsewhere in the UK and 5% had a status unknown. Of 8,411 individuals registered with a Health Board in Scotland in 2016, 7,353 (87%) had been successfully CHI seeded.

Table 17: Enhanced ACONF 2001: status of participants in September 2001 (n=12,150)

Status of cohort September 2001	All (n=12,150)		Male (n= 6,276)		Female (n=5,874)	
	Number	%	Number	%	Number	%
Registered with Health Board in Scotland	9,547	78.6	4,899	78.1	4,648	79.1
CHI seeded	*8,438*	*88.3**	*4,303*	*87.8**	*4,135*	*89.0**
Elsewhere in UK	1,305	10.7	697	11.1	608	10.4
Died	755	6.2	440	7.0	315	5.4
Unknown or embarked	543	4.5	240	3.8	303	5.2

Abbreviations: CHI, Community Health Index; ACONF, Aberdeen Children of the 1950s
*Proportion of total registered with Health Board in Scotland

Table 18: Enhanced ACONF 2016: status of participants in September 2016 (n=12,150 at baseline)

Status of cohort in September 2016	All (n=12,150)		Male (n= 6,276)		Female (n=5,874)	
	Number	%	Number	Number	%	Number
Registered with Health Board in Scotland	8,411	69.2	4,262	67.9	4,149	70.6
CHI seeded	*7,353*	*87.4**	*3,700*	*86.8**	*3,653*	*88.1**
Elsewhere in UK	1,137	9.4	607	9.7	530	9.0
Died	2,053	16.9	1,156	17.2	897	15.3
Unknown or embarked	549	4.5	251	4.0	298	5.1

Abbreviations: CHI, Community Health Index; ACONF, Aberdeen Children of the 1950s
*Proportion of total registered with Health Board in Scotland

A summary of the timeline, the status of the participants and the data available is in Figure 5. For the Enhanced ACONF 2001 population there were 10,852 individuals known to be alive (in the UK) and in the Enhanced ACONF 2016 population there were 9,548 individuals known to be alive. The ACONF is frequently described as a birth cohort as it was derived based upon all individuals with birth records from the original 1962 ACDS study.

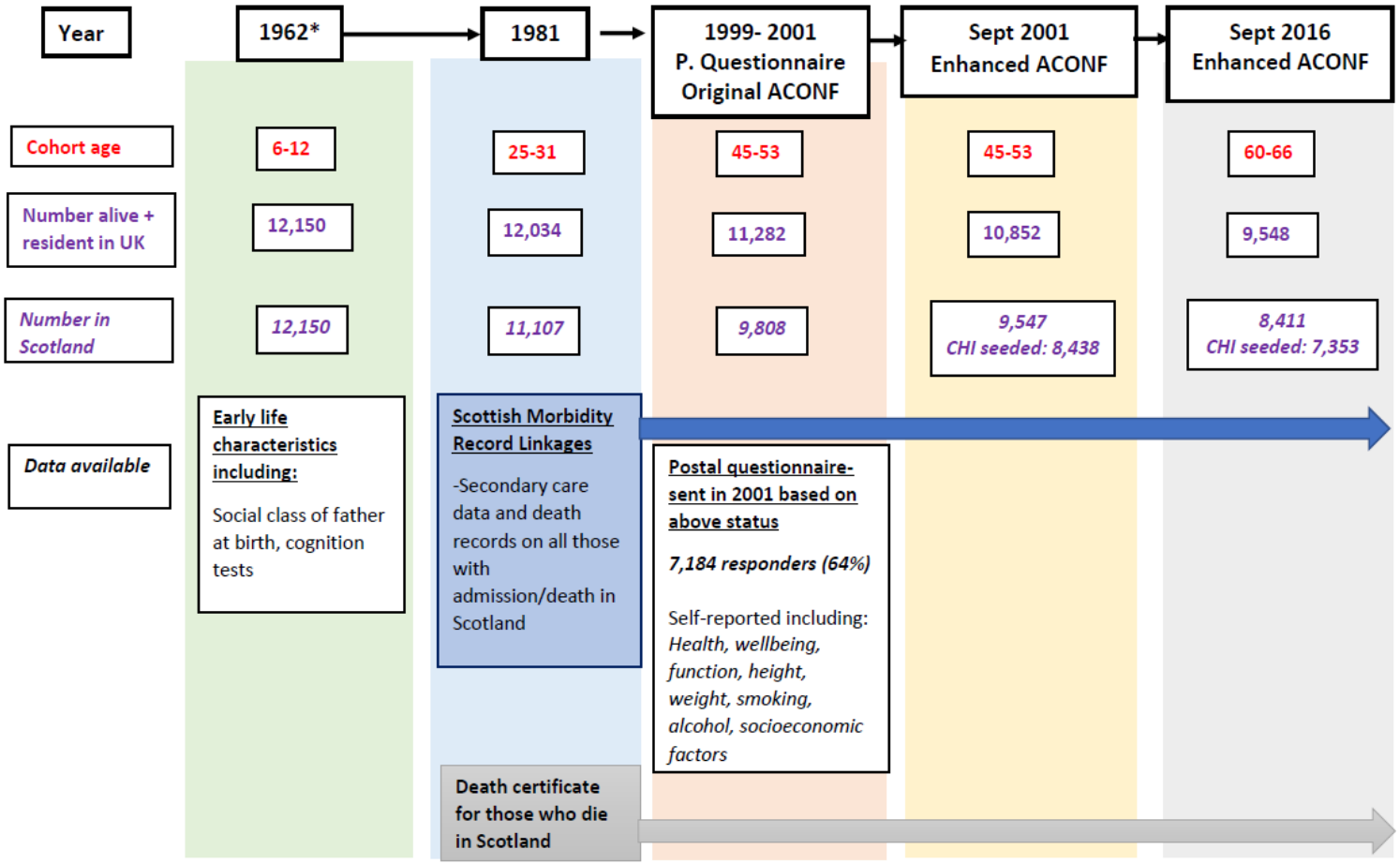


Figure 5: Methodology: Summary of data collection in ACONF cohort, 1962- 2016.
Abbreviations: ACONF, Aberdeen Children of the 1950s; P, postal; CHI, Community Health Index. *Contemporaneous birth record data available from between 1950 to 1956

Details of key ACONF variables

The variables which are used throughout the ACONF analysis in this PhD are described in detail here. Data were sourced from the AMND, school records, the postal questionnaire and Scottish administrative data. This is summarised in Table 19.

Table 19: Methodology: List of study variables in the ACONF study population

Source	Variable
Aberdeen Maternity and Neonatal databank	Date of birth (for age)
	Father's occupation at the birth of participant (for social class at birth)
School records	Cognition score at age 7
Postal questionnaire	Secondary school type
	Educational attainment
	Self-reported health conditions (for multimorbidity measure)
	Adult social class, employment and income
	Adult alcohol consumption, smoking, height and weight
	Self-rated health, activity limitation and General Health Questionnaire (for resilience measure)
ISD hospital administrative data (Scotland)	SMR01: general and acute hospital inpatients and day cases
	SMR04: psychiatric inpatient stays
	SMR06: Scottish cancer registry
ISD and National Records of Scotland	Scottish death registrations

Abbreviations: ISD, Information Services Division; SMR, Scottish Morbidity Record; ACONF, Aberdeen Children of the 1950s

Social class at birth

Social class of the participant at birth was based upon the father's occupation at birth of the participant and is coded using the General Register Office's Occupational classification (1950).[223] In the thesis I will used the phrase "social class at birth" to refer to this variable.

Social class categories and examples of included occupations are summarised in Table 20. These categories range from I (professional) to V (unskilled). Groups I and II (managerial) are combined in this PhD as per previous analysis in the ACONF. There is an additional category for those whose fathers were unemployed, unknown, disabled or dead at the time of the participant's birth. In my thesis I will refer to categories in terms of being "high" and

"low", with I/II being the "highest" social class. This is to aid interpretation but is not aimed to attach a value judgement on any one category being superior to another.

Table 20: Methodology: Social class at birth categories and examples of included occupations in ACONF

Occupational social class of participant's father at birth*	Example occupations (sourced from ACONF website)
I/ II (Professional/ Managerial)	Professional, Managerial (admin/ finance), nurses, vets, teachers
III non-manual (Skilled non-manual)	Postman, shop assistant, policeman
III manual (Skilled manual)	Woodworkers, builders, painters, plumbers
IV (Partly skilled)	Fishermen, farmworkers, bus and train conductors
V (Unskilled)	Dock labourers, unskilled fish workers
Unemployed/ unknown/disabled/dead	N/A

*For the small number of those with missing data (n<5) the father's occupation was imputed using data from 1962 when the child was aged 6 to 12. Abbreviations: ACONF, Aberdeen Children of the 1950s; N/A, not applicable

Childhood cognition at age 7

Routine cognition tests were carried out at ages 7, 9 and 11 in the 1950s in Aberdeen (within six months of the child's birthday). The scores at all three ages were strongly correlated.[224] I use the age 7 test based upon the degree of missing data for children in special needs schools. Only 14 children from special needs schools had age 9 tests and only 16 had age 11 tests, however the majority of children from these schools (143 out of 178) had age 7 tests.[225] The use of age 9 or age 11 tests would under-estimate the contribution of children with special needs and arguably reduce the generalisability of the findings. This approach towards using the age 7 test was also taken by previous ACONF research for the same reason.[225]

The age 7 test used the Moray House Picture Intelligence Tests (numbers 1 or 2) to screen for learning disability.[218,226,227] These were picture tests and involved a number of questions, for example choosing which one out of a series of pictures was out of place, or choosing which picture was analogous to a reference picture.[225] The test was age-standardised for Scotland as a whole (mean of 100, standard deviation of 15).[221,225]

Secondary school type

Selective schooling for secondary education was in place in Aberdeen in the 1950s and 1960s. Using terminology from previous ACONF research I defined these as "elite schools" for those deemed to be more academically able and "non-elite schools" for those defined as less academically able.[227] The type of school attended was based upon school test results, teacher assessment of ability and head-teacher view on "suitability" for an elite school. After the allocation procedure, parents could appeal and it was also possible to attend an elite private school if paid for.[227]

During the time the cohort attended school, the minimum school leaving age was 15. Students could stay at non-elite schools for up to four years and gain "ordinary level" qualifications and pursue vocational-type courses. Those students who wished to pursue more courses (including Higher grade exams) would need to transfer to an elite school.[227] Clark and Del Bono in a study of school type in ACONF found that "few" students did this (exact number not supplied).[227]

In the ACONF the "elite" schools consisted of three non-private and three private schools, "non-elite" contained 12 non-private schools. There were also two special needs schools and a convent which I combined with the "non-elite" schools in analysis.

Educational attainment

Educational attainment is from the postal questionnaire. Participants were asked regarding qualifications ranging from "degree level" through to "no formal qualifications" (nine questions in total).[226] To develop category names for this thesis, information was drawn from two previous ACONF publications.[226,227] Categories were updated by myself as shown in Table 21 in order to combine categories which could be argued to capture a similar level of educational attainment. For example, question 8 (school leaving certificate) and question 9 (no formal qualification) are likely to represent the same achievement due to the fact that it was a statutory requirement to attend secondary school until age 15 (and all these individuals should have received a school leaving certificate).

Table 21: Methodology: ACONF: derivation of educational attainment categories

Response options to: "Which of the following qualifications do you have?"	Category name (Lawlor[226])	Summary of meaning of category (Clark and Del Bono[227])	Updated category	Rationale
1. Degree or degree level qualification (including a higher degree)	Degree level qualification	Degree level tertiary education	Degree level tertiary education	Not required (clear from question)
2. Teaching qualification HNC/HND, BEC/TEC higher, BTEC (higher) City and Guilds Full Technological Certificate	Higher national certificate	Non-degree higher level tertiary education	Non-degree tertiary education	This question includes a number of tertiary level qualifications
3. Certificate of Sixth Year Studies, Highers A-levels, City and Guilds Advanced / Final level	Advanced-level qualifications	Higher grade school level qualifications/ non-degree lower level tertiary education qualifications	Advanced-level qualifications	Differentiate from Ordinary Level because needed to be in elite school to get these
4. 'O' Grade passes 'O' Level passes CSE grade 1 School certificate or matric City and Guild Craft/Ordinary level	Ordinary-level qualifications	Ordinary grade school level qualifications with high grade pass/ lower level tertiary education qualifications (non-advanced)	Ordinary-level qualifications	Represents qualifications can get within first four years of secondary education (all that non-elite schools can offer) The "other qualifications" is included here because it suggests a qualification but can assume not at higher level- as would otherwise be picked up in the above
5. CSE grades 2-5 Clerical /commercial qualifications	Certificate of secondary education	Ordinary grade school level qualifications with middle grade pass		
6. CSE ungraded		Ordinary grade school level qualifications-ungraded		
7. Other qualifications (where qualification or grade not defined)	Other/school leaving certificate	Unclear exactly what participants would have interpreted this as. But does suggest qualification of sort		
8. School leaving certificate		Statutory requirement to attend secondary school to age 15	School leaving certificate/no qualification	Presume they attended secondary school but did not complete any exams
9. No formal qualifications	No qualification	Statutory requirement to attend secondary school to age 15		Due to statutory requirement to attend secondary school to age 15, must presume similar to above category

Abbreviations: HNC, Higher National Certificate; HND, Higher National Diploma; BEC, Business Education Council; TEC, Technician Education Council; BTEC, Business and Technology Education Council; CSE, Certificate of secondary education; 'O', Ordinary; ACONF, Aberdeen Children of the 1950s

Self-reported morbidity

Morbidity was asked about in two ways. Firstly, respondents were asked: "Do you have any long-term illness/health problem/disability which limits daily activities?". Response options were "yes" or "no". As for the Diamond cohort, this will be the "activity limitation"

resilience measure. Individuals were also asked to list up to six "…long-term illnesses, health problems or disability which limit [their] daily activities or work [they] can do".

The original study team created 42 mutually exclusive condition categories (for example "cancer", "diabetes" and "stroke") and coded questionnaire responses on that basis. This is the data made available by the ACONF steering group for researchers and I did not have access to the original responses. The categories of conditions therefore give only an illustration of the range of conditions which were reported. For the purposes of my work this is not a concern as my multimorbidity measure is based on the number of self-reported conditions, no matter the nature of the condition. A small number (n<10) of individuals were coded as having a "complaint no longer present". I removed this from the list of morbidities. Some categories were very narrow (for example four different categories relating to ear complaints) and I combined these. The categorisation of the conditions are presented in Table 22.

Table 22: Methodology: ACONF: categorisation of self-reported conditions

Category name	Category name
Cancer	Other respiratory complaints
Diabetes	Digestive system ulcer/hernia
Endocrine /Metabolic	Upper intestine complaints
Mental Illness	Complaints of bowel/colon
Mental Handicap	Piles/Haemorrhoids
Epilepsy/fits	Kidney complaints
Migraines/headaches	Bladder problems
Other problems - nervous system	Reproductive disorders
Eye complaints	Arthritis/ rheumatism/ fibrositis
Ear complaints	Back problems
Stroke	Problems of bone/joint/muscles
Heart attack/angina	Infection/parasitic disease
Hypertension	Blood disorders and associated
Other heart problems	Skin complaints
Varicose veins	Unclassifiable or non-specified condition (individual states has a condition but does not name it)
Other blood vessels/embolic	
Bronchitis/emphysema	
Asthma	
Hayfever	

Abbreviations: ACONF, Aberdeen Children of the 1950s

In the original data, if an individual did not answer these morbidity questions this was coded as "missing". Whilst a proportion of those who did not respond may have done so by accident or for other reasons, it could also indicate that no condition was present. To account for this, the responses to the question were compared with the responses to: "do you have any long-term illness, health problem or disability which limits your daily activities or work you can do?". A small number (less than 40 individuals) responded yes to having a condition, but did not provide the name of the condition subsequently. These individuals were categorised as having a "missing condition" and this counted towards the self-reported multimorbidity measure. After this step, any remaining missing data were assumed to represent the lack of a condition.

Self-reported multimorbidity

Self-reported multimorbidity was defined as the presence of two or more self-reported health conditions by an individual using the morbidity data above.

Adult social class

The Registrar General's Social classes (as used for social class at birth in this thesis) became the Standard Occupational Classification in 1990 (SOC90). This was based upon methodology developed by the former Office of Population Censuses and Surveys (OPCS).[228] The adult social class categories from the postal questionnaire were formed using SOC90. Other than for the final category (father being unemployed, unknown, disabled or dead) which is not present, the category names are the same as for the social class at birth variable (Table 20).

It is important to note that classification of occupations has changed. The Office for National Statistics updates the UK national occupational classification every ten years, to account for the changing nature of occupations.[229] For example, by 1990 there was a more

specific approach taken towards the coding of managers to account for the increase in the breadth of managerial type occupations. Certain occupations (such as restaurant managers and hairdresser managers) were classed as III (skilled non-manual) rather than II (managerial). Sales assistants were classed as III (skilled non-manual) in 1950 and were classed as III (skilled manual) in the 1990 version. Similarly, postal workers were classed as III (skilled non-manual) in 1950 and classed as IV (partly skilled) in the 1990 version.

Adult employment status

Respondents were asked to indicate which of six employment categories best described their situation. These were:

- Paid work
- Retired from paid work
- Looking after family
- Full time student
- Unemployed
- Permanently sick

Adult income

Income was based upon total gross income from all sources and ranged from nil to £40,000 or more. The question was ambiguous regarding whether it should be interpreted as personal or family income. In the questionnaire there were nine income categories. I combined these into four categories as shown in Table 23. I adopted an approach used by the Office for National Statistics (which broadly grouped income in categories of £20,000).[230]

Table 23: Methodology: ACONF income categories

ACONF questionnaire grouping	Categories
Nil	Less than £10,000
Less than £2,000	
£2,000- £5,999	
£6,000-£9,999	
£10,000- £14,999	£10,000 - £19,999
£15,000- £19,999	
£20,000- £29,999	£20,000 - £39,999
£30,000- £39,999	
£40,000 or more	£40,000 or more

Abbreviations: ACONF, Aberdeen Children of the 1950s

Adult body mass index

Body mass index (BMI) was derived from self-reported height and self-reported weight using the standard calculation: weight (kg)/height (m)^2. Normal weight is classed as a BMI between 18.5 and 24.9. Below 18.5 is underweight and between 25 and 29.9 is overweight. A BMI of 30 and above indicates obesity, and this is further divided in to class 1, class 2 and class 3 (the latter being a BMI above 40). BMI has been found to be a good risk indicator for disease.[231]

Adult smoking status

The questionnaire asked regarding current smoking, past smoking and never smoking.

Adult alcohol consumption

There was no question about average alcohol consumption. Therefore, a proxy question regarding frequency of hangovers was used. This approach was the same as previous ACONF publications and can indicate heavy alcohol use.[232-234]

Administrative data variables

To maintain anonymisation during linkage, the ACONF was sent with pseudo-identifiers to the Information Services Division (ISD). After ISD conducted the linkage they removed the identifiers and sent back datasets with pseudo-identifiers only. I was given the SMR01, SMR04, SMR06 and mortality datasets as separate files.

The SMR files were in "long" format. Individuals have more than one row if they had more than one episode of care. As described in Chapter 4, patients may undergo more than one episode of care during a single admission (for example they may move speciality). Each episode may contain different codes. In order not to miss relevant Barnett codes I ensured I collected ICD data from all episodes. In order to calculate an accurate admission rate I then combined all multiple episode admissions into a single admission item.

The first step in assessing the presence of Barnett conditions was to develop STATA syntax containing the ICD codes for each condition and search for these in each episode. Once I had a record of the presence or absence of a Barnett condition for every episode, I converted the "long" datasets to "wide". This meant that there was a single row for each individual and along that row the dates of admission and the presence or absence of a Barnett condition for each admission were recorded. After this I merged the SMR files. From this new dataset I calculated the "Barnett multimorbidity score" for the 2001 and the 2016 populations based on the presence of a Barnett condition at any time in the 5 years prior to the index date. A condition was only counted once even if there had been multiple occurrences.

Administrative datasets also contain postcodes, which can be used to calculate the Scottish Index of Multiple Deprivation (SIMD). The SIMD is an area based measure of deprivation and is constructed as follows. Scotland is split into 6,976 small area Data Zones with roughly 760 individuals in each. A range of indicators from seven "domains" are used to rank Data Zones from the most deprived to the least deprived. These seven domains (with examples of included indicators) are:

1. Employment (including unemployment welfare benefit claims)

2. Income (including the proportion receiving income support)
3. Crime (including rates of reported crimes)
4. Housing (including the proportion of households which are over-crowded)
5. Health (including mortality)
6. Education (including the proportion of young school leavers not in education, employment or training)
7. Access (including transport time to GP) [75]

The SIMD is commonly used to inform local and national policy and funding decisions to target health (and other) inequalities. The SIMD Data Zones are often reported in terms of deciles or quintiles. I was given the SIMD quintile category for each admission with the ranking based upon the position at a national level. In other words, the ACONF participants were not ranked on the basis of their SIMD position in relation to each other, but to their position in relation to the general population in Scotland. For the 2001 and 2016 populations I kept the most recently recorded SIMD. Individuals who were CHI seeded but without administrative data have no SIMD information.

After completing these steps, I linked the merged SMR file with the entire ACONF dataset, matching on the anonymised study identifier. To this file I linked the mortality information, which consisted of the date of death for individuals.

6.3 Overview of methodological and statistical approach

6.3.1 Study design

In Table 24 I have summarised the multimorbidity and resilience measures used in this thesis. I have also given the terminology I will use to distinguish each measure.

Table 24: Methodology: summary of multimorbidity and resilience measures and terminology used in the thesis

Cohort	Population	Multimorbidity measure	Multimorbidity terminology in thesis	Resilience measure (source)	Resilience terminology in thesis
Diamond	Those who had seen a GP in the previous year and responded to a questionnaire.	Person-selected from list of 14 health conditions	Primary care MM	1. In general, would you say your health is; 5 response options… (SRH) 2. Do you have any long-term illness/health problem/disability which limits daily activities? (Activity limitation)	1. SRH resilience 2. Activity limitation resilience
Original ACONF	Responders to a postal questionnaire in 2001. Not selected on basis of healthcare use. Includes individuals from across the UK*	Self-report of up to six "…long-term illnesses, health problems or disability which limit [their] daily activities or work [they] can do"	Self-reported MM	1. Over last 12 months your health on the whole has been; 4 response options... (SRH) 2. In the past few weeks have you been able to enjoy your normal day to day activities? (Positive GHQ 1) 3. In the past few weeks have you been feeling reasonably happy, all things considered? (Positive GHQ 2) 4. In the past few weeks have you been feeling unhappy and depressed? (Negative GHQ 1) 5. In the past few weeks have you been losing confidence in yourself? (Negative GHQ 2) 6. Do you have any long-term illness/health problem/disability which limits daily activities? (Activity limitation)**	1. SRH resilience 2. Enjoyment resilience 3. Positive mood resilience 4. Negative mood resilience 5. Low self-esteem resilience 6. Activity limitation resilience**
Enhanced ACONF 2001	Members of ACONF who were alive, CHI seeded and resident in Scotland at the index date (1st September 2001)	Presence of 40 Barnett health conditions in secondary care data with five year look-back from index date	Secondary care MM		
Enhanced ACONF 2016	Members of ACONF who were alive, CHI seeded and resident in Scotland at the index date (1st September 2016)	Presence of 40 Barnett health conditions in secondary care data with five year look-back from index date	Secondary care MM	N/A	N/A

Abbreviations: GP, General Practitioner; MM, multimorbidity; SRH, Self-rated health; ACONF, Aberdeen Children of the 1950s; UK, United Kingdom; GHQ, General Health Questionnaire; CHI, Community Health Index * Exclusions are described in section 6.2.2 **Resilience measure in 2001 Enhanced ACONF only

A summary of the steps taken for each objective is in Table 25. The analysis involving the Diamond sample was cross-sectional and so there was no assessment of outcomes. The analysis of the relationship between study population variables and multimorbidity is described under the heading of "determinants" but is acknowledged that the direction of the relationship cannot be confirmed. The ACONF is a longitudinal cohort and the analysis of both ACONF datasets was a combination of longitudinal and cross-sectional design depending on the specific objective being addressed.

Table 25: Methodology: summary of analysis steps taken for each of the study populations

Analysis step	**Common to all**	**Diamond- Chapter 7**	**Original ACONF- Chapters 8 and 9**	**Enhanced ACONF – Chapters 8 and 10**
Study population characteristics	Non-response and the prevalence of missing data. Study population characteristics by gender			
Objective two: prevalence of MM	The prevalence of morbidity and MM	Assessment of the relationship between physical conditions and mental health conditions	N/A	N/A
Objective three: determinants of MM	Analysis of relationship between study population characteristics and MM	N/A	Univariate analysis of relationship between social class at birth and study population characteristics and outcomes	N/A
			Multivariate analysis: relationship between social class at birth and multimorbidity and role of educational attainment and other covariates	
Objectives two and three: prevalence and determinants of resilience to MM	Comparison of prevalence of the resilience measures in those with and without multimorbidity Prevalence of resilience	Prevalence of resilience by study population characteristics and assessment of the influence of mental health	Univariate analysis of relationship between social class at birth and resilience	N/A
Objective four: outcomes in those with MM and resilience to MM	N/A	N/A	Baseline populations: 2001 self-reported MM and 2001 secondary care MM Outcomes: presence of MM in 2016, mortality rate and rate of hospital admission	

Abbreviations: MM, multimorbidity; ACONF, Aberdeen Children of the 1950s; N/A, not applicable

As illustrated in the Table, there are a number of steps common to each of the populations. In addition to this, analysis in Diamond includes assessment of the influence of the number

of mental health conditions upon the prevalence of primary care multimorbidity and of resilience to multimorbidity.

In ACONF, objective three (the determinants of multimorbidity and the role of childhood SES) consisted of three steps. Firstly I conducted univariate analysis of the relationship between social class at birth and population characteristics and outcomes. This analysis is relevant for the Enhanced ACONF too. The second step was analysis of the relationship between study population characteristics and multimorbidity. The third step was multivariate analysis of the relationship between social class at birth and multimorbidity and the role of educational attainment and other important covariates.

Resilience assessment was cross-sectional and so resilience prevalence was assessed in the 2001 Enhanced ACONF but not in the 2016 Enhanced ACONF. There were three outcomes analysed in ACONF for both multimorbidity and resilience to multimorbidity: secondary care (Barnett) multimorbidity in 2016, mortality rate by 2016 and hospital admission rate to 2016. The baseline populations were the Original ACONF at the time of the questionnaire and the 2001 Enhanced ACONF.

The STROBE (strengthening the reporting of observational studies in epidemiology) checklists were used to guide the reporting of the studies.[235] The RECORD (Reporting of studies Conducted using Observational Routinely-collected Data) statement checklist was used to guide the steps taken during the linked data methodology development and analysis.[236] To prevent disclosure of identifiable information from the anonymised cohorts, categories with small numbers were either combined or numbers are specified in general terms (e.g. “less than five”).

6.3.2 Study populations and missing data analysis

For the Diamond sample I conducted analysis on the entire sample population. For the Original ACONF the population was those who responded to the questionnaire. For the Enhanced ACONF the population was those alive and resident in Scotland who were CHI seeded. I describe here the rational for this and also how I deal with missing data.

Missing data can be defined as missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR). When values are MCAR there are no systematic differences between those values which are missing and those which are observed. When there are systematic differences between missing and observed values, they are MAR if the existing data can explain these. When the differences between missing and observed values cannot be explained by the observed data then data are MNAR.[237]

Two techniques for dealing with missing data have been used this thesis: complete case analysis (CCA) and multiple imputation (MI) analysis. CCA restricts analysis to those cases with complete data. MI includes all individuals and imputes likely values for missing data.[237-239] The MI method I used was multiple imputation by chained equations (MICE).

Both techniques have the potential to reduce or increase bias. If data are MCAR, CCA should be unbiased, although missing data may lead to loss of precision and power.[237] If data are MAR, bias can be reduced by multiple imputation. However, where missingness relates to unobserved data (MNAR), multiple imputation may lead to as much (or even more) bias than CCA. [237,240] If there is little missing data (suggested to be less than 5% of complete cases by Lee *et al*)[240] there is unlikely to be much to gain from multiple imputation. However, if there is a lot of missing data then multiple imputation may increase bias.[240]

All Diamond study members were included in the analysis. Due to low proportions of missing data (detailed in Chapter 7), CCA was the primary technique and multiple imputation was not carried out.

The Original ACONF cohort analysis was limited to questionnaire responders due to the large volume of non-responders and the fact that key variables (self-reported multimorbidity and the resilience measures) are measured in the questionnaire only. I therefore did not conduct MICE to impute values for the questionnaire non-responders. Within the Original ACONF population (i.e. questionnaire responders only) CCA was carried out as the primary technique, due to low proportions of missing data in variables and the fact that key variables (social class at birth and self-reported multimorbidity) had no missing

data. I conducted multiple imputation as a sensitivity analysis to assess if increasing power (by increasing the sample size) affected the results.

The Enhanced ACONF cohort populations were those with successful CHI seeding who were alive and resident in Scotland in either 2001 or 2016. Variables available to me in ACONF were not sufficient to allow MICE as they did not fully explain the missing data mechanisms. I have therefore not conducted MICE to impute missing data for individuals who were alive outside Scotland or who were not CHI-seeded. Additionally, for analysis requiring questionnaire data (such as educational attainment) I did not conduct MICE to impute values for those who did not respond to the questionnaire (as more than 30% of the population did not have these data).

A summary of the approaches taken for each of the study populations is in Table 26.

Table 26: Methodology: summary of approach to missing data in study populations

Study population	Primary approach to handle missing data	Sensitivity analysis
Diamond	CCA	N/A proportion of missing data sufficiently low
Original ACONF	CCA of questionnaire responders Within the questionnaire responders: CCA	MICE of missing data in questionnaire responders
Enhanced ACONF 2001	All those alive and resident in Scotland in 2001 who were CHI seeded	N/A data MNAR
Enhanced ACONF 2016	All those alive and resident in Scotland in 2016 who were CHI seeded	N/A data MNAR

Abbreviations: CCA, complete case analysis; CHI, Community Healthcare Index; MNAR, missing not at random; ACONF, Aberdeen Children of the 1950s; N/A, not applicable; MICE, multiple imputation by chained equations

6.3.3 Analysis

Prevalence and testing of associations

In the analysis of the populations I present the population characteristics and the prevalence of morbidities, multimorbidity and resilience using frequencies and proportions for categorical variables and the mean for continuous variables. I tested continuous

variables for normality by histogram and where these were not normally distributed I presented the data as medians or categories.

I used the Chi squared test to test for statistically significant relationships between multimorbidity and resilience to multimorbidity with categorical variables (the Chi Squared test for trend was used for variables with more than two categories). For independent continuous normally distributed variables I tested associations using the unpaired t-test. Interaction between variables was tested using the likelihood ratio test.

Statistical significance was set at the 5% level (p-value). The precision of estimates such as odds ratios (OR) and hazard ratios (HR) were illustrated using 95% confidence intervals (CI). ORs, HRs and CIs were set at two decimal places. Proportions were set at one decimal place.

The next parts of this section concern analysis conducted in the ACONF only as these steps cannot be undertaken in a cross-sectional study.

Setting the hypotheses

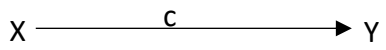
I have used path diagrams in this thesis to illustrate the hypotheses and explain the development of the statistical models. Path diagrams, also called Directed Acyclic Graphs (DAGs), are a method by which to show the direction of associations between variables and identify the role of additional covariates.[241]

In a path diagram, the direction of associations between variables dictates their role. Variable types include exposures, outcomes, confounders and mediators. A confounder is defined as being associated with both the exposure and outcome and not being on the causal pathway. Confounding variables may result in biased estimation of exposure effects and should be controlled for. Mediators are variables which are on the causal pathway- in other words the exposure is associated with this variable and the variable is in turn associated with the outcome.[241,242] Mediators can therefore account for the relationship between the exposure and outcome.

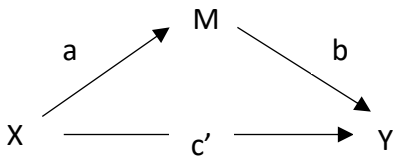
A further important concept is moderation. Moderating variables are variables which affect the strength of association between an exposure or outcome.[243] For example, if we found

medication X reduced the likelihood of mortality but that it worked better in women compared to men then we could describe gender as a moderator. Mediators may be moderators if they interact with the exposure variable.

In a path diagram the illustration of the relationship between the exposure, X, and the outcome, Y, is shown by:



Path "c" is the *total effect*. The role of a mediator is illustrated by:



Here, X is the exposure, Y is the outcome and M is the mediator. Path a is the association between exposure and mediator and path b is the association between mediator and outcome. Path c' is the *direct effect* (the effect unexplained by the mediator) and the amount of mediation is the *indirect effect*, ab.[241,244] The total effect therefore consists of the indirect effect plus the direct effect:

$c = c' + ab$

To include a mediator in a model (and describe it as such) it is important to demonstrate the exposure is associated with the mediator and that the mediator is associated with the outcome. It is also important to check whether the exposure and mediator interact. This means the effect of one of the variables in its relationship to the outcome differs depending on the value of the other and the mediator is also a moderator. If this is the case, the direct effect will vary across different values of the mediator.[242,244]

It is also important to adjust for potential confounders (which may be exposure-outcome confounders, mediator-outcome confounders and exposure-mediator confounders).[242,244]

In summary, the steps I took when modelling the relationship between exposure and outcome, assessing whether a variable mediates the relationship and accounting for confounding variables were as follows:

1. Develop a path diagram which *a priori* sets the model for testing
2. Show that the exposure variable is correlated with the outcome (path c)
3. Show that the exposure variable is correlated with the mediator and check for interaction (path a)
4. Show that the mediator is correlated with the outcome (path b)
5. Assess if the mediator variable mediates the exposure-outcome relationship by examining the impact of controlling for the mediator. If controlling for the mediator leads to the removal of the effect of X on Y (i.e. path c' is zero) this is "complete mediation". Where there is a reduction in size after adjustment, this is "partial mediation".
6. Conduct sensitivity analysis which includes other mediators (for each of these follow steps two to four) and confounders

In objective three, I aim to assess the association between social class at birth and educational attainment with multimorbidity in 2001 (both for self-reported multimorbidity in the Original ACONF and secondary care multimorbidity in the Enhanced ACONF). I have summarised my hypothesis in Figure 6. Educational attainment is the primary mediator. Cognition scores at age 7 and secondary school type are additional hypothesised mediators. Gender is a confounder (of the mediator-outcome relationship). Age is not included as it is not associated with the exposure and all participants were within six years of age of each other.

Figure 7 shows hypothesised relationship between social class at birth, educational attainment and multimorbidity in 2016 (secondary care multimorbidity in the Enhanced ACONF). This includes additional mediators: 2001 adult social class, 2001 adult BMI, 2001 adult smoking status and 2001 adult alcohol consumption (hangover frequency) from the postal questionnaire. These additional mediators are not included where multimorbidity in 2001 is the outcome as they were measured at the same time point.

The path diagram of the hypothesised association between multimorbidity in 2001 and the objective four outcomes is in Figure 8.

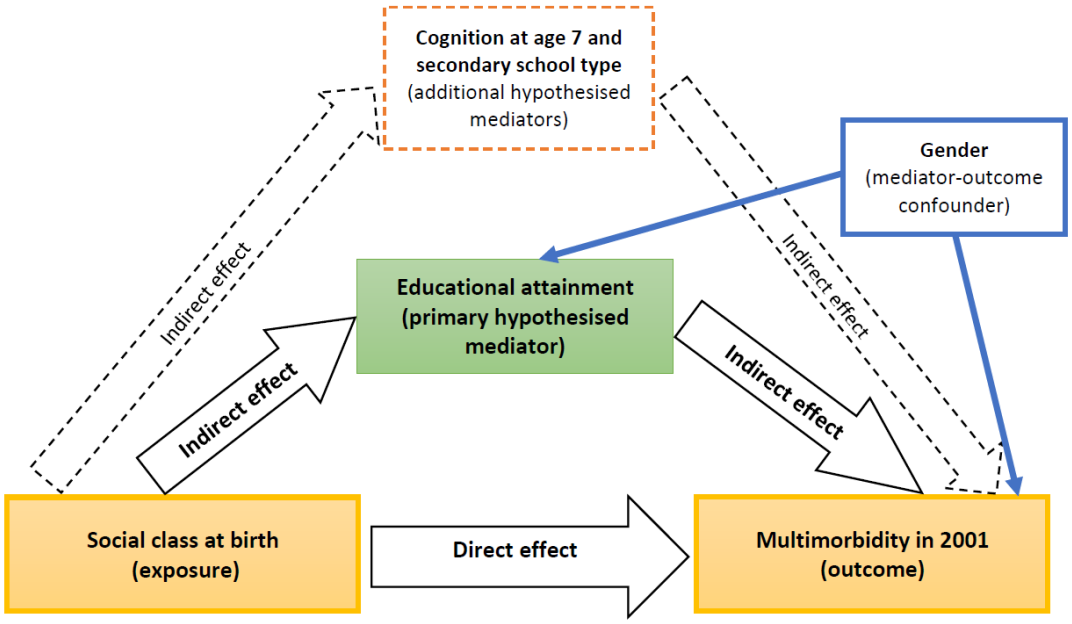


Figure 6: Methodology: Path diagram of the association between social class at birth (exposure), educational attainment (primary mediator) and 2001 multimorbidity (outcome) with illustration of hypothesised additional mediators (cognition at age 7 and secondary school type)

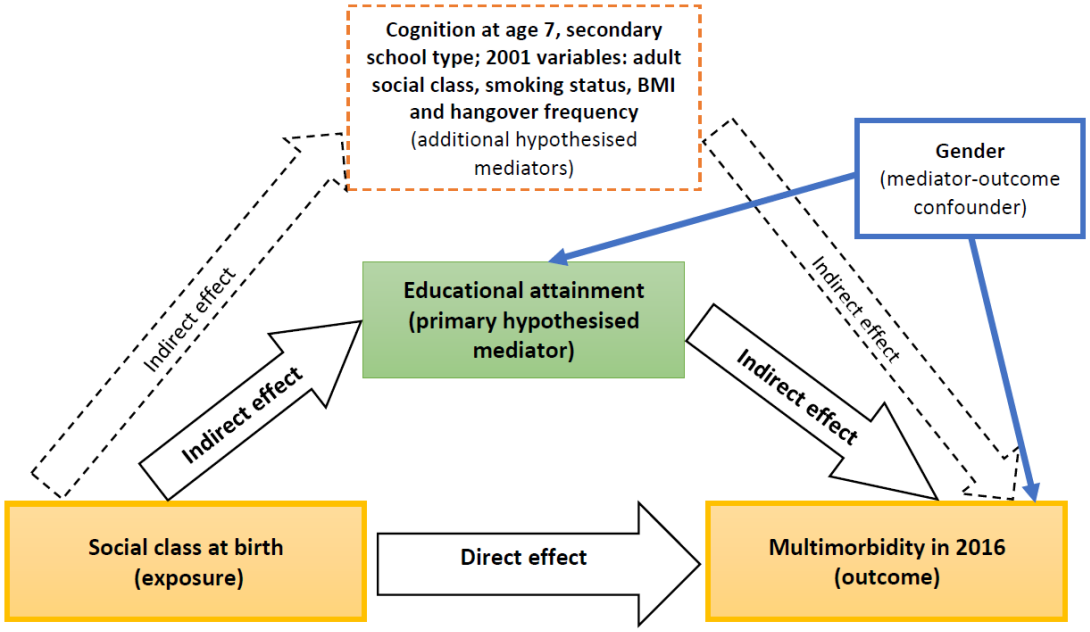


Figure 7: Methodology: Path diagram of the association between social class at birth (exposure), educational attainment (primary mediator) and 2016 multimorbidity (outcome) with illustration of hypothesised additional mediators (cognition at age 7,secondary school type, 2001 adult social class, smoking status, BMI (Body Mass Index) and hangover frequency) and gender (mediator-outcome confounder)

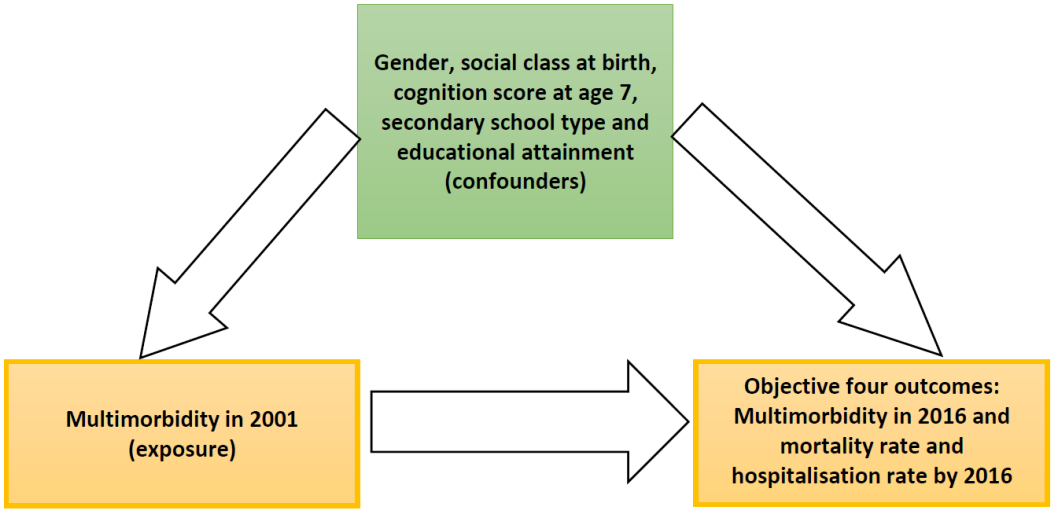


Figure 8: Methodology: Path diagram of the association between the exposures self-reported multimorbidity and secondary care multimorbidity in 2001, and the outcomes of secondary care multimorbidity in 2016, mortality rate by 2016 and hospitalisation rate by 2016; with confounding variables indicated

Statistical techniques: Binary outcomes

The binary outcomes in this thesis are multimorbidity and resilience. I used logistic regression modelling to assess the relationship between the key exposure variables, the covariates and the outcomes. Logistic regression estimates the probability that a characteristic is present (for example the presence of multimorbidity) given the values of the exposure variables. The logistic regression equation produces logistic regression coefficients which are exponentiated to form odds ratios (ORs).

The variables were imputed in regression models as indicator (dummy) variables. The exposure variable had a reference group selected based upon an *a priori* decision (for example the largest category). This reference group has an OR of one in association with the outcome. The OR in the remaining categories of that variable will either be the same, less than or more than one- indicating respectively that the odds of the outcome occurring are no different, less likely or more likely in that category compared to the reference category. I included robust standard errors to account for family clustering in the cohort (the cohort contained siblings). Using robust standard errors does not introduce a multilevel structure, but inflates the standard errors of the estimates so that they are more similar to those from a formal multilevel model.

Statistical techniques: Ordinal outcomes

Ordinal logistic regression was used where the outcome variable was composed of more than two categories and the variable was ordered. The most common form of the ordinal logistic regression model is the proportional odds model and I used this in my thesis. An assumption for this is that the effect of the exposure variable is the same (proportional) across the thresholds (splits) between each pair of categories in the ordinal outcome variable.

The ORs produced from ordinal logistic regression are called “proportional odds ratios”. To illustrate, I use a hypothetical example with an ordinal four-category outcome variable *pain score* labelled “very high”, “high”, “medium” and “low” and a binary exposure variable *gender*, labelled “male” and “female”. In this example, the resulting OR is two for female

in relation to the reference group (male). This means the proportional OR for females, compared to males, of being in the "very high" pain score category versus the "high", "medium" and "low" categories combined is two times higher. Similarly the OR is two for being in the "very high" and "high" categories combined compared to the "medium" and "low" combined and it is two for being in the "very high", "high" and "medium" categories versus the "low". This can be broadly interpreted as the odds of being in a higher pain category is higher for women compared to men.

Statistical techniques: Continuous outcomes

Linear regression was used where outcomes were continuous. In my thesis this was for the association between social class at birth and adult BMI. The coefficients produced from linear regression where the exposure is categorical indicate the average difference in units of the outcome when moving from the reference category to any particular category.

Statistical techniques: mortality rate

I used survival analysis when examining mortality as an outcome because standard methods such as logistic regression do not account for differences in the length of time between the exposure and the outcome for each individual due to different dates of death. Additionally these standard methods are misleading because they do not take into account censorship due to individuals who are either lost to follow-up before the end date of the study or have not experienced the event by the end date.

Survival analysis can account for both the time taken for individuals to reach an end-point of interest and censorship. The rate of the event of interest is commonly called the hazard rate and the occurrence of the event is often called a "failure". Survival can be summarised using Kaplan-Meier curves, which show the probability of survival on the x axis and the time along the y axis.[245-247]

There are a number of methods by which to formally test the association between an exposure and outcome in survival. Poisson regression is one technique, but it is fully

parametric and assumes the rate of the event amongst the individuals included is constant over the study period.[246,247]

The most common approach is Cox proportional hazards which has no parametric assumptions about the baseline hazard. It does assume the hazards are proportional amongst those with differing values of the explanatory variables.[245] This is not always checked but can have important implications. For example in a trial comparing the long-term survival of patients on drug A compared to drug B, let us say that an overall hazard ratio favours survival in the group taking drug A by 2 year follow-up. However, survival was non-proportional and there was better survival in drug B during the first six months of the trial. This finding is hidden in the overall finding of better long-term survival in those taking drug A.[246,247]

Some authors manage the violation of proportionality by stating the hazard is an average hazard ratio.[248] Others argue that this can be misleading as described by my example above.[249,250] In my case I have quoted standard Cox hazards if non-proportionality is present as my work does not aim to determine whether one entity is superior to another. Even if those with multimorbidity had lower earlier mortality but higher mortality by the end of follow-up for example, I would not be arguing that having multimorbidity is a superior state to not having multimorbidity.

In the analysis I examine the mortality rate in relation to three exposure variables: social class at birth, self-reported multimorbidity in 2001 and, secondary care multimorbidity in 2001.

The first step was to declare the data to be survival data in Stata and set the start of the follow-up period, the type of hazard (i.e. mortality) and the times at which contributions of risk should be censored. For the association between social class at birth and mortality by 2016, the follow-up period began in 1981. The reason for this was that death records were only available from 1981 onwards. For the multimorbidity populations in 2001, the follow-up period began at 1st May 2001.

The exact dates of emigration from Scotland and deaths outside Scotland is not known to this study. The two status updates (2001 and 2013) will indicate which participants left Scotland or died outside Scotland at any time prior to the date of the status update for the 2001 status or between 2001 and 2013 for the 2013 status. However, by setting the censorship time at 2001 or 2013 for all these individuals there will be an artificial assessment of the contribution of risk.

As a result, the populations at baseline were limited to only those who were known to be alive by September 2016 or who have a specific date of death (i.e. a Scottish recorded death). Those known to have died outside Scotland are not included because their date of death is not recorded and therefore the contribution of risk cannot be calculated.

Contributions of risk were therefore censored at the earliest of the following for the main analysis:

1. Death recorded in Scottish data
2. 30th September 2016 (the end of the follow-up period)

Once the data were set as survival data, I used Cox proportional hazards modelling to formally test whether there were significant differences in rates between the sub-groups of the exposure. I checked the assumption that the hazards were proportional amongst those with differing values of the explanatory variables using the "estate phtest" command in Stata. Where the test is non-significant ($p > 0.05$) the proportional hazards assumption is justified.

Statistical techniques: rate of hospital admissions

Mortality can only occur once per individual (single failure data) however hospital admissions can recur (multiple failure survival data). Furthermore this outcome represents recurring events within the same individual (clustered data) and this must be accounted for when modelling the association. A Cox model can have a robust standard errors term included to account for clustering but the model is limited in that it can only assess time to the first event.[251,252]

There are modelling techniques which can be used with multiple failure data and take into account an individual's failure events after the first event as well as account for the clustering effect. Two common models are the Andersen and Gill (AG) and the Prentice, Williams and Peterson Total Time (PWP-TT) models. I have used the PWP-TT model in my thesis because it allows for the underlying risk of failure to vary for each admission whilst the AG does not. This is important for hospital admission data where it is likely that those with increasing numbers of hospital admission have an increased likelihood of more admissions.[252]

The PWP-TT model works similarly to a Cox model but with stratification on the number of previous failure events and based on the assumption the events are ordered (i.e. an individual cannot have a second event until the first happens and so on).

I conducted my analysis following the steps laid out by Cleves[251] and Westbury *et al*.[252] I first converted my dataset from wide to long. This meant each individual had a separate row for each admission date (if admissions had occurred) and additionally all individuals (including those without any admissions) had a row with the censorship date. The censorship date was set based on the same principles as for the mortality analysis and was the earliest of:

1. Death recorded in Scottish data
2. 30th September 2016

For the association between social class at birth and admission rate by 2016, the follow-up period began in 1981. For the association between multimorbidity in 2001 and hospital admissions, the follow-up period began at 1st May 2001.

Each row for an individual was ordered by date and I numbered each row. For example a person with an admission in January 2002, an admission in June 2002 and a death in January 2003 (censored) would have the first row coded "1", the second "2" and the third "3". An individual still alive and with no admissions by the 30th September 2016 would have one row, dated 30th September 2016 and the row would be numbered "1".

When testing the association between the exposure variables and the outcome, I stratified the analysis by the row number. This essentially means a Cox model is fitted with a different underlying risk for each failure event. The results were reported using hazard ratios. I used the PWP-TT STATA coding set out by Cleves[251] and Westbury *et al*.[252]

Others in the literature do not use multiple failure survival analysis and instead use standard single failure survival analysis. There is not yet a consensus approach. Westbury *et al* found that the two behaved similarly.[252] As a result, I also presented standard survival analysis, which took into account the time to the first admission only in my first model (the association between social class at birth and hospital admissions in the Original ACONF). This was to illustrate that the two models behave similarly.

I restricted the sample at baseline to those who were CHI seeded and known to be resident in Scotland in September 2016, or who had a Scottish recorded death.

6.3.4 Assessment of validity and causality

When interpreting findings it is important to assess the validity of the study and consider whether the results represent causality. I describe these concepts here as they inform the reporting and interpretation of my results.

Internal validity refers to a study measuring what it purports to measure and external validity refers to the generalisability of the results from the study population to the wider population.[253]

Internal validity is assessed by examining the role of bias, residual confounding and chance in the observed results. Bias describes a systematic error in the collection of data. One form is selection bias, in which the study population characteristics differ systematically (not randomly) from the wider population in which they were selected.[254] Social desirability bias is where individuals adjust their responses to a question based on what they believe may be more acceptable to others.[255] Frequently this occurs with sensitive topics such as the over-use of alcohol or drugs or engaging in illicit activities.[255] Recall bias occurs when individuals differentially remember past events based upon their current circumstances. It

is a risk in retrospective studies.[245] Residual confounding refers to the inability to adjust for important confounding variables.[256] These variables may not be available in the study population.

Statistical association does not equal causation and as well as taking into account issues of bias and other threats to internal validity, it is important to consider whether the results are due to chance.[253] Chance refers to random error (unlike bias which is non-random error). A type one error refers to concluding there is an effect when none exists and a type two error is concluding there is no effect when there is one.[245]

The chance of a type one error is based on the significance level set (p-value). The p-value is the probability of obtaining the result or something more extreme if the null hypothesis (the hypothesis that there is no association) is true. In my thesis I have set this at a probability of 5% (p= 0.05), whereby I conclude that the null hypothesis should be rejected if the p-value is less than or equal to 0.05. In other words, if the p-value is less than or equal to 0.05 there is a less than 1 in 20 chance that the result is due to chance.[48] Multiple hypothesis testing increases the likelihood of type one errors and so setting the hypotheses based upon the primary aims of the study and specified *a priori* is crucial.[245]

The chance of a type two error relates to the power. The power is the probability of saying there is no effect when one does exist. The power of a study increases with a larger sample size, where there is low variability in the observations, where there are larger effect sizes and where the significance level is higher (although by increasing the significance level the probability of type one error is increased).[245] The 95% confidence interval represents the precision of the value. Where confidence intervals are wide it is suggestive of low power and the higher chance of a type two error.[245]

The Bradford- Hill criteria are often used as a basis to assess causation. These are a set of 9 principles and include features such as whether the observed association is plausible, whether it is consistent with existing knowledge and whether the cause preceded the effect.[253]

6.4 Ethics and data management

6.4.1 Ethical approval and permissions

Ethical approval for the Diamond study was granted by the University of Melbourne's Human Research Ethics Committee previously. I gained permission from the study team to access the data for analysis in this thesis. I attended the Department of Primary care at the University of Melbourne in December 2014 for three weeks to carry out the analysis for the work.

The ACONF dataset is registered with the National Research Ethics Service (NRES) as a research database, meaning that the steering committee may release data for research. This includes linkage to Scottish hospital administrative data provided the ACONF steering committee and the ISD Privacy Advisory Committee (PAC) give approval. Prior to commencing the work, I confirmed with the North of Scotland NRES that no further ethical approval was required. NHS Grampian Research and Development (R&D) confirmed no R&D approval was required.

I gained permission from the ACONF steering committee to use the ACONF in this study. In conjunction with support from the ISD "electronic Data Research and Innovation Service (eDRIS)" I gained permission from the national PAC (now called the "Public Benefit and Privacy Panel for Health and Social Care") to link and use Scottish administrative data. This committee scrutinises applications for administrative data and ensures principles of information governance are being upheld before applications are approved.

6.4.2 Data management

I was given permission by the Diamond study team to transfer the dataset to my secure University drive for further analysis. The analysis was conducted solely within the secure drive. All outputs were checked by me for risk of disclosure with regards to small numbers using the same principles set out by the Grampian Data Safe Haven (DaSH) as described below.

As part of the conditions of the use of ACONF and of the release of data by ISD, the ACONF and its linked data were stored by DaSH.[257] DaSH provide data management support, security and governance. DaSH supported me with:

- Developing the data management plan (how the data will be handled, stored, archived and deleted).
- Ensuring the criteria for being an Approved Researcher had been met. These are: to be employed by an approved institution (i.e. the University of Aberdeen), to have an up to date Good Clinical Practice certificate and to have an up to date certificate for an approved Information Governance training course.
- Development of the data linkage plan (defining where the data are coming from, how they will be linked and where they will be stored). The data linkage plan for the thesis is in Appendix 3.

DaSH carried out ACONF dataset anonymisation ensuring I had a dataset with no person identifiable information and I was given pseudo-anonymised study identifiers only. My ACONF dataset for analysis was stored on the DaSH computer servers (comprising of an NHS and a University of Aberdeen system). The participant identifiers were kept on the NHS server and the remaining data were kept on the University of Aberdeen server. This ensured that no single person could combine the two parts of the dataset. I analysed the data within the Safe Haven from which it was not possible to print or access the internet. Data and outputs were only released from the Safe Haven to me after they had been approved by a qualified DaSH team member. This ensures data released did not contain any potentially identifiable information. The software used for analysis was STATA version 13.

6.4.3 Dataset checking and cleaning

I was given access to the fully cleaned Diamond dataset. I carried out checks with published data and no discrepancies were found. I used variables in their existing form, other than the multimorbidity measures and the binary form of the SRH measure (as described earlier).

The ACONF was given to me in its original form, without linked administrative data initially. In order to assess data completeness and accuracy, I checked the data against existing ACONF publications with any discrepancies being discussed with the ACONF study coordinator. An additional questionnaire responder was found, bringing the total to 7,184 (where in previous publications it had been 7,183). New variables were derived where required. Where the correct variable for use was unclear from the dataset, I checked this with the ACONF study coordinator.

I described the steps I took to merge the administrative datasets with the ACONF previously. Once I did this, I conducted the same checks. Although there have been no publications with the updated linked data I checked some findings against previous publications to assess general consistency. I also conducted sense checks, for example confirming that no admissions were recorded after deaths were recorded.

7 Diamond study

7.1 Structure of chapter

In this chapter I describe the analysis I conducted in the Diamond study population. I start by describing non-response characteristics, the characteristics of the population and the degree of missing data in key variables. I then go on to present the prevalence of primary care morbidities and multimorbidity and the association between population characteristics and primary care multimorbidity. Following this I describe the association between mental health conditions and multimorbidity. After this I present analysis of the prevalence of resilience (SRH resilience and activity limitation resilience) to multimorbidity and the association between resilience measures and population characteristics. I finish by showing the association between mental health conditions and each of the resilience measures.

7.2 Population characteristics

7.2.1 Non-response characteristics

As described in Chapter 6, the response to the Diamond recruitment process was 43% (n=7,667). I did not have access to the data to assess non-response and the figures here are sourced from a published Diamond paper.[203] Compared with the sample sent the screening survey, respondent mean age was higher (51 years compared to 46 years), and the proportion of female respondents was higher than male (66% compared to 61% respectively).[203]

7.2.2 Description of study population characteristics

The characteristics of the study population (n=7,667) are presented in Table 27.

Table 27: Diamond: study population characteristics by gender (n=7,667 with missing data indicated)*

Characteristic	All n=7,667 Total	%	Males n= 2,564 Total	%	Females n=5,081 Total	%
All	7,667		-	-	-	-
Gender						
Male	2,564	33.4	-	-	-	-
Female	5,081	66.3	-	-	-	-
Missing	22	0.3	-	-	-	-
Median age in years (IQR)	51.9 (40.3 – 62.0)		56.5 (45.8-65.2)		49.1 (37.7 – 59.9)	
Age categories						
18-24	325	4.2	66	2.6	259	5.1
25-34	843	11.0	152	5.9	691	13.6
35-44	1452	18.9	377	14.7	1,075	21.2
45-54	1781	23.2	562	21.9	1,219	24.0
55-64	1736	22.6	730	28.5	1,005	19.8
65-75	1448	18.9	651	25.4	794	15.6
Missing	82	1.1	23	1.0	38	0.8
Highest level of education						
Bachelor Degree or higher	1,724	22.5	481	18.8	1,238	24.4
Certificate / Diploma	1,583	20.7	479	18.7	1,102	21.7
Completed year 12	1,227	16.0	388	15.1	839	16.5
Completed year 10	1,782	23.2	629	24.5	1,149	22.6
Left school before year 10	1,304	17.0	574	22.4	727	14.3
Missing	47	0.6	13	0.5	26	0.5
Employment status						
Employed	4,714	61.5	1,659	64.7	3,048	60.0
Unemployed	1,352	17.6	635	24.8	712	14.0
Unable to work	419	5.5	219	8.5	200	3.9
Home duties/unpaid/ maternity leave	1,076	14.0	25	0.1	1,047	20.6
Student only	78	1.0	18	0.7	60	1.2
Missing	28	0.4	8	0.3	14	0.3
Hazardous alcohol consumption levels						
No	6,357	82.9	1,899	74.1	4,445	87.5
Yes	1,245	16.2	633	24.7	611	12.0
Missing	65	0.9	32	1.3	25	0.5
Smoking status						
Never smoked	3673	47.9	1046	40.8	2619	51.5
Ex-smoker	2574	33.6	1067	41.6	1499	29.5
Occasional smoker	477	6.2	148	5.8	328	6.5
Regular smoker	900	11.7	291	11.4	609	12.0
Missing	43	0.6	12	0.5	26	0.5

Abbreviations: IQR, interquartile range

*Figures presented are numbers and proportions unless stated otherwise.

Of 7,667 participants, 66% were female. Age was not normally distributed and the median age was 52 years (IQR 40 – 62 years). The median age for men was higher than for women (57 compared to 49 years). The age of the population ranged from 18 to 75. The smallest category was "18-24" (4%) and the largest categories were "45-54" (23%) and "55-54" (23%).

Almost 23% of the sample received a Bachelor Degree or higher and 17% left school before year 10. The proportion with a degree was higher in women (24%) compared to men (19%). The proportion leaving school before year 10 was higher in men (22%) compared to women (14%). Almost 62% of the sample were in employment (65% of males, 60% of females). There was a large difference between the genders for those in unemployment (25% of males versus 14% of females). A higher proportion of men were unable to work (9% compared to 4% of women). There was a very large difference in the genders for those who were doing "home duties, unpaid work or on maternity leave" with 21% of women selecting this category compared to 0.1% of men.

Just over 16% reported drinking alcohol at hazardous levels and this was higher in men (25%) compared to women (12%). More women than men reported never smoking (52% compared to 41%). The proportion of current smokers was comparable between the genders (11% males, 12% females) with a higher proportion of men compared to women being ex-smokers (42% compared to 30%).

Missing data ranged from 0.3% (for gender) to 1% (age).

7.3 Prevalence of morbidities and primary care multimorbidity

The prevalence of all 14 self-reported conditions is shown in Table 28.

Table 28: Diamond: individual morbidity prevalence over past 12 months in all participants and by gender and mean age (n=7,620)

	All (n=7,620)		Female (n=5,047)		Male (n=2,553)		Age at survey	
	Number	%	Number	%	Number	%	Median	IQR
Physical conditions								
Back problems	2,123	27.9	1,385	27.4	738	28.9	52.0	41.4-61.2
Arthritis	1,353	17.8	903	17.9	450	17.6	60.2	53.2-67.8
Hypertension	1,255	16.5	755	15.0	500	19.6	59.8	52.0-67.7
Lipid disorder	819	10.8	488	9.7	331	13.0	59.2	52.5-66.4
Asthma	773	10.2	555	11.0	218	8.5	48.9	37.2-60.4
Dermatitis	519	6.8	378	7.5	141	5.5	47.1	36.2-57.2
Chronic sinusitis	401	5.3	310	6.1	91	3.6	51.9	41.5-61.1
Diabetes Mellitus	400	5.3	206	4.1	194	7.6	60.6	52.6-67.9
Heart disease	238	3.1	95	1.9	143	5.6	63.8	56.4-69.8
Cancer	191	2.5	105	2.1	86	3.4	62.3	52.7-68.5
Emphysema	167	2.2	87	1.7	80	3.1	61.7	51.2-68.3
Stroke	59	0.8	31	0.6	28	1.1	61.5	48.1-68.8
Mental health conditions								
Depression	1,369	18.0	984	19.5	385	15.1	48.1	37.1-57.1
Anxiety	1,265	16.6	929	18.4	336	13.2	49.0	38.5-58.6

Abbreviations: IQR, interquartile range

The physical condition with the highest prevalence was “back problems” (28%) and the condition with the lowest prevalence was “stroke” (0.8%). This pattern was the same for both men and women. Asthma, chronic sinusitis and dermatitis showed higher prevalence in women compared to men (for example the prevalence of asthma in women was 11% and in men was 9%). Emphysema, diabetes, hypertension and lipid disorder were higher in men compared to women (for example the prevalence of diabetes in women was 4% and in men was 8%). Other conditions were comparable in prevalence between the genders. The median age of those reporting each condition was lowest for dermatitis and asthma (47 and 49 respectively) and highest for cancer and heart disease (between 62 and 64).

The overall prevalence of depression and of anxiety were similar to each other (18% and 17% respectively). The prevalence of both were higher in women compared to men (for

example depression prevalence in women was 20% and in men it was 15%). The median age for depression was 48 and for anxiety was 49.

7.4 The association between primary care multimorbidity and cohort characteristics

The population characteristics of the Diamond sample by primary care multimorbidity status are in Table 29. Of 7,620 individuals, 2,922 (38%) had multimorbidity and the prevalence was similar between the genders. The prevalence of multimorbidity increased with increasing age ($p<0.001$). For example it was 27% (95% CI 22% - 32%) in 18 to 24 year olds, 38% (95% CI 35% -40%) in 45 to 54 year olds and 44% (95% CI 42%- 47%) in 65 to 75 year olds.

The prevalence of primary care multimorbidity tended to decrease with higher levels of educational attainment ($p<0.001$). For example it was 43% in those who left school before year 10 (95% CI 40% - 46%) and was 34% in those with a bachelor degree or higher (95% CI 32% - 36%).

With regards to employment status, those who were students or employed had the lowest prevalence levels of primary care multimorbidity (32% and 34% respectively). The highest levels were in the unemployed group (45%) and the "unable to work" group (63%). The association was statistically significant ($p<0.001$).

There was little difference in primary care multimorbidity prevalence in those who reported drinking alcohol at hazardous levels (40%) and those who did not (38%) and there was no statistically significant association ($p=0.211$). Of those who smoked regularly, 45% had multimorbidity (95% CI 42% - 49%) compared to 35% (95% CI 33% -36%) of those who had never smoked ($p<0.001$).

Table 29: Diamond: primary care multimorbidity prevalence by baseline characteristics (n=7,620)

Characteristic	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	p value*
All	7,620	2,922	38.3	37.3- 37.4	
Gender					
Male	2,553	975	38.2	36.3-40.1	p=0.807
Female	5,047	1,942	38.5	37.2-39.8	
Age categories					
18-24	323	86	26.6	22.1- 31.7	p<0.001
25-34	837	245	29.3	26.3-32.4	
35-44	1,441	469	32.5	30.2-35.0	
45-54	1,768	665	37.6	35.4-39.9	
55-64	1,730	795	46.0	43.6-48.3	
65-75	1,440	635	44.1	41.6-46.7	
Highest level of education					
Bachelor Degree or higher	1,718	581	33.8	31.6-36.1	p<0.001
Certificate / Diploma	1,572	625	39.8	37.4-42.2	
Completed year 12	1,219	453	37.2	34.5-39.9	
Completed year 10	1,774	690	38.9	36.7-41.2	
Left school before year 10	1,293	557	43.1	40.4-45.8	
Employment status					
Employed	4,685	1,607	34.3	33.0-35.7	p<0.001
Unemployed	1,346	605	45.0	42.3-47.6	
Unable to work	415	260	62.7	57.9-67.2	
Home duties/unpaid /maternity leave	1,071	417	38.9	36.1-41.9	
Student only	78	25	32.1	22.7-43.0	
Hazardous alcohol consumption levels					
No	6,319	2,402	38.0	36.8-39.2	p=0.211
Yes	1,238	494	39.9	37.2-42.7	
Smoking status					
Never smoked	3,647	1,266	34.7	33.2-36.3	p<0.001
Ex-smoker	2,563	1,058	41.3	39.4-43.2	
Occasional smoker	473	180	38.1	33.8-42.5	
Regular smoker	896	407	45.4	42.2-48.7	

Abbreviations: 95% CI, 95% confidence interval

* Statistical significance set at 5% level. CHI test used for binary variables, CHI test for trend for variables with more than two categories

7.5 The relationship between mental health conditions and primary care multimorbidity

Table 30 shows the relationship between the number of physical conditions and of physical condition primary care multimorbidity with the presence mental health conditions. There was a statistically significant association between the count of physical conditions and the count of mental health conditions, as well as between physical condition multimorbidity and the count of mental health conditions (p<0.001 for both).

Table 30: Diamond: Association between primary care physical conditions and primary care mental health conditions (n=7,620)

Physical condition status	Number of mental health conditions									Total
	Zero			*One*			*Two*			
	Number	%	95% CI	Number	%	95% CI	Number	%	95% CI	
Number of conditions*										
Zero	2,748	84.6	83.4-85.9	270	8.3	7.4-9.3	229	7.1	6.2-7.9	3,247
One	1,680	75.7	73.9-77.5	303	13.7	12.2-15.1	236	10.6	9.4-11.9	2,219
Two	799	69.6	66.9-72.3	184	16.0	13.9-18.2	165	14.4	12.3-16.4	1,148
Three	377	64.4	60.6-68.3	115	19.7	16.4-22.9	93	15.9	12.9-18.9	585
Four	148	57.6	51.5-63.6	46	17.9	13.2-22.6	63	24.5	19.2-29.8	257
Five to twelve	68	41.5	33.9-49.0	44	26.8	20.0-33.6	52	31.7	24.6-38.9	164
Physical condition primary care multimorbidity status*										
No multimorbidity	4,428	81.0	80.0-82.0	573	10.5	9.7-11.3	465	8.5	7.8-9.3	5,466
Multimorbidity	1,392	64.6	62.6-66.6	389	18.1	16.4-19.7	373	17.3	15.8 - 19.0	2,154
Total	5,820	76.4	75.4-77.3	962	12.6	11.9-13.4	838	11.0	10.3-11.7	7,620

Abbreviations: 95% CI, 95% confidence interval

*Association, tested using CHI squared test for trend, statistically significant, p<0.001

Of the 3,247 individuals with no reported physical condition, 85% (95% CI 83% - 86%) had no reported mental health condition. The prevalence of no coexisting mental health condition decreased with the increasing number of physical conditions. For example it was

64% (95% CI 61% - 68%) in those with three conditions and 42% (95% CI 34% - 49%) in those with over five. These trends are further illustrated in Figure 9.

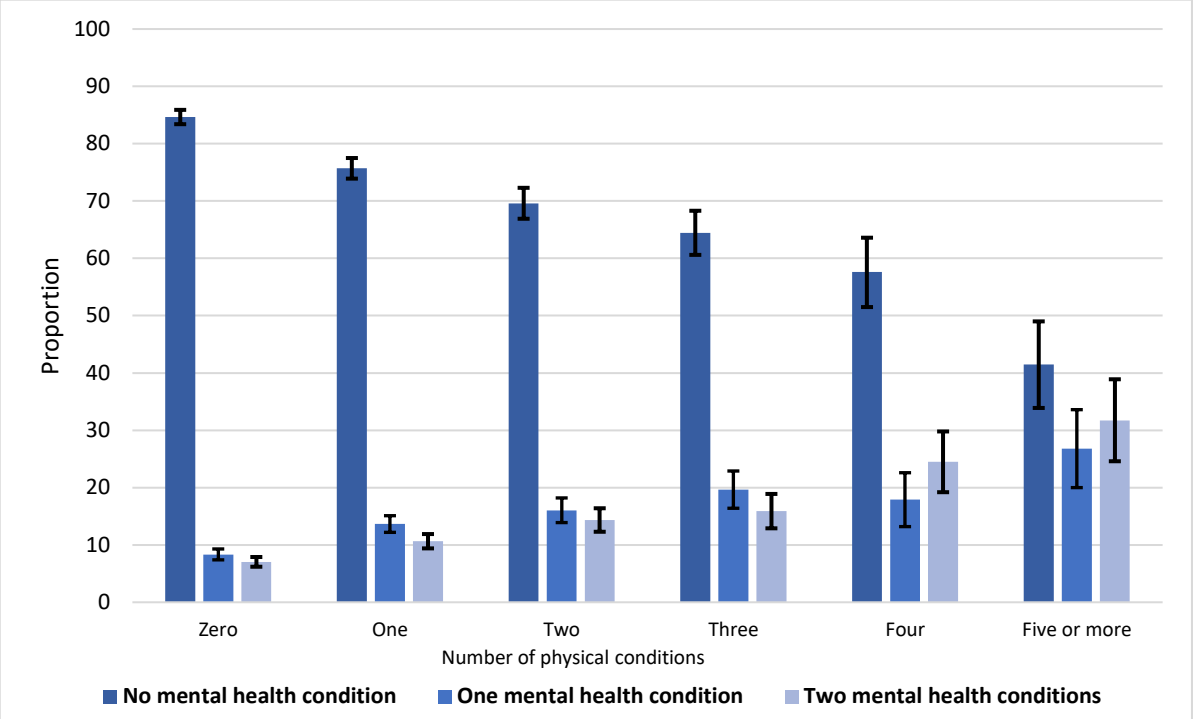


Figure 9: Diamond: proportion (%) of mental health conditions by number of physical conditions, with 95% confidence intervals (n=7,620)

When the physical disease count was summarised as a measure of multimorbidity, 1,392 (65%) with physical disease primary care multimorbidity had no associated mental health condition (95% CI 63% - 67%) whilst 4,428 (81%) of those without multimorbidity had no mental health condition (95% CI 80% - 82%).

I then limited the analysis to those with physical condition primary care multimorbidity only and assessed the relationship between the number of mental health conditions and gender (Table 31). There was a statistically significant relationship between gender and the number of co-existing mental health conditions in this population (p=0.008), however differences were small. In 786 men with physical condition multimorbidity the prevalence

of no co-existing mental health condition was 69% (95% CI 65% - 72%) and in women it was 62% (95% CI 60% - 65%).

Table 31: Diamond: Association between number of co-existing mental health conditions and gender in population with physical condition primary care multimorbidity (n=2,150)*

Number of mental health conditions	Male			Female		
	Number	% of total	95% CI	Number	% of total	95% CI
Zero	540	68.7	65.4-71.9	850	62.3	59.7- 64.9
One	131	16.7	14.2-19.4	257	18.8	16.9-21.0
Two	115	14.6	12.3-17.3	257	18.8	16.9-21.0
Total	786	100		1,364	100	

Abbreviations: 95% CI, 95% confidence interval
*Association, tested using CHI squared test for trend, statistically significant, p=0.008

7.6 The prevalence of resilience and association with population characteristics

Resilience was assessed using two measures: self-rated health (SRH) and self-reported activity limitation as summarised in Chapter 5. The association between primary care multimorbidity status and the two resilience measures is shown in Table 32.

Table 32: Diamond: Prevalence of SRH and activity limitation resilience measures by primary care multimorbidity status with test of association

Resilience measure	No multimorbidity				Multimorbidity			
		"Resilient" response**				Resilient response		
	Total	Number	%	95% CI	Total	Number	%	95% CI
Overall health and wellbeing- SRH *	4,658	4589	98.5	98.2-98.9	2,868	2,724	95.0	94.2-95.8
Activity limitation*	4,587	3536	77.1	75.9-78.3	2,846	1,473	51.8	49.9-53.6

Abbreviations: SRH, self-rated health; 95% CI, 95% confidence interval
*Difference, tested by CHI squared test for association, statistically significant, p<0.001
** Not technically resilience given resilience is defined as a positive response in those with primary care multimorbidity

I have provided the data for the "positive" response category only. For both measures there was a statistically significant association between them and primary care multimorbidity ($p<0.001$). For those without primary care multimorbidity, the prevalence of fair to excellent SRH was 99% (95% CI 98%- 99%) and for those with primary care multimorbidity it was slightly lower at 95% (95% CI 94%-96%). For those without multimorbidity, 77% responded "no" to having activity limitation and this was 52% (95% CI 50%-54%) in those with multimorbidity.

I then limited the analysis to those with primary care multimorbidity. The prevalence of resilience by population characteristics for both measures is in Table 33. I first describe the characteristics of those with SRH resilience. Due to small numbers in some categories, many confidence intervals were wide. Out of 2,911 individuals with primary care multimorbidity, the overall prevalence of SRH resilience was 95% (95% CI 94% - 96%). The prevalence by gender was similar (94% [95% CI 92%-95%] for men and 96% [95% CI 95%-97%] for women) although the difference was statistically significant ($p=0.012$). There was no significant pattern by age ($p=0.710$). For example, for those in age category "18 to 24" the prevalence was 96% (95% CI 89% - 98%) and in category "65 to 75" it was 95% (95% CI 93% - 97%).

There was a trend for decreasing SRH resilience prevalence with decreasing educational attainment ($p<0.001$). For those with degree level education, the prevalence was 97% (95% CI 96% - 98%) and for those who left school before year 10 it was 92% (95% CI 90% - 94%). For employment, those unable to work had the lowest prevalence of SRH resilience (78% [95% CI 73% - 83%]). For all others the overall prevalence was 95% or higher (for example 97% [95% CI 96% - 98%], in those who were employed). Differences were found to be statistically significant ($p<0.001$) although confidence intervals were wide indicating lack of precision. Resilience levels were similar for those with hazardous and non-hazardous alcohol consumption levels (94% compared to 95% respectively, $p=0.335$). SRH resilience was lower in regular smokers (91% [95% CI 88% -94%]) compared to never smokers (97% [95% CI 96% - 98%]). Differences were statistically significant ($p<0.001$).

Table 33: Diamond: Prevalence of SRH and activity limitation resilience by baseline characteristics, population limited to those with primary care multimorbidity and complete resilience measure data only (n=2,911 for self-rated health and n=2,888 for activity limitation)

Characteristic	Self-rated health resilience					Activity limitation resilience				
	Total	N resilient	%	95% CI	p value*	Total	N resilient	%	95% CI	p value*
All	2,911	2,767	95.1	94.2-95.8		2,888	1,508	52.2	50.4-54.0	
Gender										
Male	970	908	93.6	91.9- 95.0	p=0.012	963	371	38.5	35.5- 41.6	p<0.001
Female	1,936	1,854	95.8	94.8- 96.6		1,920	1,134	59.1	56.8- 61.2	
Age categories										
18-24	88	84	95.5	88.9- 98.2	p=0.710	88	66	75.0	64.9- 83.0	p<0.001
25-34	251	238	94.8	91.3- 96.9		249	173	69.5	63.5- 74.9	
35-44	474	455	96.0	93.8- 97.4		472	315	66.7	62.4- 70.8	
45-54	666	635	95.4	93.5- 96.7		664	370	55.7	51.9- 59.5	
55-64	782	735	94.0	92.1- 95.5		783	341	43.6	40.1- 47.1	
65-75	624	594	95.2	93.2- 96.6		605	228	37.7	33.9- 41.6	
Highest level of education										
Bachelor Degree or higher	579	564	97.4	95.8- 98.4	p<0.001	577	357	61.9	57.8- 65.8	p<0.001
Certificate / Diploma	624	599	96.5	94.2- 97.3		625	351	56.2	52.2- 60.0	
Completed year 12	457	429	93.9	91.3- 95.7		452	254	56.2	51.6- 60.7	
Completed year 10	684	648	94.7	92.8- 96.2		675	327	48.4	44.7- 52.2	
Left school before year 10	553	510	92.2	89.7- 94.2		544	213	39.2	35.1- 43.3	
Employment status										
Employed	1,606	1,562	97.3	96.3- 98.0	p<0.001	1,608	1037	64.5	62.1- 66.8	p<0.001
Unemployed	598	568	95.0	92.9- 96.5		585	225	38.5	34.6- 42.5	
Unable to work	259	203	78.4	73.0- 83.0		260	5	1.9	0.8- 4.5	
Home duties/ unpaid/ maternity leave	413	400	96.9	94.7- 98.2		400	222	55.5	50.6- 60.3	
Student only	25	25	100.0	86.7- 100.0		25	15	60.0	39.9- 77.2	
Hazardous alcohol consumption levels										
No	2,390	2,275	95.2	94.3- 96.0	p=0.335	2,369	1,236	52.2	50.2- 54.2	p=0.552
Yes	496	467	94.2	91.7- 95.9		494	265	53.6	49.2- 58.0	
Smoking status										
Never smoked	1,270	1,235	97.2	96.2- 98.0	p<0.001	1,259	717	57.0	54.2- 59.7	p<0.001
Ex-smoker	1,045	988	94.6	93.0- 95.8		1,035	499	48.2	45.2- 51.3	
Occasional smoker	180	163	90.6	85.4- 94.0		181	93	51.4	44.1- 58.6	
Regular smoker	404	369	91.3	88.2- 93.7		402	192	47.8	42.9- 52.7	

Abbreviations: N, number; 95% CI, 95% confidence interval * Statistical significance set at 5% level. CHI test used for binary variables, CHI test for trend for variables with more than two categories

I now describe the relationship between the population variables and activity limitation resilience (Table 33). Out of 2,888 individuals with primary care multimorbidity the overall prevalence of resilience was 52% (95% CI 50% - 54%). This was significantly lower in men (39% [95% CI 35% - 42%]) compared to women (59% [95% CI 57%- 61%]). The prevalence of activity limitation resilience decreased with age and this was statistically significant ($p<0.001$). The prevalence of resilience was higher in those with higher educational attainment ($p<0.001$). For example it was 62% (95% CI 58% - 66%) in those with a degree and 39% (95% CI 35% - 43%) in those who left school before year 10. The prevalence of resilience was higher in those who were employed, studying or undertaking home and related duties compared to those who were unemployed or unable to work ($p<0.001$). For example, the prevalence in those who were employed was 65% (95% CI 62% - 67%), for those who were unemployed it was 39% (95% CI 35% - 43%) and for those unable to work it was 2% (95% CI 1% - 5%). This latter category contained only five individuals.

The prevalence of activity limitation resilience was similar between the alcohol consumption groups ($p=0.552$). It was higher in those who never smoked compared to those who were current smokers (57% [95% CI 54% - 60%] versus 48% [95% CI 43%- 53%] respectively). This was statistically significant ($p<0.001$).

7.7 The association between primary care mental health conditions and resilience

The role of mental health conditions in the prevalence of SRH resilience is shown in Table 34. The prevalence of SRH resilience was higher in those with no mental health conditions (97% [95% CI 96% - 98%]) and lower in those with one or two mental health conditions (for example it was 92% [95% CI 90% - 94%] for those with two conditions). The association between SRH resilience and the number of mental health conditions was statistically significant ($p<0.001$).

Table 34: Diamond: prevalence of self-reported health resilience in those with primary care multimorbidity by number of mental health conditions

Number of mental health conditions	Total	Resilient		
		N	%	95% CI
Zero	1,363	1,319	96.8	95.8 -97.7
One	681	649	95.3	93.7-96.9
Two	824	756	91.8	89.9-93.6
Total	2,868	2,724	95.0	94.1 -95.7

Abbreviations: N, number; 95% CI, 95% confidence interval
*Model assessing association between number of mental health conditions and resilience using CHI squared test for trend was statistically significant, p<0.001

The role of mental health conditions in the prevalence of SRH resilience, split by gender, is in Table 35. In men with no mental health conditions the prevalence was 96% (95% CI 93% - 97%) and for those with two conditions the prevalence was 90% (95% CI 85% - 93%). The association between resilience and the number of mental health conditions in males was statistically significant (p=0.007). For women, the prevalence was 98% (95% CI 96% - 98%) in those with no co-existing mental health condition and 93% (95% CI 90% - 95%) in those with two. The association between resilience and the number of mental health conditions in females was also statistically significant (p<0.001).

Table 35: Diamond: prevalence of self-reported health resilience in those with primary care multimorbidity by number of mental health conditions, sub-group analysis by gender

Number of mental health conditions	Male*				Female**			
	Total	Resilient			Total	Resilient		
		N	%	95% CI		N	%	95% CI
Zero	530	506	95.5	93.4-96.9	831	811	97.6	96.3-98.4
One	205	191	93.2	88.9 -95.9	474	456	96.2	94.1-97.6
Two	224	200	89.3	84.6- 92.7	599	555	92.7	90.3- 94.5
Total	959	897	93.5	91.8- 94.9	1,904	1,822	95.7	94.7-96.2

Abbreviations: N, number; 95% CI, 95% confidence interval
*Model assessing association between number of mental health conditions and resilience in males, using CHI squared test for trend was statistically significant, p=0.007
*Model assessing association between number of mental health conditions and resilience in females, using CHI squared test for trend was statistically significant, p<0.001

The prevalence of activity limitation resilience by the number of mental health conditions is presented in Table 36. The association between the two was not statistically significant (p=0.386). For those with no mental health condition the overall prevalence was 52% (95% CI 50%- 55%), for those with one condition it was 53% (95% CI 50% - 57%) and for two co-existing mental health conditions it was 51% (95% CI 47% - 54%).

Table 36: Diamond: prevalence of activity limitation resilience in those with primary care multimorbidity by number of mental health conditions

Number of mental health conditions	All*			
	Total	Resilient		
		N	%	95% CI
Zero	1,346	697	51.8	49.1-54.5
One	676	360	53.3	49.5-57.0
Two	824	416	50.5	47.1-53.9
Total	2,846	1,473	51.8	49.9-53.6

Abbreviations: N, number; 95% CI, 95% confidence interval
*Model assessing association between number of mental health conditions and resilience using CHI squared test for trend was not statistically significant, p=0.386

The relationship by gender is in Table 37. As described previously, the prevalence of activity limitation resilience was higher in women (59%) compared to men (38%). In men there was a decrease in resilience prevalence from those with no mental health condition through to those with two. For example, the prevalence in those with no mental health condition was 42% (95% CI 37% - 46%) and for those with two it was 29% (95% CI 24% - 36%). There was a statistically significant association between resilience and the number of mental health conditions in men (p=0.006), however confidence intervals were wide. In women, the prevalence of resilience was almost identical from zero to two conditions (for example 58% for none, 59% for one and 59% for two). There was no statistically significant association (p=0.987).

Table 37: Diamond: prevalence of activity limitation resilience in those with primary care multimorbidity by number of mental health conditions, sub-group analysis by gender

Number of mental health conditions	Male*				Female**			
		Resilient				Resilient		
	Total	N	%	95% CI	Total	N	%	95% CI
Zero	523	217	41.5	37.4- 45.8	821	479	58.3	54.9-61.7
One	201	80	39.8	33.3-46.7	473	278	58.8	54.3-63.1
Two	228	67	29.4	23.9-35.6	595	349	58.7	54.7-62.5
Total	952	364	38.2	35.2-41.4	1,889	1,106	58.6	56.3-60.8

Abbreviations: N, number; 95% CI, 95% confidence interval
*Model assessing association between number of mental health conditions and resilience in males, using CHI squared test for trend was statistically significant, p=0.006
**Model assessing association between number of mental health conditions and resilience in females, using CHI squared test for trend was not statistically significant, p=0.987

7.8 Discussion

7.8.1 Summary of findings

The Diamond study population amounted to 7,667 individuals, of whom two-thirds were female and the median age was 51. The population size for analysis was 7,620 due to missing data amongst the self-reported morbidity variables.

Out of 12 physical conditions and 2 mental health conditions, the most common condition reported was “back problems” and the least common was “stroke”. The prevalence of mental health conditions was higher in women compared to men. The prevalence of primary care multimorbidity was 38%. The prevalence rose with increasing age. It was lower in those with higher educational attainment and lower in those who were employed or studying compared to those not working. I found no association between hazardous levels of alcohol consumption and primary care multimorbidity but I found that the prevalence was higher in those who smoked compared to those who had never smoked.

An increasing number of physical conditions was associated with an increased likelihood of having a mental health condition. In those with physical condition primary care

multimorbidity, men were slightly more likely than women to report no co-existing mental health condition.

The prevalence of fair to excellent SRH and of having no activity limitation was statistically significantly lower in those with primary care multimorbidity, however differences in proportions were small for SRH resilience. When limited to the population with primary care multimorbidity, the prevalence of SRH resilience was 95% and did not significantly differ by age or alcohol consumption level. The prevalence was higher in women compared to men, but although this was statistically significant the actual difference was small. The prevalence of SRH resilience was higher in those who had higher educational attainment and who were employed or studying compared to not working. Resilience levels were lower in smokers compared to non-smokers.

The prevalence of activity limitation resilience to primary care multimorbidity was 52%. This was significantly lower in men compared to women and in older age groups compared to young. The prevalence of resilience was higher in those with higher educational attainment and those employed, studying or undertaking home duties. It was significantly lower for those who were unemployed and vastly lower for those unable to work. Activity limitation resilience prevalence was not influenced by alcohol consumption levels but it was lower in smokers compared to non-smokers.

The prevalence of SRH resilience was higher in those with no mental health conditions compared to those with both. The prevalence of activity limitation resilience was not statistically significantly associated with the number of mental health conditions. However, for men only, there was a decrease in prevalence between zero and two conditions (although confidence intervals were wide).

7.8.2 Interpretation of findings and relation to wider literature

Study population characteristics

As described in the Methodology, the Diamond screening sample was the first stage in developing the Diamond longitudinal study (which is limited to those with depression

symptoms in general practice).[202] The study team conducted a pilot study which estimated a response rate of 50%, however, the overall survey response rate was 43%. It is hypothesised that this was because the pilot practices were in rural areas and there was lower motivation to respond from participants in larger urban settings (source: email correspondence with Diamond study team, June 2017). In the literature, a response rate of 60% is often quoted as being an ideal minimum response rate, although there is little evidence assessing the validity of this.[258] The lower response rate in Diamond may be seen as a limitation but is also consistent with a number of other well-conducted primary care studies.[259,260]

Patients were invited to participate if they had seen the study GP in the previous year. These invites were not stratified by population characteristics. However, Diamond study organisers have found the sample characteristics to be reasonably representative of the general primary care population from which they were sourced.[202] For example the predominance of older participants participating reflects the fact that individuals are more likely to see a GP as they age.[261]

In Diamond, selection bias may have occurred at the point of recruiting GPs and in terms of which patients agree to participate. With regards to GP recruitment, it is acknowledged that as only GPs seeing at least 600 patients per year were included this would have biased the sample towards those working full-time (which was predominantly men).[202] The mean age of responders, compared to those were invited, was higher by 5 years. Although other studies find that older age groups are less likely to respond,[262,263] in this case the mean age was still reflective of a middle aged population. Women were more likely to respond than men. These patterns are consistent with other research using surveys.[262,263]

The study population characteristic variables illustrate the SES of individuals and the presence of disease risk factors (alcohol and smoking). Variables are self-reported and thus are at risk of social desirability bias. Social desirability bias in this study may be less as participants completed the questionnaire themselves rather than being asked by an interviewer. Nevertheless, it is feasible that Diamond participants have under-reported levels of smoking and alcohol for example.

The education variable may be affected by the age range of participants. Some younger participants may not have completed education. Given the small number of participants aged under 25 (4% in total) this is unlikely to have had a significant impact on the results. The large proportion of female respondents in the employment category containing maternity leave is unsurprising given that this is specific to women.

The fact that the morbidity and resilience questions were in the same questionnaire is important as it risks "common methods bias". This describes where the process of sourcing data in the same way introduces bias.[264] For example, evidence shows the ascertainment of two potentially related self-reported factors in one questionnaire can lead to spuriously high correlations.[265] The order of items can also influence the manner of response.[265] In Diamond, individuals were asked regarding the morbidities before the resilience questions. This may "prompt" them to rate their health lower or respond yes to having a condition causing activity limitation.

Morbidities and primary care multimorbidity

The prevalence assessment of morbidities in the Diamond is a "period prevalence" over 12 months. As described in Chapter 1 a period prevalence is superior to a point prevalence. It is still possible that episodic conditions (those which are not always active) are under-estimated. Of note, both depression and anxiety may be episodic in nature whilst the majority of the physical conditions in Diamond (such as stroke and heart disease) are likely to be chronic. [266,267] There was an option to use a measure in which participants were asked if they "ever" had one of the conditions. However, depression and anxiety are also conditions which can have few or no re-occurrences after a first episode[268] and so assessing them on this basis may have over-estimated their prevalence. On balance, I decided to use the same 12 month measure for all conditions for consistency.

Patients were invited to participate in Diamond if they had seen the study GP in the previous year. As a result, I am explicit that my measure of multimorbidity is a primary care measure. The prevalence of morbidities amongst the general population, not selected on the basis of recent healthcare use, would likely be lower.

When individuals were asked to report the conditions, they were not asked if they had been clinically diagnosed. Therefore this measure will include a degree of the subjective experience of illness and may capture a higher burden of certain diseases than would be seen in the clinical record. For example, Hansen *et al*, in their study of agreement between individuals and GP reported chronic conditions found that agreement was better for conditions such as Diabetes Mellitus where diagnosis and treatment are well-defined and require clinician input. On the other hand conditions such as dizziness which are more complex to diagnose clinically and indeed which may not require clinical diagnosis showed poor agreement.[131] It is possible that the category of "back pain" in Diamond may show higher prevalence than would be reflected by clinical record as this may include some conditions which are responsive to self-management.[269]

The self-report of health conditions may be affected by both selection bias and social desirability bias. Those who choose to participate may have less severe disease than those who do not. Additionally, individuals were not eligible for invitation to the Diamond study if they were terminally ill or resided in a nursing home and so this would reduce the detection of some serious conditions. Indeed, the least frequently reported conditions were heart disease, cancer, emphysema and stroke, all of which are known to have the potential for serious sequelae. Similarly, participants aged over 75 were not included. The severity and frequency of health conditions increases with age.[31] Therefore the prevalence of morbidities would be higher.

The fact that participants were asked to consider whether the condition happened within the previous 12 months improves the accuracy of recall. Additionally, gender differences in morbidity prevalence are consistent with wider trends which provides reassurance that bias is not significantly affecting the results. For example a review of nationally representative UK datasets on cardiovascular disease in 2014 found conditions such as myocardial infarction were almost 3 times more common in men.[270] In Diamond, the prevalence of heart disease in women was 2% and in men was 6%. Similarly, the findings of a higher prevalence of emphysema in men compared to women is consistent with trends in other studies and is related to the fact smoking prevalence (an important risk factor for

both this and heart disease) was historically higher in men.[271] Indeed, whilst proportions of current smokers were comparable between the genders in Diamond, the prevalence of ex-smokers was much higher in men.

For both men and women the presence of mental ill-health may be under-reported. As I described in Chapter 1, mental health conditions are more likely to be subject to social desirability bias than physical health conditions due to stigma.[105,272] Additionally, men are less likely to seek medical attention for symptoms of mental ill-health than women.[104,105] The prevalence of mental health conditions was lower in men compared to women in this study which may reflect this. Furthermore, the prevalence of hazardous alcohol consumption was higher in men compared to women (25% compared to 12% respectively). Men may be more likely to use alcohol or other substances to alleviate symptoms of depression or other disorders rather than seek medical help.[104] Given all these factors, it may be that in those men who *have* reported mental health conditions the condition is more serious and disabling.

The median age at the time of reporting conditions also follows expected trends. Of note the median age does not reflect the age of onset of the conditions, but conditions more prevalent at younger ages would be expected to have a lower median age. It is therefore reassuring that conditions which are frequently diagnosed in childhood or early adulthood such as asthma and dermatitis have lower median age.[273,274] Conditions more commonly appearing in older age (such as heart disease and stroke)[270] have a higher median age.

Almost 40% of the population had primary care multimorbidity. The systematic review of observational studies in primary care carried out by Violan and colleagues, described in Chapter 1, found a multimorbidity prevalence ranging from 13% to 95%.[51] However, none of the included studies defined and measured multimorbidity in a manner similar enough to this study to compare directly. The main reasons studies were not comparable was that most used routine data and many restricted the population of interest to older adults (frequently 65 years or older).

In Fortin's review of prevalence studies of multimorbidity, there were 8 studies concentrating upon primary care with the prevalence ranging from 4% to 99%. Of these studies, 7 were sourced from medical records and one combined patient interview with medical chart review.[26] The study by Barnett *et al* included 40 conditions sourced from primary care databases and their prevalence was 23%.[2]

My literature reviews in Chapter 3 identified no other studies comparable to the Diamond study. For example, the study by Hansen *et al* of primary care patients was limited to those aged 65 to 85 with existing multimorbidity.[131] The study by Salisbury *et al* of English primary care patients sourced data using administrative sources. Their prevalence of multimorbidity ranged from 16% to 58% using a QOF measure and a Johns Hopkins measure respectively.[67]

The analysis in this chapter was cross-sectional and so I cannot confirm the direction of associations between variables and the prevalence of primary care multimorbidity. However, there are reasonable assumptions which can be made. Firstly, the association between age and multimorbidity is highly consistent with previous research.[31,51] I have described this in Chapter 1. The trend for increasing multimorbidity prevalence with lower educational attainment and a lack of employment is also consistent with evidence.[31,51] Additionally, the category of being "unable to work" due to health will inevitably contain individuals who have illness and therefore are more likely to contain a higher number of people with multimorbidity.

Evidence shows that higher levels of alcohol consumption lead to poorer health.[215] Therefore the lack of an association with multimorbidity is surprising. This may reflect "social desirability bias" as described in the previous section or may reflect the nature of the variable. The dichotomous split between "hazardous" and "non-hazardous" may not be sensitive enough to demonstrate the link. For example, a measure which also included a higher category ("harmful") and a lower category ("no alcohol") may detect an association.

There was an association between smoking and the prevalence of primary care multimorbidity in a direction consistent with the known harmful effects of smoking on health.[216] The relatively high prevalence of multimorbidity in ex-smokers may however be due to those who develop multimorbidity choosing to give up smoking.

The association between mental health conditions and physical disease is consistent with previous research.[2,175,275] In this cross-sectional analysis I cannot show the direction of the relationship, although, as described in Chapter 1, it is likely bidirectional.[12,13] The presence of a mental health condition may lead to physical disease due to factors such as maladaptive health risk behaviours and the physiological effects of the condition, whilst the impact of the burden of a physical disease (for example due to pain or loss of ability to do valued activities) may cause or worsen a mental health condition.[12,13] The findings in the chapter are therefore supportive of criticism of the Cartesian mind-body dualism approach to medicine. A further reason why this association is important is that it is associated with poorer outcomes.[276,277] For example, a large survey found evidence that when depression co-exists with a physical disease it leads to worse health outcomes than any combination of physical diseases without depression.[277]

In the time since I designed and conducted my work, a systematic review and meta-analysis was conducted by Read *et al* to investigate the relationship between multimorbidity and depression. The authors included 40 studies and found that depression was two times higher in those with multimorbidity compared to without. They also found evidence that an increasing number of physical conditions was associated with depression which is consistent with my findings.[278] A study by Vancampfort and colleagues analysed cross-sectional data from the World Health Survey which covered 70 countries. The data included self-report of 9 physical conditions and of anxiety. The study had similar findings to mine in that an increasing number of physical conditions was associated with an increased likelihood of the presence of anxiety.[279]

Resilience to primary care multimorbidity

With regards to resilience, a first important finding is the difference in resilience prevalence between my two measures. This supports the conclusion in my systematic review in Chapter 5 that individuals may not experience resilience across all domains.[159] The SRH measure reflects "overall health and wellbeing" whilst the activity limitation measure demonstrated how much the adversity impacts on the ability to conduct daily activities.

The reason the prevalence of activity limitation resilience is lower than SRH resilience could be due to differences in the nature of the questions. Individuals were asked about general health in SRH ("in *general*, would you say your health is…") with no reference to having disease. Whereas, in the activity limitation measure, individuals were asked to consider if they had an illness or health problem which limited activities. This, when combined with being asked to select from a list of 14 health conditions, may prompt individuals with primary care multimorbidity to respond yes.

The prevalence of SRH resilience to primary care multimorbidity did not vary greatly by gender (although the p-value was statistically significant), however activity limitation resilience prevalence was significantly lower in men. This could be due to a number of factors. The first could be that many of the more severe health conditions reported in Diamond, for example emphysema, are more common in men and conferring greater disability. Thus men may not have a truly lower prevalence of activity limitation resilience but are being more affected by the severity of multimorbidity (in other words the nature of the adversity may not be comparable between the genders). If this is the case, the finding of no significant difference in SRH prevalence between the genders is interesting. If we hypothesise men have more severe adversity than women then they may be in fact demonstrating a *higher* level of SRH resilience than women.

A different explanation could be gender differences in other parts of life. For example, men frequently make up the majority of manual occupations. These have higher physical demands and additionally such jobs often have less employment stability and individuals have less control over the nature work of undertaken. Both physical exposures and the

psychosocial impact of low job control have been shown to lead to an increased likelihood of requiring a disability pension.[280] In other words the impact of having an illness makes it more difficult for these individuals to continue to participate in work and so the illness is seen as having a greater limitation on daily activities.

For both measures of resilience, the prevalence was lower in those with lower educational attainment and those who were unemployed or unable to work. Resilience prevalence was lower in smokers compared to non-smokers. As I described in Chapter 5, resilience is an adaptive process which can change over time and which is related to both internal and external factors.[84] These findings are therefore consistent with much evidence showing that resilience (to any adversity) is lower in those with lower SES.[92,93,95] Additionally, the association with smoking may relate to the increased likelihood of disabling diseases such as emphysema and heart disease which means the nature of the adversity is more severe. The lack of an association with alcohol could once again reflect social desirability bias or the nature of the variable categories.

For SRH resilience there was an association with the number of mental health conditions, although the differences were small. This remained when conducting sub-group analysis by gender. Whilst there was no overall association between activity limitation resilience and the number of mental health conditions, there was an association when conducting sub-group analysis by gender for men only.

Mental health conditions may influence the prevalence of resilience to primary care multimorbidity in a number of ways. Firstly, the symptom profile of depression and anxiety may have more of an impact on the reporting of resilience than that of physical health conditions. For example, symptoms of low self-esteem, low energy levels and lack of enjoyment may mean an individual is less likely to respond favourably to the resilience questions.[281] Similarly, as described above, there is evidence individuals with depression have a greater likelihood of negative outcomes than do those with physical conditions. A study by Noel *et al* found this was the case for outcomes including self-reported quality of life and disability.[276] Finally, as described in Chapter 1 a large proportion of mental health conditions may be caused by wider social, economic and environmental determinants of

health. [16] What may be being observed is the impact of *these* factors upon an individual's resilience.

7.8.3 Strengths and limitations

This study population provides important insights regarding the prevalence of multimorbidity in primary care and the impact of mental health upon both the presence of primary care multimorbidity and resilience to primary care multimorbidity.

The confirmation that the prevalence values of morbidities vary by age and gender in ways consistent with the wider population, provides reassurance that selection bias and social desirability bias are no more pronounced here than in other well-conducted studies.

Due to the cross-sectional nature of the work, care has to be taken when drawing conclusions about the direction of causality. I have been careful to interpret my findings as such. An important Bradford-Hill criterion is that cause precedes effect.[282] This is difficult to show in a cross-sectional study. However, I can demonstrate that my results are plausible and are consistent with existing knowledge. Nonetheless, longitudinal study of relationships found in this chapter (in particular the relationship between mental health conditions, resilience and wider determinants of health) are recommended next steps.

As I described in Chapter 1, making a distinction between mental health conditions and physical health conditions can be criticised for being over-simplistic. I chose to distinguish between these on the basis that not only are they treated separately in WHO disease classifications but they are managed separately in most healthcare systems. A further important consideration is that those conditions categorised as being mental health conditions are more likely to be subject to stigma which can worsen their impact upon individuals. They are also under-studied in multimorbidity, and depression is a leading cause of disease burden. [99,100]

Depression and anxiety are known to be highly comorbid with each other and have overlapping symptoms such as poor appetite, disturbed sleep and fatigue.[283] This means my treatment of these as two separate disorders could be challenged. However, in the

context of this study, patients were asked to self-report regarding each condition indicating that, from the patient's perspective, those who reported having both depression and anxiety were experiencing two distinct conditions. Therefore those individuals who report having two, rather than one, condition are those which are likely to have a greater burden of disease.

Depression and anxiety are the two mental health conditions most commonly seen in primary care.[284] I acknowledge that other mental health conditions such as schizophrenia have serious impact on individuals and are more likely to be seen in secondary care.[284] However, these conditions are relatively rare amongst a primary care population and so using depression and anxiety is reasonable.

Truer assessment of the prevalence of these common mental health conditions may also be improved by incorporating assessment of symptoms of illness. In Diamond, participants were administered surveys of depressive symptoms. I chose to use only those directly self-reported conditions in my assessment of mental health so that all included morbidities would be based on patient self-report. However, future research could test the impact of supplementing the assessment of mental ill-health by including this extra information.

8 ACONF cohort characteristics

8.1 Structure of chapter

Please see "additional declaration" on page *xvi* for information regarding section 8.5. In this chapter I describe the baseline characteristics of the ACONF study population. I start the chapter by describing the historical context of the cohort. I then present the characteristics for the entire 12,150 individuals. I then describe the Original ACONF and follow this with the 2001 and 2016 Enhanced ACONF populations.

8.2 Cohort historical and contemporary environment

The ACONF is a complete population cohort of individuals living in the city of Aberdeen during a defined period of time. Around two-thirds of the Scottish based population still live in Aberdeen or in the wider Grampian region which incorporates Aberdeen (source: email correspondence with ACONF study coordinator Heather Clark, October 2017).

This relatively high degree of geographical stability may be explained by a number of factors. Historically, across the UK and Europe, there was little migration of individuals from communities. The majority of individuals would work and raise families in locations close to where they grew up.[285] In addition to this were favourable employment prospects in Aberdeen. This is due to the development of the oil and gas industry. North Sea oil fields were discovered in 1969, coinciding with the time many of the ACONF participants were entering employment with the opportunity to earn a higher than average income compared to the rest of Scotland and the UK.[218] Although traditionally, manual jobs offered lower incomes than professional, in Aberdeen wages were higher than national averages across all employment categories.[286]

The oil industry had additional impacts in supporting local businesses such as the hospitality industry. The population of Grampian (the wider region which incorporates Aberdeen)

increased as individuals moved into the area to take advantage of employment opportunities and so public services such as the NHS expanded bringing further employment.[287] Therefore, even though many oil industry jobs were predominantly employing men and men achieved higher incomes, women also had opportunities for employment.[288]

However, the oil industry has brought many challenges to Aberdeen. There have been periods of economic instability leading to unemployment and associated impacts on allied businesses.[287] Rapid cycles between economic "boom and bust" have been linked to poorer mental and physical health in those involved. Job insecurity in particular is detrimental to mental health, and the protective effects of higher incomes are lessened.[286,289]

The wealth of Aberdeen has placed a high cost of living which has been detrimental to many residents.[290] Whilst the average wealth of Grampian is higher than many parts of Scotland and the UK, there are stark inequalities. Those who are unable to access the high wages of oil industry jobs are often marginalised, living in poorer quality housing and with lower levels of health and wellbeing.[286]

For those working in the industry there are pressures of a non-traditional manner of working. Many work for long periods away from home (for example "off-shore" on oil rigs) and then return for equally long rest periods. There is evidence to suggest that this has a detrimental impact on some.[291,292] Reasons include the fact that many individuals (traditionally men) cycle between periods of alcohol abstinence "off-shore" and heavy alcohol use whilst "on-shore".[293] Family lives undergo frequent periods of disruption and the inability to establish a routine, which is also linked to poorer health.[291]

However, a comparison study of "off-shore" compared to "on-shore" workers found self-reported health lower in the latter. This study highlighted that the extensive and regular medical checks required to be allowed to work off-shore meant the population represents a highly selected healthy occupational group.[292] Therefore assessing the impact of the oil industry on health and wellbeing of workers and their families is complex.

8.3 Entire cohort

The baseline data for the 12,150 cohort members is in Table 38.

Table 38: Entire ACONF population: baseline characteristics (n=12,150)*

	All (n=12,150)		Male (n= 6,276)		Female (n=5,874)	
Characteristic	**Total**	**%**	**Total**	**%**	**Total**	**%**
Mean age 1st Dec 1962 (years)	8.8 (SD 1.5)	Range 5.8 -12.0	8.8 (SD 1.5)	Range 6.1-11.9	8.8 (SD 1.5)	Range 5.8-11.9
Social class of the father at birth of the participant						
I/II (Professional/ Managerial)	1163	9.6	615	9.8	548	9.3
III (Skilled non-manual)	1335	11.0	689	11.0	646	11.0
III (Skilled manual)	5320	43.8	2,718	43.3	2,602	44.3
IV (Partly skilled)	1689	13.9	887	14.1	802	13.7
V (Unskilled)	1963	16.2	1,034	16.5	929	15.8
Unemployed/ unknown/disabled/ dead	680	5.6	333	5.3	347	5.9
Mean cognition score age 7	Mean 107.1 (SD 16.4)	Range 49 - 166	106.7 (SD 16.3)	Range 50 -153	107.4 (SD 16.5)	Range 49 - 166

Abbreviations: SD, standard deviation; ACONF, Aberdeen Children of the 1950s
*Figures presented are numbers and proportions unless stated otherwise.

The mean age of participants in December 1962 was 9 years old (SD 1.5, range 6 to 12 years). The majority at birth had fathers in social class group III- skilled manual (44% for all participants and comparable between the genders). The mean cognition score at age 7 was 107 and was comparable between genders.

Table 39 shows the person years at risk, the number of deaths and the mortality rate for the cohort. Overall the cohort contributed 364,683 person years at risk with 1,108 deaths occurring by 30th September 2016. The mortality incidence rate per 1,000 person years was 3.0 (95% CI 2.9 -3.2) and it increased over time. For example between 1981 to 1985, when the cohort were aged between 25 to 31 at baseline, the rate was 0.9 per 1,000 person years (95% CI 0.7-1.3) and between 2011 to 2016, when the cohort was aged between 55 and 61 at baseline, the rate was 7 per 1,000 person years (95% CI 7 -8).

Table 39: Entire ACONF population: number of deaths and death rate in ACONF from 1981 to 2016

Time period from 1981	Person-years at risk	Deaths	Death rate/ 1,000 person years	95% CI	Age range at beginning of time period*
1981- 2016	364,683	1108	3.04	2.86-3.22	25-31
Categories of years from 1981					
1981-1985	52,586	50	0.95	0.72-1.25	25 –31
1986-1990	52,354	48	0.92	0.69-1.22	30-36
1991-1995	52,060	72	1.38	1.10-1.74	35-41
1996-2000	51,588	121	2.35	1.96-2.8	40- 46
2001-2005	50,828	179	3.52	3.04-4.08	45-51
2006-2010	49,819	238	4.78	4.21-5.42	50 -56
2011-2016	55,445	400	7.21	6.54-7.96	55-61

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
* Note range refers to the spread of age within the cohort at the start of the time period and not the change in age over the time period

8.4 Original ACONF

The characteristics of responders to the ACONF postal questionnaire compared to all those invited are presented in Table 40. Of 11,282 mailed individuals, 7,184 (64%) responded. Females had a higher response rate (68%) compared to males (60%). The mean age of the cohort and of the responders in May 2001 was 48 years (SD 1.5). The response rate was higher for those with a higher paternal social class at birth (for example 73% for those in social class I/II and 58% for those in social class V). Mean cognition scores were higher in responders (110, SD 15.8) compared to the population mailed (107, SD 16.3) and the distribution was not normally distributed in non-responders (histogram not shown). As a result I present cognition scores by quintiles in analysis of the Original ACONF.

When examining response by gender, it can be seen that women in a higher social class at birth were even more likely than men to respond (78% of women in social class I/II responded compared to 70% men for example). There was no difference in response rate for gender by mean cognition score or age.

Table 40: Original ACONF: postal questionnaire response rate by early life factors and age at questionnaire (baseline n=11,282 mailed responders, total responders =7,184)*

Characteristic	Total mailed	Number responding	Response rate (%)	Response in males (n=5,735)		Response in females (n=5,547)	
				Number responding	Response rate (%)	Number responding	Response rate (%)
Total	11,282	7,184	63.7		-		-
Gender							
Male	5,735	3,430	59.8		-		-
Female	5,547	3,754	67.7		-		-
Mean Age May 2001**	48.1 (SD 1.5) Range 45-51	48.2 (SD 1.5) Range 45 -51		48.3 (SD 1.5) Range 45 -51		48.2 (SD 1.5) Range 45 -51	
Social class of the father at birth of the participant							
I/II (Professional/ Managerial)	1,076	789	73.3	388	69.3	401	77.7
III (Skilled non-manual)	1,246	869	69.7	415	65.7	454	73.9
III (Skilled manual)	4,928	3,154	64.0	1482	59.7	1672	68.4
IV (Partly skilled)	1,581	976	61.7	482	58.5	494	65.3
V (Unskilled)	1,817	1,048	57.7	503	53.7	545	61.9
Unemployed/ unknown/disabled/ dead	634	348	54.9	160	53.3	188	56.5
Mean Cognition score age 7**	107.2 (SD 16.3)	109.5 (SD 15.8)		109.7 (SD 15.9)		109.2 (SD 15.7)	

Abbreviations: SD, standard deviation; ACONF, Aberdeen Children of the 1950s
*Figures presented are numbers and proportions unless stated otherwise **Values presented are mean of all mailed, then mean of responders

The study population characteristics of the questionnaire responders (i.e. the Original ACONF) are shown in Table 41. Of 7,184 responders, 52% were female and both males and females had a mean age of 48 (SD 1.5). The majority of participant's fathers were in social class III (skilled manual) at the birth of the participant (44%) and this was comparable between men and women. Cognition scores are presented by quintiles due to non-normal distribution. There were 633 men (19%) in quintile "50 -95" compared to 636 women (17%). There were 698 men (20%) in quintile "123-153" compared to 782 women (21%).

The majority of participants (66%) attended a non-elite school and this was comparable between genders. "School leaving/no qualification" and "ordinary level qualification" were the two largest categories of educational attainment for both genders. A higher proportion

of men had either a “degree” or “non-degree tertiary education” (21% and 18% respectively for men, compared to 17% and 14% respectively for women).

The majority of participants were in paid work at the time of the questionnaire, this was higher for men (90%) compared to women (80%). More women were looking after family compared to men (9% versus 0.4%). The largest 2001 adult social class category for men was managerial/ professional (48%) and the largest for women was skilled non-manual (38%). The majority of women reported incomes of less than £20,000 annually (45% less than £10,000 and 31% less than £20,000). Men reported higher incomes and 23% were in the highest category (more than £40,000) compared to 4% of women.

The body mass index (BMI) was normally distributed and the mean BMI was comparable between men and women (26.5 overall, SD 4.8). The largest categories were normal weight (40%) and overweight (35%). Smoking rates were similar between genders with 27% being smokers. More men than women reported having a hangover at least once per week (3% versus 1%). More women than men reported no hangovers in the past year (50% versus 36%).

There were no missing data for gender, age and social class of the father at the birth of the participant. The proportion of missing data for cognition at age 7 was almost 4%, for school type it was almost 5% and for educational attainment it was 1.4%. Amongst the 2001 variables, missing data ranged from 0.3% (smoking status) to 7.5% (BMI).

Table 41: Original ACONF: Baseline characteristics of questionnaire responders, by gender (n=7,184)*

Characteristic	All n=7,184 Total	%	Male n=3,430 Total	%	Female n=3,754 Total	%
Total	7,184	100	-	-	-	-
Gender						
Male	3,430	47.7	-	-	-	-
Female	3,754	52.3	-	-	-	-
Mean age in May 2001	48.2	SD 1.5	48.3	SD: 1.5	48.2	SD 1.5
Social class of the father at birth of the participant						
I/II (Professional/ Managerial)	789	11.0	388	11.3	401	10.7
III (Skilled non-manual)	869	12.1	415	12.1	454	12.1
III (Skilled manual)	3,154	43.9	1,482	43.2	1,672	44.5
IV (Partly skilled)	976	13.6	482	14.1	494	13.2
V (Unskilled)	1,048	14.6	503	14.7	545	14.5
Unemployed/ unknown/ disabled/ dead	348	4.8	160	4.7	188	5.0
Cognition score age 7 (quintiles)						
50-95	1,269	17.7	633	18.5	636	16.9
96-105	1,445	20.1	701	20.4	744	19.8
106-112	1,277	17.8	622	18.1	655	17.5
113-122	1,453	20.2	695	20.3	758	20.2
123-153	1,480	20.6	698	20.4	782	20.8
Missing	260	3.6	81	2.4	179	4.8
School Type						
Non-elite	4,726	65.8	2,242	65.4	2,484	66.2
Elite	2,067	28.8	1,006	29.3	1,061	28.3
Other	56	0.8	20	0.6	36	1.0
Missing	335	4.7	162	4.7	173	4.6
Educational attainment						
Tertiary (degree)	1,374	19.1	734	21.4	640	17.1
Tertiary (non-degree)	1,138	15.8	624	18.2	514	13.7
Advanced level	926	12.9	494	14.4	432	11.5
Ordinary level	1,970	27.4	775	22.6	1,195	31.8
School leaving/none	1,676	23.3	757	22.1	919	24.5
Missing	100	1.4	46	1.3	54	1.4
2001 Adult Employment status						
Paid work	6,080	84.6	3069	89.5	3,011	80.2
Unemployed	198	2.8	111	3.2	87	2.3
Permanently sick	424	5.9	188	5.5	236	6.3
Retired from paid work	60	0.8	28	0.8	32	0.9
Looking after family	331	4.6	13	0.4	318	8.5
Full time student	28	0.4	8	0.2	20	0.5
Missing	63	0.9	13	0.4	50	1.3
2001 adult social class						
I/II (Professional/ Managerial)	2944	41.0	1631	47.6	1313	35.0
III (Skilled non-manual)	1,758	24.5	323	9.4	1,435	38.2
III (Skilled manual)	1,271	17.7	1,012	29.5	259	6.9
IV (Partly skilled)	745	10.4	286	8.3	459	12.2
V (Unskilled)	304	4.2	99	2.9	205	5.5
Missing	162	2.3	79	2.3	83	2.2

(contin. overleaf)

Characteristic	All n=7,184 Total	%	Male n=3,430 Total	%	Female n=3,754 Total	%
2001 adult annual income						
Less than £10,000	2,054	28.6	381	11.1	1,673	44.6
£10,000 to £19,999	2,032	28.3	863	25.2	1,169	31.1
£20,000 to £39,999	2,007	27.9	1,322	38.5	685	18.3
£40,000 or more	936	13.0	803	23.4	133	3.5
Missing	155	2.2	61	1.8	94	2.5
Mean 2001 adult body mass index	26.5	SD 4.8	26.8	SD 4.0	26.2	SD 5.3
2001 adult body mass index categories						
Underweight (<18.5)	53	0.7	13	0.4	40	1.1
Normal (18.5-24.9)	2,838	39.5	1,100	32.1	1,738	46.3
Overweight (25-29.9)	2,516	35.0	1,416	41.3	1,100	29.3
Obese Class 1 (30-34.9)	885	12.3	460	13.4	425	11.3
Obese Class 2 (35-39.9)	251	3.5	82	2.4	169	4.5
Obese Class 3 (40+)	105	1.5	25	0.7	80	2.1
Missing	536	7.5	334	9.7	202	5.4
2001 adult smoking status						
Current smoker	1,958	27.3	931	27.1	1,027	27.4
Ex-smoker	1,788	24.9	939	27.4	849	22.6
Non-smoker	3,420	47.6	1,552	45.3	1,868	49.8
Missing	18	0.3	8	0.2	10	0.3
2001 adult alcohol related hangovers in past year						
At least once a week	161	2.2	111	3.2	50	1.3
1-3 times a month	766	10.7	524	15.3	242	6.5
Less than once a month	2,688	37.4	1,407	41.0	1,281	34.1
Not at all in the last year	3,122	43.5	1,238	36.1	1,884	50.2
Missing	447	6.2	150	4.4	297	7.9

Abbreviations: SD, standard deviation; ACONF, Aberdeen Children of the 1950s
*Figures presented are numbers and proportions unless stated otherwise.

8.5 Enhanced ACONF

As described in the methodology in Chapter 6, I am considering two sub-sets of the Enhanced ACONF: a 2001 population and a 2016 population. These populations contained all those who were resident in Scotland at the time of the study AND CHI seeded. In Table 42 I have presented a comparison of the characteristics of all those known to be alive in 2001 with those who were CHI seeded. Of 10,852 individuals known to be alive, 8,438 (77.8%) were CHI seeded. The proportions were similar between men and women (77% compared to 79% respectively). The proportions of those CHI seeded by social class at birth were lowest in those whose social class at birth was professional/managerial (71%) or those

whose father was unemployed, unknown, disabled or dead (72%). The proportions were highest in groups III (skilled manual) and V (unskilled) at 79% and 82% respectively. The mean cognition score was comparable (107 for both). Of all those known to be alive, 6,961 had responded to the questionnaire in 2001 and of these 5,479 (79%) were successfully CHI seeded.

Table 42: Enhanced ACONF 2001: Comparison of characteristics of all known alive ACONF participants in 2001 to those who were CHI seeded and resident in Scotland in 2001

Characteristic	Total alive in 2001	Number CHI seeded and resident in Scotland in 2001	Rate (%)
Total	10,852	8,438	77.8
Gender			
Male	5,596	4,303	76.9
Female	5,256	4,135	78.7
Mean Age September 2001	47.8 (SD 1.5) Range 45 -51	47.8 (SD 1.5) Range 45 -51	
Social class of the father at birth of the participant			
I/II (Professional/ Managerial)	1,008	718	71.2
III (Skilled non-manual)	1,199	905	75.5
III (Skilled manual)	4,760	3,753	78.8
IV (Partly skilled)	1,533	1,189	77.6
V (Unskilled)	1,760	1,447	82.2
Unemployed/ unknown/disabled/dead	592	426	72.0
Mean Cognition score age 7	107.1 (SD 16.3)	106.6 (SD 16.2)	
Responded to postal questionnaire	6,961	5,479	79.0

Abbreviations: CHI, Community Health Index; SD, standard deviation; ACONF, Aberdeen Children of the 1950s

In Table 43 I have shown the comparison of characteristics of all those alive (9,548) compared to those CHI seeded (7,353) in the 2016 population. The rate of CHI seeding was similar to the 2001 population at 77%. The rate for men was 76% and for women it was 78%. The rate was lowest in social class at birth categories “professional/managerial” and father “unemployed, unknown, disabled or dead” (71% for each). The mean cognition score was 107 for both (SD 16) and of the 6,196 individuals who had responded to the questionnaire, 4,827 (78%) were CHI seeded.

Table 43: Enhanced ACONF 2016: Comparison of characteristics of all alive ACONF participants to those who were CHI seeded and resident in Scotland in 2016

Characteristic	Total alive	Number CHI seeded	Rate (%)
Total	9,548	7,353	77.0
Gender			
Male	4,869	3,700	76.0
Female	4,679	3,653	78.1
Mean Age September 2016	63.5 (SD 1.5) Range 60-66	63.5 (SD 1.5) Range 60-66	
Social class of the father at birth of the participant			
I/II (Professional/ Managerial)	891	636	71.4
III (Skilled non-manual)	1,054	786	74.6
III (Skilled manual)	4,233	3,300	78.0
IV (Partly skilled)	1,350	1,045	77.4
V (Unskilled)	1,506	1,221	81.1
Unemployed/ unknown/disabled/dead	514	365	71.0
Mean Cognition score age 7	107.2 (SD 16.3)	106.7 (SD 16.1)	
Responded to postal questionnaire	6,196	4,827	77.9

Abbreviations: CHI, Community Health Index; SD, standard deviation; ACONF, Aberdeen Children of the 1950s

The baseline characteristics of the Enhanced 2001 population, by gender are summarised in Table 44. Of 8,438 individuals, 4,303 (51%) were male and 4,135 (49%) were female. Almost 65% of the population had responded to the postal questionnaire and this was higher in women compared to men (69% of women compared to 61% of men respectively). The mean age at September 2001 was 48.

The majority of the population were in social class III (manual) at birth (45%). The cognition scores at age 7 were normally distributed and the mean was 107 (106 for men and 107 for women, SD 16). The majority of participants attended non-elite schools (45%). The largest educational attainment category was “ordinary level qualifications” (18%). In adulthood in 2001, the majority were in paid work (55%) and this was the same for the genders. For women the next highest proportion (not including missing data) was in the category “looking after family” (6%). For men the second highest proportion was “permanently sick” (3%).

Table 44: Enhanced ACONF 2001: Characteristics of population, by gender (n=8,438)*

Characteristic	All n=8,438 Total	%	Male n=4,303 Total	%	Female n=4,135 Total	%
Total	8,438	100				
Gender						
Male	4,303	51.0				
Female	4,135	49.0				
Responded to 2001 postal questionnaire	5,479	64.9	2,617	60.8	2,862	69.2
Mean age at September 2001	47.8 (SD 1.5)		47.8 (SD 1.4)		47.7 (SD 1.5)	
Social class of the father at birth of the participant						
I/II (Professional/ Managerial)	718	8.5	375	8.7	343	8.3
III (Skilled non-manual)	905	10.7	460	10.7	445	10.8
III (Skilled manual)	3,753	44.5	1,897	44.1	1,856	44.9
IV (Partly skilled)	1,189	14.1	631	14.7	558	13.5
V (Unskilled)	1,447	17.2	731	17.0	716	17.3
Unemployed/ unknown/disabled/dead	426	5.1	209	4.9	217	5.3
Mean cognition age 7	106.6 (SD 16.2)		106.3 (SD 16.1)		106.9 (SD 16.1)	
School Type						
Non-elite	3,770	44.7	1,785	41.5	1,985	48.0
Elite	1,472	17.4	721	16.8	751	18.2
Other	45	0.5	17	0.4	28	0.7
Missing	3,151	37.3	1,780	41.4	1,371	33.2
Educational attainment						
Tertiary (degree)	942	11.2	503	11.7	439	10.6
Tertiary (non-degree)	874	10.4	490	11.4	384	9.3
Advanced level	712	8.4	384	8.9	328	7.9
Ordinary level	1,529	18.1	615	14.3	914	22.1
School leaving/none	1,346	16.0	592	13.8	754	18.2
Missing	3,035	36.0	1,719	40.0	1,316	31.8
2001 adult Employment status						
Paid work	4,627	54.8	2,348	54.6	2,279	55.1
Unemployed	152	1.8	86	2.0	66	1.6
Permanently sick	334	4.0	139	3.2	195	4.7
Retired from paid work	39	0.5	21	0.5	18	0.4
Looking after family	255	3.0	8	0.2	247	6.0
Full time student	20	0.2	6	0.1	14	0.3
Missing	3,011	35.7	1,695	39.4	1,316	31.8
2001 adult social class						
I/II (Professional/ Managerial)	2,103	24.9	1,187	27.6	916	22.2
III (Skilled non-manual)	1,386	16.4	251	5.8	1,135	27.5
III (Skilled manual)	1,029	12.2	823	19.1	206	5.0
IV (Partly skilled)	571	6.8	216	5.0	355	8.6
V (Unskilled)	255	3.0	80	1.9	175	4.2
Missing	3,094	36.7	1,746	40.6	1,348	32.6
2001 adult annual income						
Less than £10,000	1,598	18.9	293	6.8	1,305	31.6
£10000 to £19,999	1,594	18.9	677	15.7	917	22.2
£20000 to £39999	1,494	17.7	1,029	23.9	465	11.3
£40000 or more	662	7.9	570	13.3	92	2.2
Missing	3,090	36.6	1,734	40.3	1,356	32.8
2001 mean adult body mass index	26.5 (SD 4.7)		26.8 (SD 3.9)		26.3 (SD 5.4)	

(contin. overleaf)

Characteristic	All n=8,438 Total	%	Male n=4,303 Total	%	Female n=4,135 Total	%
2001 adult body mass index categories						
Underweight (<18.5)	38	0.5	8	0.2	30	0.7
Normal (18.5-24.9)	2,130	25.2	838	19.5	1,292	31.3
Overweight (25-29.9)	1,944	23.0	1,085	25.2	859	20.8
Obese Class 1 (30-34.9)	695	8.2	365	8.5	330	8.0
Obese Class 2 (35-39.9)	189	2.2	56	1.3	133	3.2
Obese Class 3 (40+)	84	1.0	17	0.4	67	1.6
Missing	3,358	39.8	1,934	45.0	1,424	34.4
2001 adult smoking status						
Current smoker	1,496	17.7	718	16.7	778	18.8
Ex-smoker	1,367	16.2	711	16.5	656	15.9
Non-smoker	2,601	30.8	1,182	27.5	1,419	34.3
Missing	2,974	35.3	1,692	39.3	1,282	31.0
2001 adult alcohol related hangovers in past year						
At least once a week	124	1.5	86	2.0	38	0.9
1-3 times a month	604	7.1	422	9.8	182	4.4
Less than once a month	2,040	24.2	1,069	24.8	971	23.5
Not at all in the last year	2,368	28.1	931	21.6	1,437	34.8
Missing	3,302	39.1	1,795	41.7	1,507	36.4

Abbreviations: SD, standard deviation; ACONF, Aberdeen Children of the 1950s
*Figures presented are numbers and proportions unless stated otherwise.

The largest social class category in adulthood was I/II (professional/managerial) with 25%. For men this was the highest category but for women the highest category was III (skilled non-manual). Women were more likely to report incomes less than £10,000 per year than men (this was the largest category for women and the smallest category for men). Over 13% of men reported incomes of £40,000 or more annually. For women this was the smallest category (2.2%).

The mean BMI was not normally distributed. The largest categories were normal weight (25%) and overweight (23%). For women the largest category was “normal” (31%) and the second highest was “overweight” (21%). For men the highest category was “overweight” (25%) and the second highest was normal (20%). The largest smoking category was “non-smoker” (31%).

There were no missing data for gender, age or social class at birth. There were high proportions of missing data amongst the postal questionnaire variables ranging from 35%

(smoking status) to 40% (BMI). Missing data proportions were higher in men compared to women.

The baseline characteristics of the 2016 Enhanced ACONF population are shown in Appendix 2, Table 94 as the trends were comparable to those of the 2001 population. Of 7,353 individuals, 3,700 (50%) were male and 3,653 (50%) were female. The mean age was 66. Almost 66% of the population had responded to the postal questionnaire and this was higher in women compared to men (69% of women compared to 61% of men respectively). The remaining findings followed the same patterns as the 2001 population and there were almost identical proportions of missing data.

8.6 Discussion

8.6.1 Summary of findings

There were 12,150 individuals at baseline in the ACONF. The majority at birth had fathers in social class group III (manual) at birth and the mean cognition score at age 7 was 107. The mortality rate per 1,000 person years was 3.

Of 11,282 individuals invited to respond to the postal questionnaire, 7,184 (64%) responded. The response rate was higher in females, in those with a higher paternal social class at birth and in those with higher cognition scores at age 7. In the 7,184 individuals making up the Original ACONF, 52% were female and the mean age was 48. The majority of participant's fathers were in social class III (skilled manual) at the birth of the participant. "School leaving/no qualification" and "ordinary level qualification" were the two largest categories of educational attainment for both genders. The majority of participants were in paid work at the time of the questionnaire

When comparing all individuals known to be alive in 2001 to all those CHI seeded I found that 78% were CHI seeded. The proportion was 77% in the 2016 population. There were 8,438 individuals at baseline in the 2001 Enhanced population, 49% were female and the mean age was 48. There were 7,353 individuals at baseline in the Enhanced 2016

population, 50% were female and the mean age was 66 years. There were large proportions of missing data for questionnaire variables in the Enhanced populations.

8.6.2 Interpretation of findings

There was little difference in cognition score by gender in the entire cohort at baseline and this finding was mirrored in the Original and Enhanced ACONF populations. A study using a Scottish cohort who were born in 1921 with cognition testing at age 11 (using a test very similar to the ACONF population) had a comparable finding.[294] However, a review by Hedges and Nowell found research findings are not in consensus with regards to whether sex differences do exist in cognitive testing.[295] This provides support for including gender in my later models.

There is evidence of selection bias in the response to the ACONF postal questionnaire. As described in the previous chapter, a response rate of at least 60% is often advocated as "ideal" but there is no validation of this.[258] A review of survey responses in studies published in the medical literature found the mean response rate to be 60%.[296] The response rate to ACONF is therefore consistent with other studies.

The response rate was higher in women compared to men which is similar with patterns seen in other surveys (including Diamond).[262,263] There was little difference in mean age between responders and non-responders, which is expected given that the cohort age range is small (6 years). The response rate was higher in those whose fathers were in higher social classes compared to those in lower social classes. This socio-economically patterned response rate is highly consistent with the published literature.[297,298]

Responders had a higher mean cognition score at age 7 compared to non-responders. Wadsworth *et al* had a similar finding in their study of a 1946 British birth cohort, whereby continued participation in follow-up through life was lower in those with lower cognition scores measured at age 8.[298] They additionally found participation was lower in those in the most disadvantaged socio-economic circumstances in childhood. [298]

Another source of selection bias is differences between those who have been CHI seeded and those who have not and this relates to two levels of loss to follow-up: those who have migrated from Scotland and those who were known to be resident in Scotland but were not CHI seeded. Research into ACONF has found that those born into higher social classes were more likely to leave Scotland than those born into lower social classes. The authors of that study found that of those born into social class I (managerial), 50% remained in Grampian and of those born into social class V (unskilled) 85% remained in Grampian.[218] This finding is consistent with research in other populations showing that those who migrate are those with higher SES.[299,300] In my analysis I found that the rate of CHI seeding in all those known to be alive was lower in those born into the highest social class.

There are other reasons individuals cannot be CHI seeded. Evidence shows that those who have no fixed address, are from more socio-economically deprived areas, are from ethnic minorities and those not born in the UK are more likely to have "missed matches".[301] Thus there may be an under-representation of those from more deprived backgrounds and who still live in Scotland. I found that those at birth whose fathers were unemployed, disabled, unknown or dead had low proportions of CHI seeding.

Another issue for the Enhanced ACONF populations is that postal questionnaire data are only available for around 65%. This is expected given the overall response to the postal questionnaire was 64%. I have described missing data techniques in the Methodology and my reason for using CCA (with MICE as a sensitivity analysis) in the Original ACONF, and CCA only in the Enhanced ACONF.

The lack of a difference by gender for school type attended is unexpected. The literature supports that historically boys were more likely to access elite schools than girls.[302] Indeed, research conducted in ACONF found that boys were more likely to access private elite school education when they did not qualify for elite schools via the standard route at the time, as parents would choose to pay.[227] My finding may reflect the biased questionnaire response rate towards women and in particular women with a higher social class at birth. Those not responding to the questionnaire may have been more likely to attend non-elite schools.

However, consistent with expectations, men were more likely to have higher educational attainment than women. Men were also more likely to be in paid work and be in the highest adult social class. These factors are clearly linked and they reflect wider population trends at the time.[302] In the 1950s and 1960s there was still a greater expectation put on boys compared to girls to achieve higher levels of education. Gender stereotypes frequently dictated that young women would not pursue careers and would instead look after family.[302] Additionally even men in less skilled occupations than women may have higher income as men may be more likely than women to have highly paid oil and gas related occupations.[288]

As for Diamond, all questionnaire responses may be affected by social desirability and in particular rates of alcohol and smoking, and the value of BMI may be under-reported. There was a trend for men to report a higher BMI than women (with more falling into the overweight and obese categories). Research suggests that the BMI measure often over-estimates male body mass as men have more muscle mass (which is heavier than fat) than women on average.[303] Additionally, women may be more affected by cultural pressures to stay thin and may therefore under-report their true BMI due to social desirability bias.[304]

Smoking prevalence has been declining in the United Kingdom for decades and evidence shows it continues to decline. Men tend to have higher smoking rates than women,[305] although this was not observed in my results here. Men reported more hangovers than women which is comparable to wider population findings (particularly historically) that men consume more alcohol than women. Interestingly, research suggests that female alcohol consumption has begun to become comparable to men in recent years which may be due to women's employment opportunities becoming more equal to men's.[306]

8.6.3 Strengths and limitations of the ACONF study populations

A major strength of the ACONF cohort is that it has extensive contemporaneously collected early life data. It has an acceptable response rate to a mid-life questionnaire and those resident in Scotland can be linked to administrative data. These all provide huge advantages

when studying multimorbidity from a life-course perspective. However, the disadvantages must be acknowledged. An important issue is the lack of contemporaneously collected life-course information between childhood and mid-life and between mid-life and early older age. Data from mid-life is self-reported raising issues of bias as I have described earlier. The response to the postal questionnaire and the availability of linked data both contribute to selection bias.

A relatively stable cohort population brings advantages and disadvantages. An advantage is that it is possible to better assess how environmental and social and cultural changes over time have affected individuals. For this cohort, the oil and gas industry is a clear factor to account for, as is the relative lack of ethnic diversity. A disadvantage is that it could limit the generalisability of findings to the wider population. Generalisability of the cohort is an important issue and relates both to the fact the cohort is sourced from one specific geographical area and that it is a historical cohort. All historical cohorts are inevitably affected by the time in which individuals grew up. Therefore extrapolating finding such as mine to children growing up today needs to be carefully done.

Linked data were only available for 88% of Scottish ACONF residents. It is likely that those who leave Scotland have higher birth SES and it may be that those who remain were unable to leave due to poorer personal or family health. Those Scottish residents who have not been linked may have poorer adult SES (and related poorer health) than those who were linked. As I do not have access to variables which may explain both reasons why individuals have left Scotland (other than social class at birth), reasons why individuals have been lost to follow-up and reasons why individuals have not been CHI seeded, I have had to conduct CCA only. Whilst missing data are a limitation I have avoided the common pit-fall of using MICE without proper consideration of its potential to significantly increase bias. Despite this, the relative geographical stability of the population means linked data are available for more than two-thirds of those who could be traced.

I included missing data in my assessment of the baseline characteristics across the populations. The gender differences in the volume of missing data, particularly for the Enhanced ACONF, mean that findings need to be interpreted cautiously for the genders.

However, I did this as I am using CCA for the Enhanced populations and this highlights that missing questionnaire data is an important issue. In the main analysis of the Enhanced ACONF (Chapter 10) these missing data are not presented.

The lack of regular status updates on the cohort is a clear disadvantage. The status of the ACONF for the questionnaire was ascertained over the period of January 1999 to May 2001, as outlined in Chapter 6. It is possible that individuals identified early in that process had in fact died or moved by the time the questionnaire was sent.

The 2001 and 2016 Enhanced ACONF populations were developed on the basis of the postal questionnaire status and the 2013 status respectively. They were further updated using extra information available with regards to Scottish recorded deaths and admissions. This was the best possible approach. There will be updated ACONF status information available soon to researchers, but not to myself in the timescale of the PhD. Once again, the geographical stability of the population helps mitigate this disadvantage. I chose not to restrict follow-up to 2013 so as to make full use of the follow-up period given by the linked data.

There are some issues to note with the available variables. The income variable is problematic as the question was ambiguous regarding whether it is personal income or family income. The variable may be under-reporting income for some and over-reporting it for others, making it unreliable. I have included it in baseline characteristics but have not included it in my analysis models later. Adult social class and employment status are inevitably linked. Employment status is not a true ordinal categorical variable. As a result I only include adult social class in my analysis models but I do present employment status in baseline characteristics. Furthermore, the nature of the jobs individuals have is not known meaning it is not possible to ascertain who is employed in the oil and gas industry.

The measure of alcohol consumption was chosen as the best available option in the questionnaire and was consistent with others studying the ACONF cohort. However, it is unlikely to be a sensitive measure as it will likely detect more severe alcohol consumption

levels but not detect lower levels which may still have an impact on health. Furthermore, individuals with heavy alcohol consumption may in fact not experience hangovers.

9 Original ACONF

9.1 Structure of chapter

Please see "additional declaration" on page *xvi* for information regarding sections 9.6 and 9.8. In this chapter I describe the findings for objectives two to four in the Original ACONF population. I firstly analyse the prevalence of self-reported multimorbidity and its association with key population characteristics. Following this I show the relationship between social class at birth and population characteristics and outcomes. I then assess the relationship between social class at birth with self-reported multimorbidity and the role of educational attainment and other important covariates. I then illustrate the outcomes of self-reported multimorbidity. In the remainder of the chapter I present results of analysis of the prevalence, determinants and outcomes of resilience to self-reported multimorbidity. The resilience measures are: SRH, enjoyment, positive mood, negative mood and self-esteem resilience.

9.2 Prevalence of self-reported morbidities and multimorbidity

The frequency of self-reported condition categories is shown in Table 45. The most common condition categories were: "back problems" (4% of the study population), "arthritis, rheumatism or fibrositis" (3%) and "mental illness" (2%). There were 64 individuals with "unclassifiable" conditions. The least common categories were "bronchitis or emphysema" (seven individuals), "hayfever, varicose veins or piles/ haemorrhoids" (six individuals) and "blood disorders and associated disorders"(five individuals).

The prevalence of the number of self-reported conditions and the prevalence of self-reported multimorbidity is shown in

Table 46. Of 7,184 individuals, 83% (95% CI 82%–84%) reported no condition and of those who did report a condition the single largest group reported one (12%, 95% CI 11% – 13%). The prevalence of self-reported multimorbidity was 5% (95% CI 5% -6%).

Table 45: Original ACONF: Frequency of self-reported condition category ordered from highest to lowest (n=7,184)

Category	N	%	Category	N	%	Category	N	%
Back Problems	255	3.5	Heart attack/angina	51	0.7	Migraines/headaches	19	0.3
Arthritis/ rheumatism/ fibrositis	190	2.6	Hypertension	48	0.7	Kidney complaints	15	0.2
Mental illness	168	2.3	Other heart problems	44	0.6	Stroke	14	0.2
Problems of bone/joint/ muscles	161	2.2	Sight problems	39	0.5	Reproductive system	14	0.2
Asthma	131	1.8	Hearing and ear problems	32	0.4	Bladder problems	11	0.2
Other problems - nervous system	110	1.5	Epilepsy/ fits	30	0.4	Mental handicap	8	0.1
Complaints of bowel/colon	84	1.2	Upper intestine complaints	30	0.4	Infection/ parasitic disease	8	0.1
Endocrine /metabolic	69	1.0	Other blood vessels/ embolic	28	0.4	Bronchitis/ emphysema	7	0.1
Unclassifiable	64	0.9	Other respiratory complaints	28	0.4	Hayfever, Varicose veins, Piles/ haemorrhoids	6	0.1
Diabetes	60	0.8	Digestive system ulcer/ hernia	22	0.3	Blood disorders and associated	5	0.1
Cancer	59	0.8	Skin complaints	21	0.3			

Abbreviations: ACONF, Aberdeen Children of the 1950s; N, number

Table 46: Original ACONF: Number of self-reported conditions and prevalence of self-reported multimorbidity (n=7,184)

Morbidity status	Number	%	95 % CI
Number of conditions reported			
Zero	5,953	82.9	82.0 – 83.7
One	843	11.7	11.0 – 12.5
Two	255	3.6	3.1 – 4.0
Three	82	1.1	0.9 – 1.4
Four	32	0.5	0.3 – 0.6
Five or Six	19	0.3	0.1 – 0.4
Multimorbidity status			
No multimorbidity	6,796	94.6	94.1 – 95.0
Multimorbidity	388	5.4	4.9 -5.9

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

9.3 The association between self-reported multimorbidity and study population characteristics

The self-reported multimorbidity prevalence by study population characteristics is presented in Table 47. The prevalence in men was 5% (95% CI 4%-6%) and in women it was 6% (95% CI 5% - 7%). The estimates were statistically different from each other (p=0.020) although the actual difference was small. The mean age was 48 in both those with and without multimorbidity.

There was a statistically significant association between all remaining variables and self-reported multimorbidity. For example, there was an increased multimorbidity prevalence from the highest social class (I/II) through to the category of participants whose fathers were unemployed, unknown, disabled or dead (3% [95% CI 2%- 5%] in the former and 8% [95% CI 6% - 12%] in the latter).

The prevalence of self-reported multimorbidity was highest in those in the lowest quintile of cognition scores compared to all other quintiles. However, there was no trend for decreasing prevalence with higher score in the remaining categories. For example, the prevalence in the lowest quintile was 9% (95% CI 8% -11%), the prevalence in quintile “106-112” was 6% (95% CI 4% - 7%) and it was 4%, (95% CI 3% - 5%) in the highest quintile (“123-153”).

The prevalence of self-reported multimorbidity was higher in those who attended “non-elite or other” schools (6%) compared to elite (4%) secondary schools (p<0.001). The prevalence of multimorbidity increased with decreasing educational attainment (p<0.001). For example it was 3% (95% CI 3% -5%) for degree level and 9% (95% CI 7% -10%) for school leaving certificate or no qualification.

Table 47: Original ACONF: self-reported multimorbidity prevalence by baseline characteristics with measures of association (n=7,184)*

Categories	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	P value**
Total	7,184	388	5.4	4.9 –5.9	
Gender					
Male	3,430	163	4.8	4.1-5.5	p=0.020
Female	3,754	225	6.0	5.3-6.8	
Mean age in September 2001	48.2 (SD 1.5)	48.4 (SD 1.6)			p=0.060
Social class of the father at birth of the participant					
I/II (Professional/ Managerial)	789	25	3.2	2.2-4.6	p=0.001
III (Skilled non-manual)	869	43	5.0	3.7-6.6	
III (Skilled manual)	3,154	158	5.0	4.3-5.8	
IV (Partly skilled)	976	60	6.2	4.8-7.8	
V (Unskilled)	1,048	73	7.0	5.6-8.7	
Unemployed/ unknown/disabled/dead	348	29	8.3	5.9-11.7	
Cognition score age 7 (quintiles)					
50-95	1,269	115	9.1	7.6-10.8	p<0.001
96-105	1,445	74	5.1	4.1-6.4	
106-112	1,277	71	5.6	4.4-7.0	
113-122	1,453	50	3.4	2.6-4.5	
123-153	1,480	61	4.1	3.2-5.3	
School Type					
Non-elite or other	4,782	287	6.0	5.4-6.7	p<0.001
Elite	2,067	85	4.1	3.3-5.1	
Educational attainment					
Tertiary (degree)	1,374	47	3.4	2.6-4.5	p<0.001
Tertiary (non-degree)	1,138	47	4.1	3.1-5.5	
Advanced level	926	39	4.2	3.1-5.7	
Ordinary level	1,970	95	4.8	4.0-5.9	
School leaving/none	1,676	143	8.5	7.3-10.0	
2001 adult Employment status					
Paid work	6,080	141	2.3	2.0-2.7	p<0.001
Not in paid work (unemployed/student)***	226	24	10.6	7.2-15.3	
Permanently sick	424	190	44.8	40.2-49.6	
Retired from paid work	60	11	18.3	10.6-29.9	
Looking after family	331	16	4.8	3.0-7.7	
2001 adult social class					
I/II (Professional/ Managerial)	2944	106	3.6	3.0-4.3	p<0.001
III (Skilled non-manual)	1,758	87	5.0	4.0-6.1	
III (Skilled manual)	1,271	79	6.2	5.0-7.7	
IV (Partly skilled)	745	60	8.1	6.3-10.2	
V (Unskilled)	304	39	12.8	9.5-17.1	
2001 adult annual income					
Less than £10,000	2,054	238	11.6	10.3-13.0	p<0.001
£10,000 to £19,999	2,032	75	3.7	3.0-4.6	
£20,000 to £39,999	2,007	48	2.4	1.8-3.2	
£40,000 or more	936	16	1.7	1.1-2.8	

(contin. overleaf)

Categories	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	P value**
2001 adult body mass index					
Underweight (<18.5)	53	7	13.2	6.6-24.8	p<0.001
Normal (18.5-24.9)	2,838	131	4.6	3.9-5.5	
Overweight (25-29.9)	2,516	105	4.2	3.5-5.0	
Obese Class 1 (30-34.9)	885	69	7.8	6.2-9.8	
Obese Class 2 (35-39.9)	251	32	12.8	9.2-17.4	
Obese Class 3 (40+)	105	18	17.1	11.1-25.5	
2001 adult smoking status					
Current smoker	1,958	170	8.7	7.5-10.0	p<0.001
Ex-smoker	1,788	93	5.2	4.3-6.3	
Non-smoker	3,420	124	3.6	3.1-4.3	
2001 adult alcohol related hangovers in past year					
At least once a week	161	18	11.2	7.2-17.0	p<0.001
1-3 times a month	766	19	2.5	1.6-3.8	
Less than once a month	2,688	104	3.9	3.2-4.7	
Not at all in the last year	3,122	179	5.7	5.0-6.6	

Abbreviations: 95% CI, 95% confidence interval; SD, standard deviation; ACONF, Aberdeen Children of the 1950s

* Figures presented are numbers and proportions unless stated otherwise.

** Statistical significance set at 5% level. CHI test used for binary variables, CHI test for trend for variables with more than two categories, independent t test of means

*** These categories are combined due to small numbers

For 2001 adult employment, the prevalence was lowest in those in paid work (2%, 95% CI 2%-3%) and who were looking after family (5% [95% CI 3%-8%]). It was highest in those who were permanently sick (45% [95% CI 40% - 50%]). The prevalence of self-reported multimorbidity was lowest in those in 2001 adult social class I/II (4% [95% CI 3%- 4%]) and increased through to class V (13% [95% CI 10%- 17%]). The prevalence of self-reported multimorbidity decreased as annual income increased. For example it was 12% (95% CI 10% -13%) in those with incomes less than £10,000 and was 2% (95% CI 1% - 3%) in those with incomes over £40,000.

Prevalence was lowest in those whose BMI was normal (5% [95% CI 4% -6%]) and those who were overweight (4% [95% CI 4%-5%]) compared to those who were obese. For example it was 17% (95% CI 11% - 26%) in those in obese class 3. The prevalence was higher in current smokers (9%, 95% CI 8%-10%) compared to non-smokers (4% [95% CI 3% -4%]). The prevalence was highest in those who had at least one hangover per week (11% [95% CI 7% -17%]) and lowest in those with one to three hangovers per month (3% [95% CI 2% - 4%]).

9.4 The association between social class at birth and population characteristics and outcomes

9.4.1 Relationship with population characteristics

The association between social class at birth and educational attainment, cognition at age 7 and secondary school type is shown in Table 48. Logistic regression was conducted where school type (a binary variable) was the outcome and ordinal regression was conducted for cognition at age 7 and educational attainment.

Those in higher birth social classes were more likely to have a higher educational attainment ($p<0.001$). For example, the proportional OR of being in the highest educational attainment category (tertiary degree) compared to the other four categories combined was 4.4 (95% CI 3.8-5.1) in social class category I/II in relation to the reference group of III (skilled manual). Similarly, the OR of being in the top two educational categories versus all others combined was 4.4 (95% CI 3.8-5.1) for social class I/II versus the reference group, and so on. Conversely, those in lower birth social classes were less likely to have a higher educational attainment. For example, the OR of being in the highest educational attainment category versus all others combined was 0.5 (95% CI 0.4-0.5) for those in birth social class category V in relation to the reference group.

Those in higher birth social classes were more likely to attend an elite school ($p<0.001$). For example, in relation to the reference category the OR of attending an elite school if born into social class I/II was 6.8 (95% CI 5.7-8.1) and was 0.3 (95% CI 0.3-0.4) if born into category V.

Those in higher birth social classes were more likely to be in a higher cognition quintile category ($p<0.001$). For example, the proportional OR of being in the highest cognition quintile ("123 -153") compared to the other four cognition quintile categories combined was 3.6 (95% CI 3.1-4.2) in social class category I/II in relation to the reference group of III (skilled manual). Similarly, the OR of being in the top two cognition quintile categories versus all others combined was 3.6 (95% CI 3.1-4.2) and so on. On the contrary, those in

lower birth social classes were less likely to be in a higher cognition quintile category. For example, the OR for being in the highest cognition quintile category, versus all others combined, was 0.5 (95% CI 0.4-0.5) for those in birth social class category V in relation to the reference group.

The results for the association between social class at birth and BMI, smoking status and hangover frequency are shown in Table 49. The association between the exposure and BMI was assessed using linear regression and was statistically significant ($p<0.001$). In comparison to the reference group of III (manual) the average difference in BMI was 1.2 kg/m^2 less (95% CI -1.6 to -0.9) in those born into category I/II and was 0.5 kg/m^2 more (95% CI 0.1 to 0.9) in those born into category V.

Table 48: Original ACONF: analysis of the association between social class of the father at the birth of the participant and educational attainment (ordinal regression), secondary school type (logistic regression) and cognition score quintiles at age 7 (ordinal regression)

Social class of the father at birth of the participant	Outcome: Educational attainment* (n=7,084)		Outcome: Secondary school type** (n=6,849)		Outcome: Cognition at age 7* (n=6,924)	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
I/II (Professional/ Managerial)	4.41	3.80-5.11	6.77	5.65-8.11	3.60	3.09-4.19
III (Skilled non-manual)	1.78	1.55-2.03	2.12	1.81-2.48	1.78	1.55-2.04
III (Skilled manual)	1 (reference group)					
IV (Partly skilled)	0.56	0.49-0.64	0.46	0.38-0.56	0.58	0.51-0.66
V (Unskilled)	0.45	0.39-0.51	0.34	0.28-0.42	0.47	0.41-0.53
Unemployed/ unknown/disabled/dead	0.86	0.69-1.07	0.81	0.62-1.06	0.62	0.51-0.77

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models statistically significant, p<0.001

Table 49: Original ACONF: analysis of the association between social class of the father at birth and Body Mass Index (linear regression), smoking status (ordinal regression), and hangover frequency (ordinal regression)

Social class of the father at birth of the participant category	Outcome: Body Mass Index* N=6648		Outcome: Smoking status* N=7166		Outcome: Hangover frequency** N=6737	
	Coefficient	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
I/II (Professional/ Managerial)	-1.21	-1.55 - -0.87	1.34	1.16-1.56	0.89	0.76-1.03
III (Skilled non-manual)	-0.36	-0.70 - -0.01	1.36	1.18-1.57	1.03	0.89-1.18
III (Skilled manual)	0 (reference group)		1 (reference group)			
IV (Partly skilled)	0.34	-0.02 - 0.70	0.72	0.63-0.82	0.89	0.77-1.03
V (Unskilled)	0.48	0.10 - 0.85	0.72	0.63-0.82	1.11	0.96-1.27
Unemployed/ unknown/ disabled/ dead	0.70	0.10 - 1.31	0.86	0.69-1.07	0.96	0.77-1.21

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models statistically significant, p<0.001 **Model not statistically significant, p=0.107

There was an association between social class at birth and smoking status (p<0.001). For example, the OR of being a non-smoker versus being an ex-smoker or a smoker combined was 1.3 (95% CI 1.2-1.6) in social class category I/II in relation to the reference group of III (skilled manual). The OR of being a non-smoker or an ex-smoker combined versus being a smoker was 1.3 (95% CI 1.2-1.6) in social class category I/II in relation to the reference group of III (skilled manual). Conversely, the OR of being a non-smoker versus being an ex-smoker or a smoker combined was 0.7 (95% CI 0.6-0.8) in social class category V in relation to the reference group. Similarly, the OR of being a non-smoker or an ex-smoker combined versus being a smoker was 0.7 (95% CI 0.6-0.8) in social class category V in relation to the reference group.

For hangover frequency, assessed using ordinal regression, all OR confidence intervals crossed one and there was no trend in OR. The model was not statistically significant (p=0.107). For example the OR of having a hangover at least once per week compared to the three other categories combined (1-3 times a month, less than once a month and not at all in the last year) in those born into category I/II was 0.9 (95% CI 0.8 – 1.0) in relation to the reference group III (skilled manual). The OR of having a hangover at least once per week compared to the three other categories combined was 0.9 (95% CI 0.8-1.0) in category IV compared to the reference group.

In Table 50 I have shown the relationship between social class at birth and 2001 adult social class assessed by ordinal logistic regression. Those born into higher social classes were more likely to be in a higher adult social class. This was statistically significant (p<0.001). In relation to the birth social class reference group III (manual), the proportional OR of being in the highest adult social class group (I/II) compared to the other four combined (III non-manual, III manual, IV and V) was 3.1 (95% CI 2.6-3.6) in those born into category I/II. Thus, the proportional OR of being in the highest (I/II) and second highest (III non-manual) adult social class categories combined versus the remaining three combined was 3.1 (95% CI 2.6-3.6) in those born into category I/II. Conversely, those born into lower social classes were less likely to be in a higher adult social class category. For example, in relation to the birth social class reference group III (manual), the proportional OR of being in the highest adult

social class group (I/II) compared to the other four combined was 0.5 (95% CI 0.5 – 0.6) in those born into category V.

Table 50: Original ACONF: Ordinal regression analysis of the association between social class of the father at birth and adult social class in 2001 (n=7,022)

Social class of the father at birth of the participant category*	Odds Ratio	95% CI
I/II (Professional/ Managerial)	3.10	2.64-3.64
III (Skilled non-manual)	1.73	1.50-1.99
III (Skilled manual)	1 (reference group)	
IV (Partly skilled)	0.64	0.56-0.72
V (Unskilled)	0.51	0.45-0.58
Unemployed/ unknown/ disabled/ dead	1.02	0.82-1.28

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model statistically significant, p<0.001

9.4.2 Relationship with outcomes

A summary of the person-years at risk and the mortality rate per 1,000 person years, by social class at birth status, is in Table 51.

Table 51: Entire ACONF: number of deaths and mortality rate, by social class of the father at the birth of the participant, from 1981 to 2016, n=10,543 at baseline

Social class of the father at birth of the participant category	Number at baseline	Person-years at risk	Deaths	Mortality rate/ 1,000 person years	95% CI
I/II (Professional/ Managerial)	959	33,022	117	3.54	2.96-4.25
III (Skilled non-manual)	1,169	40,316	139	3.45	2.92-4.07
III (Skilled manual)	4,640	160,979	455	2.83	2.58-3.10
IV (Partly skilled)	1,490	51,773	141	2.72	2.31-3.21
V (Unskilled)	1,721	59,172	197	3.33	2.90-3.83
Unemployed/ unknown/ disabled/ dead	564	19,421	59	3.04	2.35-3.92
Total	10,543	364,684	1,108	3.04	2.86-3.22

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

There were 1,108 deaths in total over the follow-up period. The rate per 1,000 person years was similar across all social class at birth categories. For example it was 3.5 (95% CI 2.9-4.2) in I/II and 3.3 (95% CI 2.9-3.8) in category V.

The Cox regression analysis of the association between social class at birth and mortality is in Table 52. The test for non-proportionality showed there was violation of proportionality. The model was not statistically significant, p=0.050. In relation to the reference group of III (skilled manual) no clear trend was observed. The hazard ratio of mortality was higher in all but category IV (partly skilled). However, HR confidence intervals were either one or crossed one indicating no association. For example, the HR for mortality in I/II (professional/managerial) was 1.3 (95% CI 1.0 – 1.6) and for category V (unskilled) was 1.2 (95% CI 1.0 – 1.4).

Table 52: Entire ACONF: Cox regression analysis of association between social class at birth and mortality from 1981 to 2016, n=10,543 at baseline

Social class of the father at birth of the participant category*	Hazard Ratio	95% CI
I/II (Professional/ Managerial)	1.26	1.03-1.55
III (Skilled non-manual)	1.23	1.01-1.48
III (Skilled manual)	1 (reference group)	
IV (Partly skilled)	0.96	0.80-1.16
V (Unskilled)	1.18	1.00-1.40
Unemployed/ unknown/ disabled/ dead	1.08	0.82-1.41

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.050

The association between social class at birth and hospital admission using multiple failure and single failure survival analysis is in Table 53. Using either technique, there was no association between social class at birth and hospital admission rate. For both, the HR were close to one indicating that in comparison to the reference group of III (skilled manual) there was no difference in the rate of hospital admission by social class at birth category.

Table 53: Entire ACONF: association between social class at birth and hospital admissions, from 1981 to 2016, multiple failure survival analysis and single failure survival analysis, n=10,533

Social class of the father at birth of the participant category	Multiple failure survival analysis*		Single failure survival analysis**	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
I/II (Professional/ Managerial)	1.00	0.95-1.05	1.03	0.95-1.12
III (Skilled non-manual)	1.03	0.99-1.08	1.01	0.94-1.09
III (Skilled manual)	1 (reference group)			
IV (Partly skilled)	0.99	0.95-1.04	0.95	0.89-1.02
V (Unskilled)	1.00	0.96-1.04	1.03	0.96-1.10
Unemployed/ unknown/ disabled/ dead	0.96	0.90-1.02	0.94	0.84-1.03

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.514 **Model not statistically significant, p=0.250

9.5 The association between social class at birth and self-reported multimorbidity, and the role of educational attainment and other mediating variables

9.5.1 Summary of approach

The aim of this section was to assess the association between social class at birth and self-reported multimorbidity, and to assess the role of educational attainment and other mediating variables. The hypothesis (presented in the path diagram in Figure 6) and a detailed description of the analysis steps are in Chapter 6. These steps are summarised here:

1. Develop a path diagram which *a priori* sets the model for testing
2. Show that the exposure variable is correlated with the outcome
3. Show that the exposure variable is correlated with the mediator and check for interaction
4. Show that the mediator is correlated with the outcome
5. Assess if the mediator variable mediates the exposure-outcome relationship by examining the impact of controlling for the mediator

6. Conduct sensitivity analysis which includes other mediators (for each of these follow steps two to four) and confounders

9.5.2 Analysis steps two to four: relationships between exposure, outcome and mediators

In the analysis, the exposure was social class at birth, the outcome was self-reported multimorbidity and the primary mediating variable of interest was educational attainment. The additional hypothesised mediators were cognition scores at age 7 and secondary school type.

I have conducted analysis corresponding to some of these steps earlier in this chapter. In Table 47 I showed that the exposure (social class at birth) was associated with the outcome (self-reported multimorbidity). This was step two.

In Table 48 I showed that social class at birth was associated with the mediators (educational attainment, cognition at age 7 and secondary school type). The additional analysis for step three was testing for interaction between the exposure and mediators. The likelihood ratio test showed there was no interaction between social class at birth and educational attainment (p=0.368). There was no interaction between social class and cognition at age 7 (p=0.350). There was an interaction between social class and secondary school type (p=0.046). Secondary school type was therefore also a moderator.

For step four, I conducted analysis to show the relationship between each of the mediators and the outcome (self-reported multimorbidity). This is shown in Table 54. Of note, although these variables are presented in the same Table, they each represent a separate univariate analysis (i.e. they are not adjusted for each other).

The models showed a statistically significant association for each of the exposures with the outcome ($p<0.001$ for all). For educational attainment, in relation to the reference group (tertiary- degree), there were increasing ORs of self-reported multimorbidity as educational attainment decreased. Confidence intervals for “tertiary (non-degree)” and “advanced level” crossed one. The lower confidence interval for “ordinary level” was one. For school

type, in relation to the reference group of "non-elite or other", the OR of self-reported multimorbidity was lower for those attending "elite" schools (OR 0.7, 95% CI 0.5-0.9). For cognition at age 7, in relation to the reference group of "106-112" the OR of self-reported multimorbidity was higher in the lowest quintile (1.7, 95% CI 1.3-2.3). However, there was no step-wise trend amongst the remaining higher score quintiles. For example the OR of self-reported multimorbidity was 0.9 in quintile "96-105", 0.6 in "113-122" and 0.7 in "123-153".

Table 54: Original ACONF: Logistic regression analysis of the association between hypothesised mediators (educational attainment, secondary school type and cognition score at age 7) and self-reported multimorbidity

Exposure variable	Odds Ratio	95% CI
Educational attainment category (n=7,084)*		
Tertiary (degree)	1 (reference group)	
Tertiary (non-degree)	1.22	0.81-1.84
Advanced level	1.24	0.81-1.91
Ordinary level	1.43	1.00-2.04
School leaving/none	2.63	1.88-3.69
Secondary school type (n=6,849)*		
Non-elite or other	1 (reference group)	
Elite	0.67	0.52-0.86
Cognition score at age 7 quintile (n=6,924)*		
50-95	1.69	1.25-2.30
96-105	0.92	0.66-1.28
106-112	1 (reference group)	
113-122	0.61	0.42-0.88
123-153	0.73	0.51-1.04

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models statistically significant, p<0.001

The analysis described in this section shows that educational attainment, secondary school type and cognition at age 7 qualify as potential mediators of the relationship between social class at birth and self-reported multimorbidity.

9.5.3 Analysis steps five and six: regression analysis

The association between social class at birth and self-reported multimorbidity is in Table 55. In relation to the reference group III (manual) the OR of self-reported multimorbidity in 2001 was lower for the highest social class category (0.6 [95% CI 0.40-0.9]) and higher for those who fathers were unemployed, unknown, disabled or dead at the participant's

birth (1.7 [95% CI 1.1-2.6]). There was a trend for increasing OR of self-reported multimorbidity with decreasing social class category. This model was statistically significant.

The association between social class at birth and self-reported multimorbidity adjusted by educational attainment (and the mediator-outcome confounder gender) is also in Table 55. This model was also statistically significant. In comparison with the unadjusted analysis, the inclusion of the mediator causes all ORs to approach one. For example, in the unadjusted analysis the OR of self-reported multimorbidity in I/II was 0.6 (95% CI 0.4-0.9) and in the adjusted analysis it was 0.8 (0.5-1.2). In the unadjusted analysis the OR of multimorbidity in those born into category V was 1.4 (95% CI 1.1-1.9) and in the adjusted analysis it was 1.3 (0.9-1.7). The addition of educational attainment does not remove all association and thus is a partial mediator of the relationship between social class at birth and self-reported multimorbidity.

Table 55: Original ACONF: logistic regression analysis of the association between social class of the father at the birth of the participant and self-reported multimorbidity, models unadjusted, adjusted by educational attainment and gender, and adjusted by educational attainment, gender, cognition at age 7 and school type

Social class of the father at birth of the participant	Number (unadjusted model, n=7,184)	Unadjusted (n=7,184)*		Adjusted by educational attainment and gender (n=7,084)*		Adjusted by educational attainment, gender, cognition at age 7 and school type (n=6,561)*	
		Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
I/II (Professional/ Managerial)	789	0.62	0.40 - 0.95	0.80	0.51- 1.25	0.73	0.44-1.20
III (Skilled non-manual)	869	0.99	0.70 - 1.39	1.08	0.76-1.55	1.03	0.71-1.50
III (Skilled manual)	3,154	1 (reference group)					
IV (Partly skilled)	976	1.24	0.91 - 1.69	1.14	0.83-1.57	1.07	0.77-1.49
V (Unskilled)	1,048	1.42	1.07 - 1.89	1.28	0.95-1.72	1.24	0.91-1.70
Unemployed/ unknown/ disabled/ dead	348	1.72	1.14 - 2.60	1.66	1.08-2.55	1.74	1.11-2.72

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

*Models statistically significant, p<0.001

The inclusion of secondary school type and cognition at age 7 had no additional impact on the effect of educational attainment (Table 55). For example the OR in group I/II was 0.73 (95% CI 0.44-1.20) in the model adjusted by all variables compared to 0.80 (95% CI 0.51-1.25) in the model adjusted by educational attainment and gender only. This model was statistically significant.

9.5.4 Assessment of the impact of missing data

I assessed the impact of imputing missing data on the analyses presented in Table 55, using Multiple Imputation by Chained Equations (MICE). The methods and results are detailed in Appendix 4. Imputing missing values had no impact upon the findings, and conclusions are unchanged.

9.6 Outcomes in those with self-reported multimorbidity

9.6.1 Secondary care multimorbidity in 2016

The follow-up data available for the Original ACONF are shown in Table 56. Of 7,184 individuals there were 646 deaths. There were 6,049 known to be alive and resident in Scotland in 2016 and 4,827 (67%) were CHI seeded. This latter group form the population for analysis in this section.

Table 56: Original ACONF: follow-up status of individuals from 2001 to 2016

Status variable	Number	% of baseline
Total at baseline	7,184	100
Died by 2016	646	9.0
Elsewhere in UK or status unknown by 2016	489	6.8
Alive and resident in Scotland in 2016	6,049	84.2
*CHI seeded**	*4,827*	*67.2*

Abbreviations: CHI, Community Health Index; ACONF, Aberdeen Children of the 1950s

The association between self-reported multimorbidity at the postal questionnaire and the presence of secondary care multimorbidity in 2016 is shown in Table 57. Of those without self-reported multimorbidity in 2001, 10% (95% CI 9%-11%) had secondary care multimorbidity in 2016. Of those with self-reported multimorbidity in 2001 a similar proportion (9% [95% CI 6%-13%]) had secondary care multimorbidity in 2016.

Table 57: Original ACONF: relationship between self-reported multimorbidity in 2001 and secondary care multimorbidity in 2016

Self-reported multimorbidity status in 2001	Total population	Number with secondary care multimorbidity in 2016	%	95% CI
No multimorbidity	4,584	452	9.9	9.0-10.8
Multimorbidity	243	21	8.6	5.7-12.9
Total	4,827	473	9.8	9.0-10.7

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

The regression analysis of the relationship, both unadjusted and adjusted by gender, social class at birth, cognition at age 7, educational attainment and school type is in Table 58. The OR of having secondary care multimorbidity in 2016 in those with self-reported multimorbidity in 2001 was 0.9 (95% CI 0.5-1.4) in relation to the reference group (no self-reported multimorbidity in 2001). When adjusted by other covariates there was no change in the finding of no association (p=0.453) and the OR was 0.9 (95% CI 0.5-1.4).

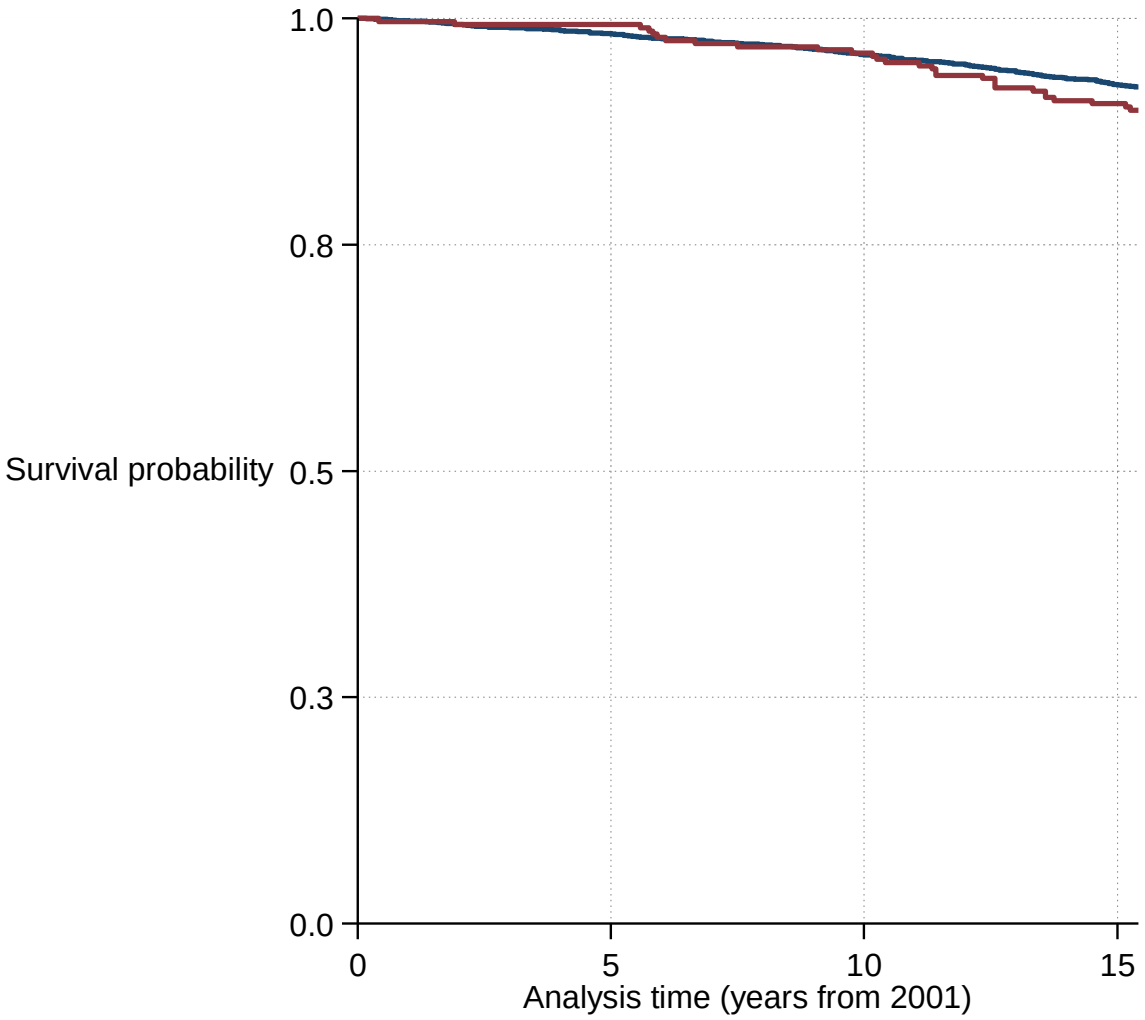
Table 58: Original ACONF: association between self-reported multimorbidity in 2001 and secondary care multimorbidity in 2016, unadjusted, and adjusted by social class at birth, education, cognition, gender and school type

Self-reported multimorbidity status in 2001	Unadjusted (n=4,827)*		Adjusted by social class at birth, education, cognition, gender, and school type (n=4,614)**	
	Odds Ratio	95% CI	Odds ratio	95% CI
Absent	1 (reference group)		1 (reference group)	
Present	0.86	0.55-1.37	0.88	0.54-1.43

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.534
**Model not statistically significant, p=0.453

9.6.2 Mortality

The survival curve of the association between self-reported multimorbidity at the questionnaire and mortality is in Figure 10.



Number at risk from baseline and at five year intervals

No multimorbidity	5,029	4,942	4,826	4,647
Multimorbidity	286	284	275	257

Figure 10: Original ACONF: mortality survival analysis curve, by self-reported multimorbidity status, follow-up from 2001 to 2016 with number at risk
Abbreviations: ACONF, Aberdeen Children of the 1950s

There was violation of proportionality. There were 5,029 individuals without self-reported multimorbidity and 286 individuals with self-reported multimorbidity at baseline. It can be seen on the graph that survival in those with multimorbidity begins to separate from those without multimorbidity around 12 years from the start of follow-up indicating lower survival.

The survival data and the mortality rates are illustrated in Table 59. There were 411 deaths overall, with 29 occurring in those with self-reported multimorbidity. The mortality rate per 1,000 person years was 5.1 (95% CI 4.6-5.6) in those without self-reported multimorbidity and was 6.8 (95% CI 4.7-9.8) in those with self-reported multimorbidity.

Table 59: Original ACONF: number of deaths and mortality rate, by self-reported multimorbidity status, from 2001 to 2016

Self-reported multimorbidity status in 2001	Number at baseline	Person-years at risk	Number of Deaths	Mortality rate/ 1,000 person years	95% CI
Absent	5,029	75,066	382	5.09	4.60-5.63
Present	286	4,252	29	6.82	4.74-9.81
Total	5,315	79,318	411	5.18	4.70-5.71

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

The Cox regression results of the association between self-reported multimorbidity and mortality is in Table 60 and show no association with mortality rate.

Table 60: Original ACONF: association between self-reported multimorbidity in 2001 and mortality rate, survival analysis, unadjusted, and adjusted by social class at birth, education, cognition, gender, age and school type

Self-reported multimorbidity status in 2001	Unadjusted (n=5,315)*		Adjusted by social class at birth, education, cognition, gender, age and school type (n=5,067)*	
	Hazard Ratio	95% CI	Hazard ratio	95% CI
Absent	1 (reference group)		1 (reference group)	
Present	1.34	0.92-1.96	1.32	0.88-1.98

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.123 **Model not statistically significant, p=0.927

In the unadjusted model, the HR for mortality for those with self-reported multimorbidity was 1.3 (95% CI 0.9-2) in comparison to the reference group of no multimorbidity. In the model adjusted by social class at birth, educational attainment, cognition at age 7, gender, age and secondary school type the HR in those with self-reported multimorbidity was 1.3 (95% CI 0.9-2.0) in comparison to the reference group.

9.6.3 Admissions

The association between self-reported multimorbidity and hospital admission rate using multiple failure survival analysis is in Table 61. There was no relationship in both the unadjusted model (p=0.147) and the unadjusted model (p=0.063). For example, in relation to the reference group of no self-reported multimorbidity, those with self-reported multimorbidity had a HR of 0.9 (95% CI 0.8-1.0) of hospital admission. This is almost identical when adjusted by social class at birth, education, cognition, gender, age and secondary school type.

Table 61: Original ACONF: Association between self-reported multimorbidity in 2001 and hospital admissions, multiple failure analysis, unadjusted, and adjusted by social class at birth, education, cognition, gender, age and school type

Self-reported multimorbidity status in 2001	Unadjusted (n=4,995)*		Adjusted by social class at birth, education, cognition, gender, age and school type (n=4,768)*	
	Hazard Ratio	95% CI	Hazard ratio	95% CI
Absent	1 (reference group)			
Present	0.91	0.80-1.03	0.93	0.82-1.06

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.147 **Model not statistically significant, p=0.063

9.7 Prevalence and determinants of resilience to self-reported multimorbidity

I examined the prevalence of “resilient” responses across the five resilience measures in those with self-reported multimorbidity compared to those without (Table 62) and then examined the prevalence by gender (Table 63).

Table 62: Original ACONF: Prevalence of resilience measures by self-reported multimorbidity status with test of association

Resilience measure	No multimorbidity				Multimorbidity			
	Total	Number with "resilient" response**	%	95% CI	Total	Number with resilient response	%	95% CI
Overall health and wellbeing- SRH *	6760	6,560	97.0	96.6-97.4	384	232	60.4	55.4-65.2
Enjoyment- Positive GHQ 1*	6775	6,220	91.8	91.1-92.4	387	207	53.5	48.5-58.4
Positive mood state – Positive GHQ 2 *	6752	6,056	89.7	88.9-90.4	382	252	66.0	61.1-70.6
Negative mood state- Negative GHQ 1 *	6760	2,918	43.2	42.0-44.4	383	72	18.8	15.2-23.0
Low self-esteem – Negative GHQ 2 *	6753	3,598	53.3	52.1-54.5	384	102	26.6	22.4-31.2

Abbreviations: SRH= self-rated health; GHQ = General Health Questionnaire; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Difference, tested by CHI squared test for association, statistically significant, p<0.001
** Not technically resilience given resilience is defined as the positive response in those with multimorbidity

Table 63: Original ACONF: Prevalence of resilience to self-reported multimorbidity by gender with test of association (n=388 with self-reported multimorbidity, totals presented with missing data excluded)

Resilience measure	All				Male				Female				p-value*
	Total	Number resilient	%	95% CI	Total	Number resilient	% male	95% CI	Total	Number resilient	% female	95% CI	
Overall health and wellbeing- SRH	384	232	60.4	55.4-65.2	161	92	57.1	49.4-64.6	223	140	62.8	56.2 –68.9	0.265
Enjoyment- Positive GHQ 1*	387	207	53.4	48.5-58.4	163	93	57.1	49.3–64.5	224	114	50.9	44.3 –57.4	0.230
Positive mood state – Positive GHQ 2	382	252	66.0	61.0-70.6	162	107	66.1	58.4 –73.0	220	145	65.9	59.4 –71.9	0.977
Negative mood state- Negative GHQ 1	383	72	18.8	15.2-23.0	162	38	23.3	17.4-30.4	220	34	15.5	11.2- 20.9	0.052
Low self-esteem – Negative GHQ 2	384	102	26.6	22.4-31.2	163	51	31.3	24.6 – 38.9	221	51	23.1	18.0 -29.1	0.072

Abbreviations: SRH, self-rated health; GHQ, General Health Questionnaire; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Difference by gender, tested by CHI squared test for association

Across all measures, these responses were of higher prevalence in those without self-reported multimorbidity compared to those with and this was statistically significant ($p<0.001$ in all). For example, the prevalence of fair to excellent SRH was 97% (9% CI 96.6%-97.4%) in those without self-reported multimorbidity and 60% (95% CI 55%-65%) in those with it. The prevalence of a "resilient" response to a negative mood state was 43% (95% CI 42% - 44%) in those without self-reported multimorbidity and 19% (95% CI 15% -23%) in those with self-reported multimorbidity.

I then limited the population to those with self-reported multimorbidity, amounting to 388 individuals (when not accounting for missing data in each of the resilience measures). The prevalence of resilience to self-reported multimorbidity by gender, for each of the five measures, is in Table 63. For "SRH" 232 out of 384 individuals (60%, 95% CI 55% - 65%) were resilient. For "enjoyment" (positive GHQ 1) the prevalence was 53% (95% CI 49% - 58%) and for "positive mood state" (positive GHQ 2) the prevalence was 66% (95% CI 61% - 70%). There were 72 individuals with self-reported multimorbidity classed as resilient to a "negative mood state" (negative GHQ 1) amounting to 19% (95% CI 15% - 23%). There were 102 individuals classed as resilient to "low self-esteem" (negative GHQ 2) amounting to 27% (95% CI 22% to 31%). There was no statistically significant difference by gender for any of the measures.

The number of domains in which participants were resilient is shown in Table 64. There were 66 individuals with self-reported multimorbidity (18% [95% CI 14% - 22%]) who were resilient in no domains. The single largest category was that of three domains (26% [95% CI 21%- 30%]). The confidence intervals were wide and there was no statistically significant difference by gender ($p=0.098$).

The association between social class at birth and each of the five resilience domains is shown in Table 65. None of the models were statistically significant. There were no obvious trends in ORs and all confidence intervals crossed one. Confidence intervals were wide, reflecting the small numbers within the sample.

Table 64: Original ACONF: Number of domains in which participants are resilient, by gender (N=377 with self-reported multimorbidity and no missing data)

Number of domains in which resilient*	All			Male			Female		
	Number	% of total	95% CI	Number	% of total males	95% CI	Number	% of total females	95% CI
None	66	17.5	14.0- 21.7	30	18.8	13.4- 25.6	36	16.6	12.2- 22.2
One	65	17.2	13.7- 21.4	25	15.6	10.8- 22.2	40	18.4	13.8- 24.2
Two	73	19.4	15.7- 23.7	29	18.1	12.9- 24.9	44	20.3	15.4- 26.2
Three	96	25.5	21.3- 30.1	33	20.6	15.0- 27.6	63	29.0	23.4- 35.5
Four	36	9.5	7.0- 13.0	21	13.1	8.7- 19.3	15	6.9	4.2- 11.2
Five	41	10.9	8.1- 14.5	22	13.8	9.2- 20.0	19	8.8	5.6- 13.3
Total	377	100		160	100		217	100	

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

*Difference by gender, tested by CHI squared test for association, not statistically significant, p=0.098

Table 65: Original ACONF: logistic regression analysis of the association between social class at birth and each of the five resilience domains

Social class of the father at birth of the participant	SRH (n=384)		Enjoyment (n=387)		Positive mood state (n=382)		Negative mood state (n=383)		Low self-esteem (n=384)	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
I/II (Professional/ Managerial)	0.65	0.28-1.52	1.92	0.80-4.60	0.98	0.41-2.36	1.27	0.47-3.46	0.76	0.28-2.01
III (Skilled non-manual)	1.20	0.59-2.47	1.65	0.83-3.28	1.27	0.61-2.63	0.92	0.39-2.18	0.46	0.19-1.12
III (Skilled manual)	1 (reference group)									
IV (Partly skilled)	1.01	0.55-1.88	1.47	0.80-2.68	1.13	0.60-2.14	0.76	0.34-1.71	1.08	0.56-2.07
V (Unskilled)	0.67	0.38-1.18	1.24	0.71-2.16	1.10	0.61-1.98	0.87	0.43-1.79	0.73	0.38-1.38
Unemployed/ unknown/disabled/dead	0.99	0.44-2.23	1.33	0.60-2.94	1.05	0.45-2.40	0.84	0.30-2.38	0.91	0.38-2.21
p-value for model	0.611		0.513		0.991		0.964		0.502	

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s; SRH, self-rated health

9.8 Outcomes in those with resilience to self-reported multimorbidity

9.8.1 Secondary care multimorbidity in 2016

I found no association between any of the resilience measures and the presence of secondary care multimorbidity in 2016 and confidence intervals were wide (Table 66). For example, for "SRH" 7% (95% CI 3%-14%) of the expected group had secondary care multimorbidity in 2016 and 9% (95% CI 6%-15%) of the resilient group had secondary care multimorbidity (p=0.493).

Table 66: Original ACONF: Association between resilience measures and secondary care multimorbidity in 2016, with 95% confidence intervals of proportions

Resilience measure	Total population	Number with 2016 MM	% with MM	95% CI	p value*
Overall health and wellbeing- SRH					
Expected	89	6	6.7	3.1-13.9	0.493
Resilient	151	14	9.3	5.6-15.0	
Enjoyment- Positive GHQ 1					
Expected	114	10	8.8	4.8-15.4	0.961
Resilient	128	11	8.6	4.9-14.7	
Positive mood state –Positive GHQ 2					
Expected	81	7	8.6	4.2-16.8	0.924
Resilient	157	13	8.3	4.9-13.7	
Negative mood state- Negative GHQ 1					
Expected	194	17	8.8	5.5-13.6	0.647
Resilient	45	3	6.7	2.3-17.9	
Low self-esteem – Negative GHQ 2					
Expected	172	15	8.7	5.4-13.9	0.730
Resilient	68	5	7.4	3.2-16.1	

Abbreviations: MM, multimorbidity; SRH, self-rated health; GHQ, General Health Questionnaire; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Assessed using CHI test for association

9.8.2 Mortality

The Cox regression analysis of the relationship between each of the five resilience measures and mortality is in Table 67. There was an association between SRH resilience

and mortality (p=0.024). The resilient group had a lower hazard ratio for mortality compared to the expected group (HR 0.4, 95% CI 0.2 – 0.9). There was no association between the other resilience categories and mortality. All hazard ratios were less than one for the resilient groups, but the confidence intervals crossed one.

Table 67: Original ACONF: Cox regression survival analysis of the association between resilience measures in 2001 and mortality by 2016

Resilience measure	p-value*	Hazard ratio	95% CI
Overall health and wellbeing- SRH (n=283)			
Expected	0.024	1 reference group	
Resilient		0.43	0.21-0.89
Enjoyment- Positive GHQ 1 (n=285)			
Expected	0.218	1 reference group	
Resilient		0.63	0.30-1.31
Positive mood state –Positive GHQ 2 (n=281)			
Expected	0.881	1 reference group	
Resilient		0.56	0.27-1.15
Negative mood state- Negative GHQ 1 (n=282)			
Expected	0.413	1 reference group	
Resilient		0.93	0.36-2.41
Low self-esteem – Negative GHQ 2 (n=283)			
Expected	0.115	1 reference group	
Resilient		0.69	0.28-1.68

Abbreviations: SRH, self-rated health; GHQ, General Health Questionnaire; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

*Assessment of association using CHI-squared test

I have illustrated the findings for SRH resilience in the survival curve in Figure 11. The number of deaths and the mortality rate for the population are shown in Table 68. There were 29 deaths in the population over the study period, of which 12 were in the resilient group. The death rate per 1,000 years was 4.6 (95% CI 2.6-8.1) in the resilient group and 10.6 (95% CI 6.6-17.0) in the expected group.

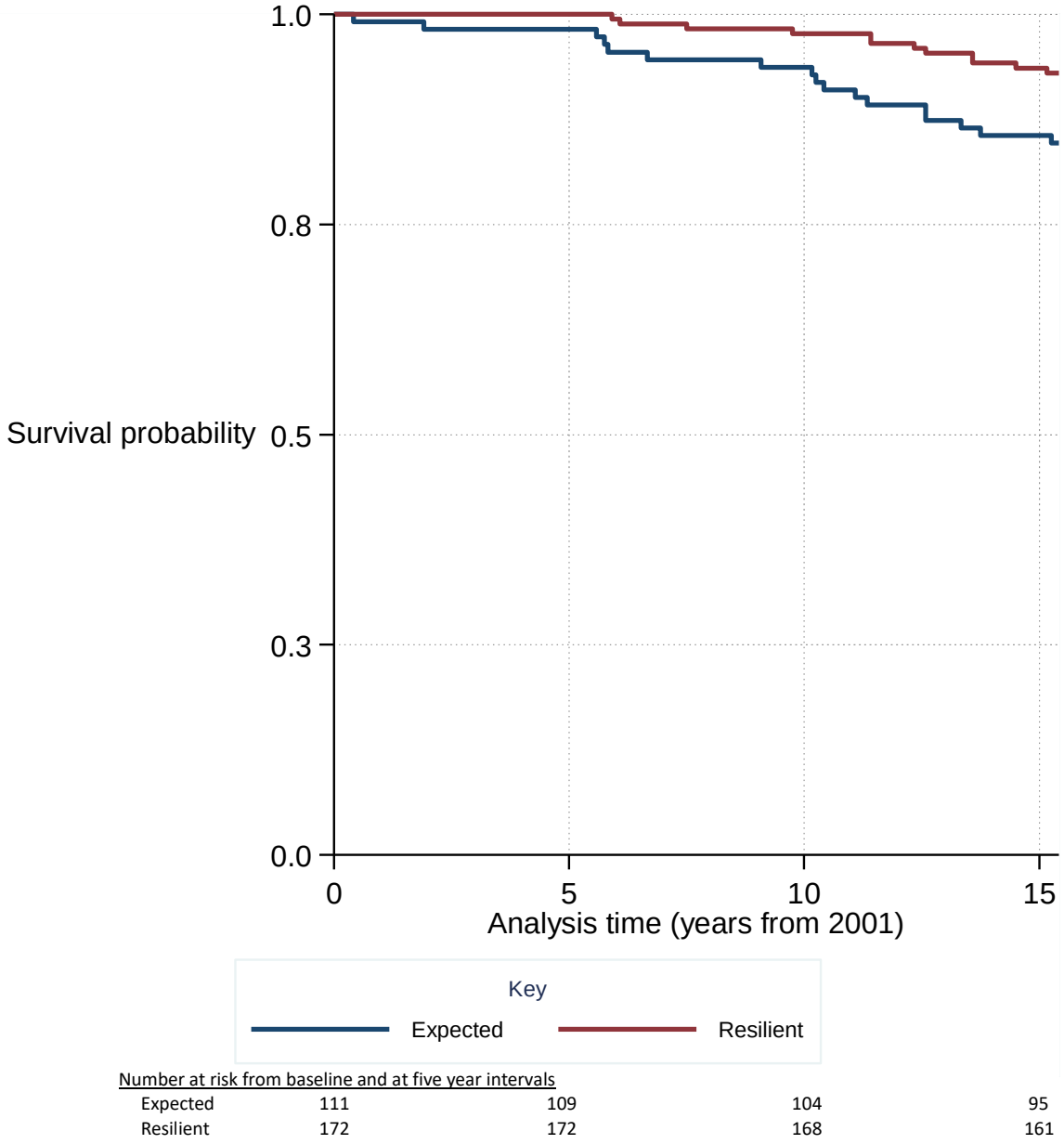


Figure 11: Original ACONF: mortality survival analysis curve, by self-rated health resilience status in 2001, follow-up from 2001 to 2016

Abbreviations: ACONF, Aberdeen Children of the 1950s

Table 68: Original ACONF: number of deaths and mortality rate, by self-rated health resilience status, from 2001 to 2016

Overall health and wellbeing- SRH	Number at baseline	Person-years at risk	Deaths	Mortality rate/ 1,000 person years	95% CI
Expected	111	1,605	17	10.59	6.58-17.04
Resilient	172	2,601	12	4.61	2.62-8.13
Total	283	4,206	29	6.90	4.79-9.92

Abbreviations: SRH, self-rated health; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

9.8.3 Admissions

The results of multiple failure survival analysis assessing the association between the resilience measures and the rate of hospital admission is in Table 69. I found no association between any of the resilience measures and hospitalisation rate. For example the HR of the SRH resilient group in relation to the reference group (expected) was 1.3 (95% CI 1.0-1.6) with p=0.101.

Table 69: Original ACONF: Association between resilience measures in 2001 and rate of hospital admission by 2016 using multiple failure survival analysis

Resilience measure	p-value*	Hazard ratio	95% CI
Overall health and wellbeing- SRH (n=261)			
Expected	0.101	1 reference group	
Resilient		1.25	0.96-1.63
Enjoyment- Positive GHQ 1 (n=263)			
Expected	0.625	1 reference group	
Resilient		0.94	0.72-1.22
Positive mood state –Positive GHQ 2 (n=259)			
Expected	0.230	1 reference group	
Resilient		0.94	0.71-1.23
Negative mood state- Negative GHQ 1 (n=260)			
Expected	0.699	1 reference group	
Resilient		1.06	0.78-1.46
Low self-esteem – Negative GHQ 2 (n=261)			
Expected	0.318	1 reference group	
Resilient		1.14	0.88-1.49

Abbreviations: SRH, self-rated health; GHQ, General Health Questionnaire; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

*Assessment of association using CHI-squared test

9.9 Discussion

9.9.1 Summary of findings

There were 7,184 individuals in the Original ACONF population and of these the majority reported no health conditions (83%). The prevalence of self-reported multimorbidity was 5%, with no difference by age and similar by gender. Self-reported multimorbidity prevalence increased as social class at both birth and in adulthood decreased. Similar trends were found in other markers of SES (for example the prevalence increased with decreasing educational attainment, decreasing income and for those permanently sick from work). The prevalence was slightly higher in non-elite compared to elite schools. Cognition score was statistically significantly associated with self-reported multimorbidity. Self-reported multimorbidity was higher in those who were obese or underweight, was higher in current smokers and higher in those with frequent hangovers.

I found that a lower social class at birth was associated with lower educational attainment, having a lower cognition score at age 7 and attending a non-elite school. A lower social class at birth was associated with a slightly higher BMI and being more likely to smoke in 2001. There was no association with hangover frequency. There was no association between social class at birth and mortality rate or hospital admission rate. For the latter, there was no difference in finding between single and multiple failure survival analysis techniques.

I found that being born into a lower social class led to an increased likelihood of self-reported multimorbidity, however if an individual achieved a higher educational attainment this partially mediated the effect of lower social class. These findings were unaffected by taking into account cognition scores at age 7 and whether the individual attended an elite or non-elite secondary school.

There was no association between self-reported multimorbidity in 2001 and the presence or secondary care multimorbidity in 2016. There was also no association with mortality rate or hospital admission rate.

The prevalence of "resilient" responses was higher in those without self-reported multimorbidity compared to those with. The prevalence of resilience to self-reported multimorbidity was similar for the SRH measure (60%) and the two positive GHQ measures (53% for enjoyment resilience and 66% for positive mood resilience). The prevalence was lower when measured by the two negative GHQ measures (19% for negative mood state and 27% for low self-esteem). There was no significant difference by gender for all measures.

Almost 18% of the sample were resilient in none of the measures and 11% were resilient across all five. I found no association between social class at birth and each of the five resilience measures. There was no association between any of the resilience measures and the presence of secondary care multimorbidity in 2016 or the rate of hospital admission. For SRH resilience only, I found that the resilient group had a lower mortality rate than the expected group but the number of deaths were low.

9.9.2 Interpretation of findings

Self-reported multimorbidity

Prevalence

The multimorbidity measure in the Original ACONF is a self-reported measure in which individuals are asked to report any condition which is high-burden to them. The original 42 condition categories were designed to be mutually exclusive. A small number of categories were combined by myself in order to prevent disclosure of potentially identifiable information and so I cannot indicate how many individuals are covered twice or more in these categories. However, as the purpose of my work is to primarily examine the *number* of conditions rather than the *nature* of conditions this is not a significant limitation.

The condition categories varied in specificity. For example "back problems" could indicate a variety of underlying pathologies whilst "asthma" indicates a single condition. Therefore I will not discuss the patterns in the prevalence of conditions in detail but will note some key points.

Mental illness is recorded in the Original ACONF. However, I have not examined in detail the role of these conditions in the way I did for Diamond. This is partly because numbers are small and so my study is not powered to detect any associations. Additionally, individuals were not asked to consider mental health conditions specifically. As described earlier in my thesis, mental health conditions are subject to far greater self-stigma and under-reporting than physical health conditions. By not specifically asking about these conditions it is likely the bias from under-reporting would be too great to trust any finding. Additionally, as I do not have access to the original responses, I do not know the nature of mental health conditions reported in order to assess how they may be playing a role.

The prevalence of self-reported multimorbidity was 5%. In looking for studies using self-report, I examined the prevalence in studies included in the systematic reviews of Violan *et al*[51], Marengoni *et al*[31] and Fortin *et al*.[26] I additionally searched the cohort studies from my review described in Chapter 1 and Chapter 3. I was unable to find any study using a comparable measure. Those using self-reported measures of multimorbidity in the general population generated these either from individuals being asked to list clinician diagnosed conditions or being asked to select from a pre-set list.[307-312]

Determinants of self-reported multimorbidity

I found an association between social class at birth and self-reported multimorbidity in middle age and an association between social class at birth and adult social class. Population health research strongly supports that inequalities are driven by wider social, environmental and economic factors.[313-315] Societies form systems of social and economic stratification which influence the distribution of resources and social goods and it is where the distribution and accumulation of these resources is unequal that differences in health arise between socio-economic groups.[316]

Furthermore evidence shows that the larger the difference between rich and poor the greater the impact upon health and wellbeing.[317] Individuals with a "lower" position in society in terms of employment, income and social circumstances have been shown to have a lower sense of control and higher stress due to feelings of subordination and social

comparison ("not doing as well as others").[18,314,317] Therefore, even though individuals today enjoy greater material advantage than those historically, ongoing relative differences between groups mean findings in this chapter are likely generalisable to children today.

There are a number of routes by which these socio-economic factors affect children in families with lower parental or care-giver SES (from here-on I will use the term "parent" to cover both parents and other care-givers). Parents with lower SES are likely to have low-income occupations which are more commonly insecure with anti-social hours leading to stress and health problems.[314,318-320] The related ability to afford healthy food or to have the time to cook healthy meals may be limited.[314,318-320] Parents with lower income may not be able to afford high quality housing and children may live in cramped conditions. Families may be more likely to live in areas with higher crime rates, exposing children to stressful situations from a young age. Parental stress may impact on the family wellbeing and cohesion, leading to stress in the child.[314,318-320] The lack of an available adult role model may impact on a child's ability to engage with education and carry out home-work and other extracurricular activities.[314,318-320]

These factors impact on an individual's future health and life chances in a range of linked ways and accumulate over time. Exposure to stressors when young can impact directly on neurobiological development.[321] For example, studies have shown that children in families in poverty have changes in brain function due to the impact of cortisol (the stress hormone) on the developing brain. This can manifest as poorer language skills, learning ability and mental health.[321-323] Chronic stress also can lead to poorer physical health, even in childhood.[79] Control and empowerment have been shown to lead to improved health and wellbeing.[314,324] These are inextricably linked to the factors described above and are shown to be lower in individuals with lower SES.[314,324]

Higher educational attainment may positively affect health and wellbeing. This can be explained by the fact that higher educational qualifications give opportunities to access higher income occupations and confer the protections of higher SES.[324] Additionally, the sense of achievement, empowerment and control due to gaining qualifications and achieving higher status occupations can confer psychosocial protections.[314,324] It is

sometimes posited that a higher education level means individuals understand health promotion messages better. However evidence shows that individuals with lower educational attainment understand these messages but that take-up is limited by the financial and psychosocial barriers I have described above.[325]

Much of what I have described in this section also relates to factors which confer resilience. In Diamond I found a link between educational attainment and employment status with SRH and activity limitation resilience. I was unable to study this in detail in the ACONF due to the small sample size with resilience to self-reported multimorbidity. The lack of the association with birth social class for example, could be due to low power.

In this cohort, the oil and gas industry will have had an impact on the determinants of health. Many Aberdonians enjoyed higher incomes than may have been the case elsewhere for a given educational attainment or employment status. This would have the effect of lessening the role of educational attainment in my study.

I found that cognition scores at age 7 were associated with self-reported multimorbidity but only on the basis that those in the lowest quintile had a higher OR for multimorbidity. This likely relates to the fact that the lowest quintile can encompass those with other disabilities. For example, individuals with Down's syndrome would have lower test scores and these individuals will also be more likely to develop a number of health conditions over life. [326]

I found that social class at birth was associated with a lower cognition score. This ties in with my discussion above regarding the evidence base for the impact of poorer SES on brain function and schooling. Additionally, cognition tests can be prepared for, and those with parents who have higher educational attainment themselves may experience greater advantage when sitting the test.[327]

I also found that a lower social class at birth meant an individual was more likely to attend a non-elite school and that the prevalence of self-reported multimorbidity was higher in those who had attended non-elite compared to elite schools. These findings are consistent with others who have found that selective schooling may widen inequalities.[253,328] This is

both because attendance at an elite school is more likely in those in families with higher SES and that elite school attendance can increase the likelihood of higher future educational attainment and higher future SES.[328] As described in Chapter 6, those attending a non-elite school in Aberdeen during the time period of the cohort, were unable to complete higher qualifications and therefore would be limited in achieving higher educational attainment. The attendance at an elite school was also partly based upon cognition scores. Therefore it is likely that the pathway between childhood SES to later life health and the role of educational attainment can be at least partly explained by the structure of the educational system. A paper by Clark and Del Bono used the ACONF to examine the impact of schooling type and found elite school attendance improved educational attainment.[227]

There was a cross-sectional relationship between self-reported multimorbidity and adult social class, employment status and income. As described in the previous chapter, these variables are closely linked and are all markers of SES. This relationship is consistent with those studies showing an association between multimorbidity and adult SES.[2,60,63] Due to the cross-sectional nature of the measurement in my study it could equally be argued that those with multimorbidity may not be able to work, to achieve high incomes or to be employed in occupations which would be scored as "higher" social class. As a result, and following my *a priori* set hypothesis and methodology, I do not adjust for these variables in the model of the relationship between social class at birth and self-reported multimorbidity.

The finding of an association between being underweight or obese with higher self-reported multimorbidity prevalence ties in with the evidence regarding the influence of BMI on health.[231] Similarly the findings that multimorbidity prevalence was higher in current smokers is consistent with evidence regarding smoking and poor health.[216] Social class at birth was also associated with these variables. This is an important illustration of the life-long impact of SES.

Self-reported multimorbidity prevalence was slightly higher in those who reported having a hangover less than once a month compared to those reporting none in the past year.

However, the difference was slight. As described in the previous chapter, this measure of alcohol consumption is not ideal and so I do not think it is reasonable to suggest that this finding is "clinically" significant.

Since conducting my analysis a number of further studies have examined socio-economic determinants of multimorbidity. Katikireddi *et al* conducted analysis on the West of Scotland Twenty-07 study, which commenced in 1987 and included participants born between the 1930s and 1970s. The study found adult SES predicted the development of multimorbidity and that inequalities were largest between 50 and 70 years. The authors also found that smoking, poor diet and other risk factors were important predictors, but that they did not fully mediate the relationship between SES and multimorbidity.[329]

A study of 10,186 longitudinal cohort members (not a birth cohort) in Canada examined determinants of multimorbidity. Multimorbidity was self-reported on the basis of the presence of a clinically diagnosed condition from a list of 17 chronic conditions. Follow-up was over 18 years and almost 40% were lost to follow-up.[330] Multimorbidity prevalence was higher with age and was higher in women compared to men and in those with lower incomes. There was a faster accumulation of multimorbidity in those with a lower rather than a higher income level. This indicates that socio-economic differences may become more marked over time.

Outcomes

There was no association between social class at birth and mortality or hospital admissions. Given the evidence that these outcomes are socio-economically patterned, [18,331] this is an interesting finding of note. I hypothesise that the age of the population by the end of follow-up could be too low to detect this or that it is an effect of selection bias in terms of which individuals were CHI seeded.

As evidence shows that the number of morbidities tends to increase with age,[26,31] the lack of an association between self-reported multimorbidity in middle age and secondary care multimorbidity burden in early older age is unexpected. Seeman *et al* found that multimorbidity at baseline was associated with the development of multiple new

conditions at follow-up.[68] Quinones *et al* examined multimorbidity as an exposure and multimorbidity accumulation by different racial and ethnic groups in the United States as the outcome.[65] The study found that multimorbidity accumulation was higher when individuals had higher functional impairment, poorer self-rated health, a higher level of depressive symptoms and higher BMI at baseline.[65] The finding is interesting and warrants further investigation of the relationship between contrasting measures of multimorbidity and the role of multimorbidity as an outcome in those with multimorbidity.

I did not find a statistically significant association between self-reported multimorbidity and mortality rate. However there was a suggestion of a higher rate of mortality in those with multimorbidity in the Kaplan-Meier graph as the follow-up period ended. Follow-up of this as the cohort ages is therefore recommended.

In Chapter 1 I described that there is mixed evidence regarding the association between multimorbidity and mortality and hospitalisation.[31,54,59,61,62,64,67-70] Since my study was conducted there have been further studies with mixed findings.[332-334] For example, a recent study by Hewitt *et al*, of 413 older adults admitted for emergency general surgical procedures in the UK, measured multimorbidity on the basis of a count of 18 pre-defined conditions (sourced from the Charlson index and recommendations from the Diederichs review). Multimorbidity was defined as two or more conditions and data were sourced from case-note review. The authors found no association with the length of hospital stay, readmission or 90 day mortality.[332] Dattalo *et al* compared four different measures of multimorbidity in administrative data and found the ability to predict 30 day hospital readmission varied between each.[334]

For the outcome of hospital admissions, I included all hospital admissions to either the general acute hospital or psychiatry. For the latter, individuals may experience very long periods of stay (lasting more than a year) with short episodes out of hospital, which in the SMR04 database may not count as a discharge. For the purposes of my thesis I did not examine the rate of admissions with psychiatric stays removed but this would be an interesting area of future research.

Resilience to self-reported multimorbidity

I started the analysis by examining how the "resilient" responses varied between those with and those without self-reported multimorbidity. This is not a measure of resilience as resilience is defined as a "positive" response despite adversity (multimorbidity). However, as I am using novel approaches to measure resilience to self-reported multimorbidity, it is reassuring to see that the prevalence of "positive" responses is higher in those without the adversity across all five measures (SRH, enjoyment, positive mood, negative mood and low self-esteem).

The prevalence of resilience varied across all five measures. As my study used a number of novel measures to measure resilience (informed by a comprehensive literature review) there are complexities in drawing comparison with the literature. This was made additionally difficult by the lack of consensus over the definition or measurement of resilience. Indeed, the review by Windle which I described in Chapter 5 quotes resilience prevalence figures ranging from 25% to 84%.[84]

Self-report of morbidity, where individuals have not been asked to consider if it has been diagnosed clinically, can reasonably be argued to be a measure of resilience in itself. Individuals who are "resilient" may not report any conditions and may not be classed as multimorbid. Therefore, the multimorbidity population studied in this chapter may itself be representative of a population with lower levels of resilience (across any domain).

As for Diamond, the resilience data I am using are drawn from the same questionnaire as the information on morbidities and other characteristics. If this has an impact it would likely that individuals reporting morbidities are more likely to respond in a manner which means they are classified as having lower resilience. The SRH measure in ACONF was asked before the morbidity questions (which helps reduce this impact) however the GHQ measures (enjoyment, positive mood state, negative mood state and self-esteem) were asked after. It could be that the prevalence of resilience measured by the GHQ would be higher if the questions had occurred before the measurement of morbidities.

Small sample size impacted on the ability to study the determinants and outcomes of resilience. Therefore the finding of no association between social class at birth and resilience to self-reported multimorbidity and no association between any of the measures and secondary care multimorbidity in 2016 and the hospitalisation rate needs to be interpreted cautiously.

The finding of an association between SRH resilience and mortality is interesting and ties in with literature regarding the SRH being a useful predictor of outcome as described in Chapter 5.[85,174,180,181] The measure is hypothesised to capture a range of features including an individual's internal and external resources (such as psychological factors and the wider social, economic and environmental determinants of health).[85,174,180,181] It may be a sensitive measure of objective health status. An individual may be consciously or unconsciously taking into account their medical history and other factors such as symptoms of as yet undiagnosed disease.[174,180] SRH may be a dynamic evaluation of an individual's health and reflect a trajectory of health which is not visible to the external observer. For example an individual may have noticed a decline in health from a previous state judged to be healthy and so rate their health as low. This could represent an ongoing downwards trajectory for that individual.[180]

9.9.3 Strengths and limitations

I described in Chapter 1 that there is a well-established evidence base showing an association between SES and health outcomes[18] but also that there are a number of evidence gaps with regards to this (particularly childhood SES) and multimorbidity. My findings therefore make important additions to the evidence base.

I found that social class at birth was associated with self-reported multimorbidity but acknowledge the associations are not strong and also that confidence intervals are wide reflecting a lack of precision. As described in the Methodology, the Bradford-Hill criteria are often used to assess whether an observed relationship is causal and an important feature is that cause precedes effect, which can be shown in the model. A gradient of effect is also supportive of causation,[253] so the finding of an increase in OR of association between

social class at birth and self-reported multimorbidity with decreasing social class category is reassuring.

It could be argued that poor health in childhood may lead to poorer educational attainment as individuals are prevented from completing higher education. I do not have access to health data in childhood in the ACONF but evidence from other studies shows these effects are small.[335]

Questionnaire responders were more likely to have higher birth social class and this could impact my findings in two key ways. Firstly, the results in the lower categories may be less precise, and indeed there were wide confidence intervals observed. A second issue is that those who have responded from lower birth social class categories may not be representative of the remainder of the group. Although this will somewhat affect all the categories, the effect may be greater. For example, it could be that those who do not have self-reported multimorbidity were more likely to respond and it could be that those who do have multimorbidity were more likely to respond if they had higher educational attainment.

In general, those not responding to the questionnaire may have more severe illnesses or lower levels of resilience to illness than those who do. It is likely therefore that if bias does exist, it means that the prevalence of self-reported multimorbidity and of resilience to self-reported multimorbidity are under-estimated compared to the general population.

The fact that important features such as BMI, smoking and adult social class could not be included in the model analysing the association between social class at birth and self-reported multimorbidity is of concern, as these are important residual confounders. However, I also argue that not doing so is the correct methodological approach given that we cannot be certain of the causal relationship between the variables and self-reported multimorbidity as they were measured cross-sectionally.

Educational attainment and secondary school type were measured at the time of the questionnaire. However, for school type, given that it must have occurred in the past, my approach is reasonable. Educational attainment primarily concerns school qualifications.

However, there may be individuals who are currently students and will be achieving degree level qualification. However, I showed in the previous chapter that only 28 individuals (0.4%) reported being a student. Therefore the impact of this is negligible. The nature of occupations included in the social class categories changed over time to reflect changing nature of occupations. However, this was not an issue in my study as the classification system is based upon the same principles.

I used ordinal logistic regression to assess the association between birth social class and a number of ordinal variables (educational attainment, cognition quintiles, hangover frequency, smoking status and adult social class). As described in Chapter 6, an assumption for this type of analysis is that the effect of the exposure variable is proportional across the thresholds between each pair of categories in the ordinal outcome variable. This is plausible for educational attainment, cognition quintiles, hangover frequency and adult social class. However, it is less so for smoking where it is debatable that it is an ordinal variable. The ex-smoker group is usually very heterogeneous and may include individuals who smoked lightly many years previously and those who smoked heavily and stopped due to poor health.[336] I do not have access to data on when ex-smokers stopped smoking and how heavy their smoking was whilst they were a smoker. Conducting ordinal regression with smoking status can therefore be challenged. An alternative could have been to assess whether an association existed using the CHI squared test. However, as the relationship being studied is not fundamental to the primary aims of this chapter, the impact of treating smoking status as an ordinal variable is minimal.

The observed results could be due to chance. I have noted above that a number of confidence intervals were wide and that I am careful not to interpret the lack of association as being “true”. Low power is a concern in my resilience analysis. I had determined that this would be an issue in my thesis protocol but proceeded as my aim was to develop a consensus definition and approach to measuring resilience and then test this.

I was unable to access the original responses to the questionnaire regarding the nature of self-reported morbidities and only have information based upon categorisation by the original study team. However, in terms of my study aim, which is to assess the burden of

self-reported multimorbidity this is not a limitation. My multimorbidity measure explicitly captures the *number* of conditions (of any nature) which are of sufficiently high burden to be reported by an individual. Researchers wishing to explore this further could seek permission from the ACONF steering group to examine the responses in detail, however this information has not previously been approved for release.

In order to develop the evidence base regarding life-course determinants of multimorbidity, I have deliberately focussed on social class at birth and the role of educational attainment. As part of exploratory univariate analyses I found a number of other important variables which influenced the development of self-reported multimorbidity. To explore the role of childhood SES on self-reported multimorbidity, I also conducted univariate analyses of the association between social class at birth and the majority of key cohort characteristics. I did this because it provides insight as to the possible mechanisms behind the findings in the chapter. There are other techniques available for testing multiple inter-related variables across the life-course. However, these are the next steps in research into life-course multimorbidity. I discuss this in more detail in the final chapter.

The outcomes were measured using linked health and mortality data. As a result, there was a large proportion of missing outcome data for the postal questionnaire responders. I therefore have been cautious in my interpretation of the findings, as bias and low power will likely play a much greater role. For the outcome measurement, the lack of regular updated status information is a clear source of bias. For example, the lack of information regarding movements into and out of Scotland is an issue. Individuals known to be alive, resident and Scotland and CHI seeded in September 2016 may still have had periods where they lived outside Scotland and had a hospital admission for example.

10 Enhanced ACONF

10.1 Structure of chapter

Please see "additional declaration" on page *xvi* for information regarding sections 10.3 to 10.6. In this chapter I describe the findings for objectives two to four in the 2001 and 2016 Enhanced ACONF populations. I start the chapter by presenting the prevalence of Barnett morbidities and multimorbidity, and show the association between secondary care multimorbidity and key population characteristics. After this, I model the relationship between social class at birth and secondary care multimorbidity and assess the role of educational attainment and other key variables. I then present analysis of outcomes in those with secondary care multimorbidity in 2001. Following this I examine the prevalence of resilience to secondary care multimorbidity and outcomes in those with resilience. The resilience measures are: SRH, enjoyment, positive mood, negative mood, low self-esteem and activity limitation resilience.

10.2 Prevalence of secondary care morbidities and multimorbidity

10.2.1 Enhanced ACONF: 2001 population

The number of individuals with each of the Barnett conditions in the 2001 population is in Table 70. The most common conditions were "pain" (426 individuals, 5%), "alcohol misuse" (2%), "cancer" (1%) and "coronary heart disease" (1%). The least common (with 10 or less individuals) included "heart failure", "chronic obstructive pulmonary disease" (COPD), "Parkinson's Disease" and "dementia".

Table 70: Enhanced ACONF 2001: Number and prevalence (%) of Barnett conditions ordered from highest to lowest from left, down columns to right (n=8,438)

Condition name	Number	%	Condition name	Number	%	Condition name	Number	%	Condition name	Number	%
Pain	426	5.0	Liver	30	0.4	Epilepsy	19	0.2	Hearing	10 or less	0.1 or less
Alcohol misuse	195	2.3	Hypertension	28	0.3	Prostate	16	0.2	Drug problems		
Cancer	81	1.0	Constipation	27	0.3	Irritable Bowel Syndrome	16	0.2	Migraine		
Coronary Heart Disease	62	0.7	Peripheral vascular disease	26	0.3	Viral Hepatitis	14	0.2	Anxiety		
Rheumatoid Arthritis	39	0.5	Stroke	25	0.3	Dyspepsia	13	0.2	Glaucoma		
Inflammatory Bowel Disease	39	0.5	Schizophrenia/bipolar	23	0.3	Skin problems	12	0.1	Anorexia		
Depression	37	0.4	Multiple Sclerosis	22	0.3	Heart Failure	10 or less	0.1 or less	Parkinson's Disease		
Asthma	35	0.4	Sinusitis	22	0.3	COPD			Dementia		
Diabetes	31	0.4	Thyroid	20	0.2	Vision			Learning disability		
Diverticulitis	30	0.4	Atrial fibrillation	19	0.2	Chronic kidney disease			Bronchiectasis		

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; ACONF, Aberdeen Children of the 1950s

The frequency of Barnett conditions and the prevalence of secondary care multimorbidity is in Table 71. The maximum number of conditions any individual had was six. There were 7,424 individuals with no recorded condition (88% [95% CI 87%- 89%]), 762 with one (9% [95% CI 8%- 10%]) and 23 (0.3% [95% CI 0.2% - 0.4%]) with four to six. There were 252 individuals with secondary care multimorbidity, amounting to 3% (95% CI 2.6% - 3.4%).

Table 71: Enhanced ACONF 2001: Number of Barnett conditions and prevalence (%) of secondary care multimorbidity (n=8438)

Morbidity status	Number	%	95 % CI
Number of conditions			
Zero	7,424	88.0	87.3-88.7
One	762	9.0	8.4-9.7
Two	178	2.1	1.8-2.4
Three	51	0.6	0.5-0.8
Four to six	23	0.3	0.2-0.4
Multimorbidity status			
No multimorbidity	8,186	97.0	96.6-97.4
Multimorbidity	252	3.0	2.6-3.4
Total	8,438	100	

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

10.2.2 Enhanced ACONF: 2016 population

The number of individuals with codes for each of the Barnett conditions in the 2016 population is in Table 72. The most common conditions were “pain” (7%), “diverticulitis” (4%), “hypertension” (3%), “alcohol misuse” (3%) and “cancer” (3%). The least common, affecting ten or less individuals, included “glaucoma”, “Parkinson’s Disease” and “dementia”.

Table 72: Enhanced ACONF 2016: Number and prevalence (%) of Barnett conditions ordered from highest to lowest from left, down columns to right (n=7,353)

Condition name	Number	%	Condition name	Number	%	Condition name	Number	%	Condition name	Number	%
Pain	539	7.3	Peripheral Vascular Disease	102	1.4	Chronic Kidney Disease	43	0.6	Glaucoma	10 or less	0.1 or less
Diverticulitis	274	3.7	Prostate	85	1.2	Heart Failure	31	0.4	Viral Hepatitis		
Hypertension	240	3.3	Atrial Fibrillation	84	1.1	Epilepsy	22	0.3	Dementia		
Alcohol misuse	222	3.0	Stroke	75	1.0	Depression	19	0.3	Sinusitis		
Cancer	210	2.9	Rheumatoid Arthritis	57	0.8	Schizophrenia / Bipolar	19	0.3	Hearing		
Coronary Heart Disease	153	2.1	Thyroid	55	0.7	Multiple Sclerosis	18	0.2	Bronchiectasis		
Diabetes Mellitus	140	1.9	Constipation	53	0.7	Migraine	15	0.2	Drug misuse		
COPD	128	1.7	Liver	50	0.7	Irritable Bowel Syndrome	12	0.2	Parkinson's Disease		
Vision	124	1.7	Dyspepsia	46	0.6	Skin	11	0.1	Learning Disability		
Asthma	123	1.7	Inflammatory Bowel Disease	44	0.6	Anxiety	10 or less	0.1 or less	Anorexia		

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; ACONF, Aberdeen Children of the 1950s

The frequency of the Barnett conditions and the prevalence of secondary care multimorbidity is in Table 73. The maximum number of conditions any individual had was 8. Out of 7,353 individuals, there were 5,422 individuals (74% [95% CI 73% -75%]) with no recorded Barnett conditions, 1,193 with one (16% [95% CI 15%- 17%]) and 85 (1% [95% CI 0.9%-1.4%]) with four or more. The prevalence of secondary care multimorbidity was 10% (95% CI 9%- 11%).

Table 73: Enhanced ACONF 2016: Number of Barnett conditions and prevalence of secondary care multimorbidity (n=7353)

Morbidity status	Number	%	95% CI
Number of conditions			
Zero	5,422	73.7	72.7-74.7
One	1,193	16.2	15.4-17.1
Two	487	6.6	6.1-7.2
Three	166	2.3	1.9-2.6
Four to eight	85	1.2	0.9-1.4
Multimorbidity status			
No multimorbidity	6,615	90.0	89.3-90.6
Multimorbidity	738	10.0	9.4-10.7
Total	7,353	100	

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

10.3 The association between secondary care multimorbidity and study population characteristics

10.3.1 Enhanced ACONF: 2001 population

Table 74 shows the secondary care multimorbidity prevalence by cohort characteristics in the 2001 population. Of 4,303 men, 3% (95% CI 3% - 4%) had multimorbidity, which was comparable to the prevalence in women (3% [95% CI 2%- 4%]). The mean age of those with secondary care multimorbidity was comparable to those without (48 years, SD 1.5 for both).

Table 74: Enhanced ACONF 2001: secondary care multimorbidity by baseline variables with measures of association (n=8,438)*

Categories	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	p value**
Total	8438	252	3.0	2.6-3.4	
Gender					
Male	4,303	132	3.1	2.6-3.6	0.655
Female	4,135	120	2.9	2.4-3.5	
Mean age in September 2001	47.8 (SD 1.5)	47.6 (SD 1.5)			0.218
Scottish Index of Multiple Deprivation quintile					
One (most deprived)	287	38	13.2	9.8-17.7	<0.001
Two	614	78	12.7	10.3-15.6	
Three	426	45	10.6	8.0-13.9	
Four	511	40	7.8	5.8-10.5	
Five (least deprived)	828	51	6.2	4.7-8.0	
Social class of the father at birth of the participant					
I/II (Professional/ Managerial)	718	17	2.4	1.5-3.8	0.556
III (Skilled non-manual)	905	34	3.8	2.7-5.2	
III (Skilled manual)	3,753	109	2.9	2.4-3.5	
IV (Partly skilled)	1,189	31	2.6	1.8-3.7	
V (Unskilled)	1,447	47	3.3	2.4-4.3	
Unemployed/ unknown/disabled/dead	426	14	3.3	2.0-5.5	
Mean cognition score age 7	106.6 (SD 16.2)	105.6 (SD 16.6)			0.311
School Type					
Non-elite or other	3,815	107	2.8	2.3-3.4	0.471
Elite	1,472	36	2.5	1.8-3.4	
Educational attainment					
Tertiary (degree)	942	23	2.4	1.6-3.6	0.689
Tertiary (non-degree)	874	23	2.6	1.8-3.9	
Advanced level	712	17	2.4	1.5-3.8	
Ordinary level	1,529	35	2.3	1.6-3.2	
School leaving/none	1,346	42	3.1	2.3-4.2	

(contin. overleaf)

Categories	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	p value**
2001 adult Employment status					
Paid work	4,627	117	2.5	2.1-3.0	0.221
Not in paid work (unemployed/student)***	172	7	4.1	1.9-8.3	
Permanently sick	334	10	3.0	1.6-5.5	
Retired from paid work	39	3	7.7	2.5-21.6	
Looking after family	255	6	2.4	1.1-5.1	
2001 adult social class					
I/II (Professional/ Managerial)	2,103	51	2.4	1.8-3.2	0.930
III (Skilled non-manual)	1,386	39	2.8	2.1-3.8	
III (Skilled manual)	1,029	28	2.7	1.9-3.9	
IV (Partly skilled)	571	16	2.8	1.7-4.5	
V (Unskilled)	255	8	3.1	1.6-6.2	
2001 adult annual income					
Less than £10,000	1,598	48	3.0	2.3-4.0	0.034
£10,000 to £19,999	1,594	46	2.9	2.2-3.8	
£20,000 to £39,999	1,494	41	2.7	2.0-3.7	
£40,000 or more	662	6	0.9	0.4-2.0	
Mean 2001 adult body mass index	26.5 (SD 4.7)	26.6 (SD 6.5)			0.953
2001 adult smoking status					
Current smoker	1,496	46	3.1	2.3-4.1	0.343
Ex-smoker	1,367	30	2.2	1.5-3.1	
Non-smoker	2,601	69	2.7	2.1-3.3	
2001 adult alcohol related hangovers in past year					
At least once a week	124	6	4.8	2.2-10.4	0.046
1-3 times a month	604	7	1.2	0.6-2.4	
Less than once a month	2,040	55	2.7	2.1-3.5	
Not at all in the last year	2,368	68	2.9	2.3-3.6	
2001 self-reported multimorbidity					
Present	298	13	4.4	2.6-7.3	0.155
Absent	5,181	132	2.6	2.2 -3.0	

Abbreviations: 95% CI, 95% confidence interval; SD, standard deviation; ACONF, Aberdeen Children of the 1950s

* Figures presented are numbers and proportions unless stated otherwise ** Statistical significance set at 5% level. CHI test used for binary variables, CHI test for trend for variables with more than two categories, independent t test of means *** These categories are combined due to small numbers

The prevalence of secondary care multimorbidity was highest in the most deprived SIMD quintile (13% [95% CI 10% - 18%]) and lowest in the least SIMD deprived quintile (6% [95% CI 5% -8%]). This was statistically significant (p<0.001). There was no statistically significant association with social class of the father at birth (p=0.556). The prevalence was 2% (95% CI 2% -4%) in those born into class I/II and 3% (95% CI 2% - 6%) in those whose fathers were unemployed, disabled or dead. The mean cognition score at age 7 was comparable between those with and without secondary care multimorbidity (107, SD 16.2 for those without multimorbidity and 106, SD 16.6 for those with multimorbidity).

There was no association between secondary care multimorbidity and secondary school type, educational attainment, adult employment status, adult social class, BMI, smoking status and hangover frequency. There was a statistically significant association between adult income and secondary care multimorbidity prevalence (p=0.034) but actual differences were small and confidence intervals were wide reflecting the small numbers in the categories.

There was no association between self-reported multimorbidity and secondary care multimorbidity in 2001 (p=0.155). Of 298 individuals with self-reported multimorbidity, 13 had secondary care multimorbidity (4% [95% CI 3% -7%]). Of 5,181 individuals without self-reported multimorbidity, 132 had Barnett multimorbidity (3% [95% CI 2%-3%]).

10.3.2 Enhanced ACONF: 2016 population

The secondary care multimorbidity prevalence in the 2016 population by cohort characteristics is shown in Table 75. The prevalence was comparable between men and women (11% [95% CI 10%- 12%], versus 10% [95% CI 9% -11%] respectively). The mean age was the same for those without multimorbidity compared to those with multimorbidity (64 years, SD 1.5 for both).

Table 75: Enhanced ACONF 2016: secondary care multimorbidity prevalence by baseline variables with measures of association (n=7353)*

Categories	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	p value**
Total	7353	738	10.0		
Gender					
Male	3,700	390	10.5	9.6-11.6	0.148
Female	3,653	348	9.5	8.6-10.5	
Mean age in September 2016	63.5 (SD 1.5)	63.5 (SD 1.5)			0.533
Scottish Index of Multiple Deprivation quintile					
One (most deprived)	295	121	29.1	24.9-33.6	<0.001
Two	418	159	27.6	24.1-31.4	
Three	388	141	26.7	23.1-31.0	
Four	446	112	20.1	16.9-23.6	
Five (least deprived)	894	205	18.7	16.5-21.1	
Social class of the father at birth of the participant					
I/II (Professional/ Managerial)	636	59	9.3	7.3-11.8	0.486
III (Skilled non-manual)	786	91	11.6	9.5-14.0	
III (Skilled manual)	3,300	316	9.6	8.6-10.6	
IV (Partly skilled)	1,045	101	9.7	8.0-11.6	
V (Unskilled)	1,221	133	10.9	9.3-12.8	
Unemployed/ unknown/disabled/dead	365	38	10.4	7.7-14.0	
Mean cognition score age 7	106.7 (SD 16.1)	105.5 (SD 15.6)			0.507
School Type					
Non-elite or other	3,344	329	9.8	8.9-10.9	0.944
Elite	1,310	128	9.8	8.3-11.5	
Educational attainment					
Tertiary (degree)	840	98	11.7	9.7-14.0	0.089
Tertiary (non-degree)	751	74	9.9	7.9-12.2	
Advanced level	632	57	9.0	7.0-11.5	
Ordinary level	1,356	132	9.7	8.3-11.4	
School leaving/none	1,181	106	9.0	7.5-10.7	

(contin. overleaf)

Categories	Total number	Number with multimorbidity	Multimorbidity prevalence (%)	95% CI	p value**
2001 adult Employment status					
Paid work	4,118	409	9.9	9.1-10.9	0.355
Not in paid work (unemployed/student)***	140	11	7.9	4.4-13.7	
Permanently sick	260	24	9.2	6.3-13.4	
Retired from paid work	32	3	9.4	3.0-25.7	
Looking after family	230	20	8.7	5.7-13.1	
2001 adult social class					
I/II (Professional/ Managerial)	1,872	202	10.8	9.5-12.3	0.153
III (Skilled non-manual)	1,221	109	8.9	7.5-10.7	
III (Skilled manual)	900	90	10.0	8.2-12.1	
IV (Partly skilled)	496	47	9.5	7.2-12.4	
V (Unskilled)	216	17	7.9	4.9-12.3	
2001 adult annual income					
Less than £10,000	1,391	120	8.6	7.3-10.2	0.070
£10,000 to £19,999	1,398	140	10.0	8.5-11.7	
£20,000 to £39,999	1,332	126	9.5	8.0-11.2	
£40,000 or more	592	71	12.0	9.6-14.9	
Mean 2001 adult body mass index	26.6 (SD 4.7)	26.4 (SD 5.1)			0.103
2001 adult smoking status					
Current smoker	1,257	113	9.0	7.5-10.7	0.045
Ex-smoker	1,206	105	8.7	7.2-10.4	
Non-smoker	2,353	253	10.8	9.6-12.1	
2001 adult alcohol related hangovers in past year					
At least once a week	104	9	8.7	4.5-15.8	0.348
1-3 times a month	537	50	9.3	7.1-12.1	
Less than once a month	1,808	166	9.2	7.9-10.6	
Not at all in the last year	2,088	210	10.1	8.8-11.4	

Abbreviations: 95% CI, 95% confidence interval; SD, standard deviation; ACONF, Aberdeen Children of the 1950s

* Figures presented are numbers and proportions unless stated otherwise ** Statistical significance set at 5% level. CHI test used for binary variables, CHI test for trend for variables with more than two categories, independent t test of means *** These categories are combined due to small numbers

There was a statistically significant association between secondary care multimorbidity and SIMD quintiles (p<0.001). The prevalence of multimorbidity in the most deprived SIMD quintile was 29% (95% CI 25%- 34%) and was 19% (95% CI 17% -21%) in the least deprived. As for the 2001 Enhanced population, no trend by secondary care multimorbidity was observed for remaining variables. For example, the prevalence was comparable across all social class categories at birth (9% in category I/II and 11% in category V). The mean cognition score at age 7 was 107, SD 16.1 in those without multimorbidity and 106, SD 15.6 in those with multimorbidity.

10.4 The association between social class at birth and secondary care multimorbidity, and the role of educational attainment and other mediating variables

10.4.1 Enhanced ACONF: 2001 population

The association between social class at birth and secondary care multimorbidity in 2001 is in Table 76. There were 8,438 individuals in the unadjusted model and the model was not statistically significant (p=0.560). No trend can be seen and all confidence intervals cross one. For example in relation to the reference group of III (manual) the OR in I/II was 0.8 (95% CI 0.5-1.4) and the OR in group V was 1.1 (95% CI 0.8-1.6).

Given the lack of the association between the exposure and outcome, I did not complete the mediation analysis steps as I did in the previous chapter. Instead I demonstrated, for illustration, the model adjusted by gender, educational attainment, secondary school type and cognition at age 7. This had no impact on the findings. For example the OR in group I/II was 1.0 (95% CI 0.5-2.0) and in group V it was 1.2 (95% CI 0.7-2.0). The confidence intervals were wider reflecting the loss in power due to missing data.

Table 76: Enhanced ACONF 2001: logistic regression analysis of association between social class of the father at birth and secondary care multimorbidity, models unadjusted and adjusted by gender, educational attainment, cognition at age 7 and secondary school type

Social class of the father at birth of the participant category	Number (unadjusted model, n=8,438)	Unadjusted n=8,438*		Adjusted by gender, educational attainment, cognition at age 7 and school type n=5,070*	
		Odds Ratio	95% CI	Odds Ratio	95% CI
I/II (Professional/ Managerial)	718	0.81	0.48-1.36	1.01	0.50-2.03
III (Skilled non-manual)	905	1.31	0.88-1.93	1.87	1.14-3.05
III (Skilled manual)	3,753	1 (reference group)			
IV (Partly skilled)	1,189	0.89	0.60-1.34	0.92	0.51-1.64
V (Unskilled)	1,447	1.12	0.79-1.59	1.21	0.72-2.02
Unemployed/ unknown/ disabled/ dead	426	1.14	0.65-2.00	1.46	0.66-3.25

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.560 **Model not statistically significant, p=0.542

10.4.2 Enhanced ACONF: 2016 population

There was no association between social class at birth and secondary care multimorbidity in 2016, p=0.487 (Table 77).

Table 77: Enhanced ACONF 2016: logistic regression analysis of association between social class of the father at birth and secondary care multimorbidity, models unadjusted and adjusted by gender, educational attainment, cognition at age 7, secondary school type, 2001 adult social class, body mass index, smoking status and hangover frequency

Social class of the father at birth of the participant category	Number (unadjusted model)	Unadjusted n=7,353*		Adjusted by gender, educational attainment, cognition at age 7, school type, 2001 adult social class, body mass index, smoking status and hangover frequency n=3,944*	
		Odds Ratio	**95% CI**	**Odds Ratio**	**95% CI**
I/II (Professional/ Managerial)	636	0.97	0.72-1.29	1.02	0.69-1.52
III (Skilled non-manual)	786	1.24	0.97-1.58	1.13	0.81-1.58
III (Skilled manual)	3,300	1 (reference group)			
IV (Partly skilled)	1,045	1.01	0.80-1.28	0.99	0.71-1.38
V (Unskilled)	1,221	1.15	0.93-1.43	0.96	0.70-1.33
Unemployed/ unknown/ disabled/ dead	365	1.10	0.77-1.57	1.17	0.69-1.98

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.487 **Model not statistically significant, p=0.410

For example, in relation to the reference group of III (manual) the OR in category I/II was 1.0 (95% CI 0.7-1.3) and the OR in category V was 1.1 (95% CI 0.9-1.4). The model was adjusted by gender, educational attainment, secondary school type, cognition at age 7, 2001 adult social class, 2001 adult smoking status, BMI and hangover frequency. There was no change to the overall finding of no association (p=0.410). For example, the OR in I/II was 1.0 (0.7-1.5) and the OR in category V was 1.0 (0.7-1.3).

10.5 Outcomes in those with secondary care multimorbidity in 2001

10.5.1 Status in 2016

The status of the 2001 cohort in 2016 is shown in Table 78. Of 8,438 individuals in 2001, 631 had died by 2016 (8%), 470 were elsewhere in the UK or had an unknown status (6%) and 7,337 were known to be alive and resident in Scotland (87%).

Table 78: Enhanced ACONF 2001: Follow-up status of individuals from 2001 to 2016

Status variable	Number	% of baseline
Total at baseline	8,438	100
Died by 2016	631	7.5
Elsewhere in UK or status unknown by 2016	470	5.6
Alive and resident in Scotland in 2016	7,337	87.0

Abbreviations: ACONF, Aberdeen Children of the 1950s

10.5.2 Secondary care multimorbidity in 2016

The relationship between secondary care multimorbidity in 2001 and in 2016 is in Table 79. The sample was limited to those with follow-up information to 2016 (n=7,337). There were 735 individuals with secondary care multimorbidity in 2016 (10% [95% CI 9%-11%]). Of those with secondary care multimorbidity in 2001, 39% (95% CI 32%-47%) had secondary care multimorbidity in 2016. Of those without secondary care multimorbidity in 2001, 9% (95% CI 9% -10%) had secondary care multimorbidity in 2016.

Table 79: Enhanced ACONF: relationship between secondary care multimorbidity in 2001 and secondary care multimorbidity in 2016

Secondary care multimorbidity status in 2001	Total population 2016	Number with secondary care multimorbidity in 2016	%	95% CI
No multimorbidity	7,181	674	9.4	8.7-10.1
Multimorbidity	156	61	39.1	31.8-46.9
Total	7,337	735	10.0	9.4-10.7

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

These findings are illustrated in the logistic regression analysis in Table 80. In the unadjusted model, the OR of having secondary care multimorbidity in 2016 was 6.2 (95% CI 4.5-8.6) in those who had secondary care multimorbidity in 2001, compared to the reference group of those without secondary care multimorbidity in 2001. This strong association remained when adjusting by important covariates.

Table 80: Enhanced ACONF 2001: association between secondary care multimorbidity in 2001 and secondary care multimorbidity in 2016, unadjusted, and adjusted by social class at birth, education, cognition, gender, age and school type

Secondary care multimorbidity status in 2001	Unadjusted (n=7,337)*		Adjusted by social class at birth, education, cognition, gender and school type (n=4,610)*	
	Odds Ratio	95% CI	Odds ratio	95% CI
Absent	1 (reference group)			
Present	6.20	4.45-8.63	5.36	3.36-8.53

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models statistically significant, p<0.001

10.5.3 Mortality

There were 8,094 individuals with complete follow-up information in 2001 for mortality survival analysis. The survival curve is in Figure 12. There was a violation of proportionality. It can be seen in the curve that survival is lower in those with secondary care multimorbidity in 2001 and that the gap between those with multimorbidity and without multimorbidity is increasing.

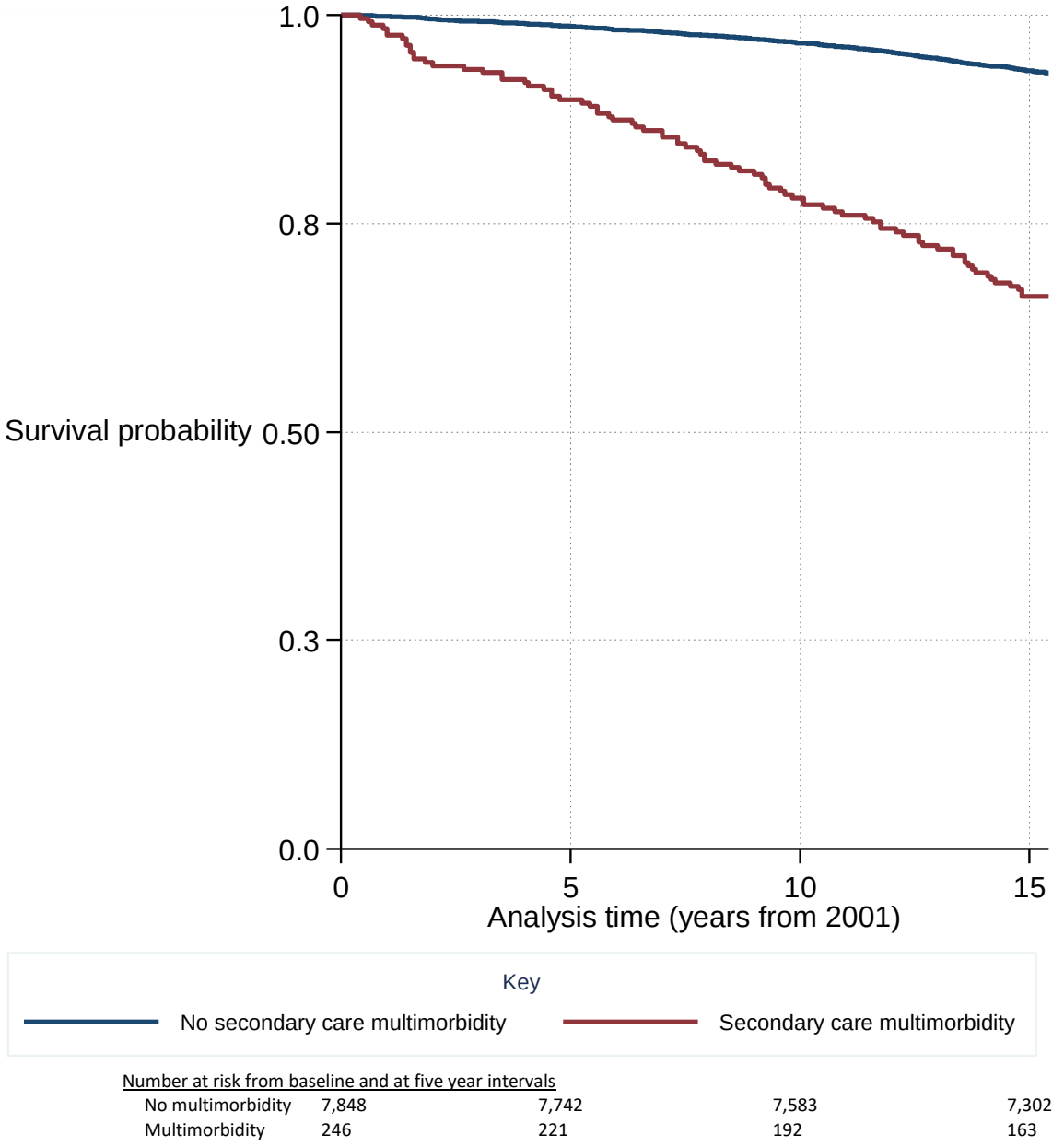


Figure 12: Enhanced ACONF 2001: Survival curve for secondary care multimorbidity from 2001 to 2016
Abbreviations: ACONF, Aberdeen Children of the 1950s

The mortality rate per 1,000 person years by secondary care multimorbidity status is illustrated in Table 81. There were 629 deaths in total, of which 83 were in those with

secondary care multimorbidity. The mortality rate per 1,000 person years was 26.2 (95% CI 21.2 – 32.5) in those with multimorbidity and 4.6 (95% CI 4.3-5.0) in those without multimorbidity.

Table 81: Enhanced ACONF: number of deaths and mortality rate, by secondary care multimorbidity status, from 2001 to 2016 (n=8,094)

Secondary care multimorbidity status in 2001	Number at baseline	Person-years at risk	Deaths	Mortality rate/ 1,000 person years	95% CI
Absent	7,848	117,705	546	4.64	4.27-5.04
Present	246	3,163	83	26.24	21.16-32.54
Total	8,094	120,868	629	5.20	4.81-5.63

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

The Cox regression results of the association between secondary care multimorbidity and mortality is in Table 82. In relation to the reference group of no secondary care multimorbidity, those with secondary care multimorbidity in 2001 had a mortality HR of 5.9 (95% CI 4.6-7.4) and this was broadly unchanged when adjusted by important covariates (HR 6.2, 95% CI 4.4-8.5). The models were statistically significant (p<0.001).

Table 82: Enhanced ACONF 2001: association between secondary care multimorbidity in 2001 and mortality rate, survival analysis, unadjusted and adjusted by social class at birth, education, cognition, gender and school type

Secondary care multimorbidity status in 2001	Unadjusted (n=8,094)*		Adjusted by social class at birth, education, cognition, gender and school type (n=5,049)*	
	Hazard Ratio	95% CI	Hazard ratio	95% CI
Absent	1 (reference group)			
Present	5.86	4.63-7.42	6.15	4.42-8.53

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models statistically significant, p<0.001

10.5.4 Admissions

The association between secondary care multimorbidity in 2001 and hospital admission rate using multiple failure survival analysis is in Table 83. In relation to the reference group of no secondary care multimorbidity, those with secondary care multimorbidity in 2001 had an admission HR of 1 (95% CI 0.9-1.1) and this was 0.9 (95% CI 0.8-1.1) when adjusted by important covariates. Neither model was statistically significant.

Table 83: Enhanced ACONF 2001: Association between secondary care multimorbidity in 2001 and rate of hospital admission using multiple failure survival analysis, unadjusted and adjusted by social class at birth, education, cognition, gender, age and school type

Secondary care multimorbidity status in 2001	Unadjusted (n=7,591)*		Adjusted by Social class at birth, education, cognition, gender and school type (n=4,755)**	
	Hazard Ratio	95% CI	Hazard ratio	95% CI
Absent				
Present	1.00	0.89-1.13	0.99	0.84-1.15

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Model not statistically significant, p=0.991
**Model not statistically significant, p=0.071

10.6 Prevalence and outcomes of resilience to secondary care multimorbidity in 2001

As described in the Methodology, I am measuring resilience cross-sectionally in 2001. Due to the small sample size, I have not shown findings for the association of social class at birth with resilience and between resilience and the outcome of secondary care multimorbidity in 2016.

10.6.1 Prevalence

The prevalence of resilience to secondary care multimorbidity in 2001 for each of the six domains is in Table 84 alongside the prevalence of the "resilient response" in those without secondary care multimorbidity. Due to the risk of disclosure this is not shown by gender as

numbers were too small. The prevalence of these responses were comparable between those with and without secondary care multimorbidity for all measures. For example, for “overall health wellbeing” the prevalence of fair to excellent SRH was 95% (95% CI 94%-96%) in those without secondary care multimorbidity and was 94% (95% CI 89%-97%) in those with secondary care multimorbidity (p= 0.738).

When focussing on the secondary care multimorbidity population only (Table 84), it can be seen that the prevalence of resilience was highest in the SRH and the positive GHQ measures (enjoyment and positive mood) and lowest in the negative GHQ measures (negative mood and low self-esteem). Of 144 individuals who responded to the SRH question, 136 (94%, 95% CI 89% - 97%) were classed as resilient. The proportions resilient to the positive GHQ questions were 88% (95% CI 81% - 92%) for enjoyment and 87% (95% CI 80% - 91%) for positive mood state.

Table 84: Enhanced ACONF 2001: Prevalence of resilience measures by secondary care multimorbidity status with test of association

		No multimorbidity				Multimorbidity			
Resilience measure	**p-value***	**Total**	**Number with resilient response****	**%**	**95% CI**	**Total**	**Number with resilient response**	**%**	**95% CI**
Overall health and wellbeing- SRH	0.738	5,301	5,039	95.1	94.4-95.6	144	136	94.4	89.3-97.2
Enjoyment- Positive GHQ 1	0.360	5,315	4,775	89.8	89.0-90.6	144	126	87.5	81.0-92.0
Positive mood state – Positive GHQ 2	0.436	5,292	4,695	88.7	87.8-89.5	142	123	86.6	80.0-91.3
Negative mood state- Negative GHQ 1	0.738	5,304	2,220	41.9	40.5-43.2	141	61	43.3	35.3-51.6
Low self-esteem – Negative GHQ 2	0.869	5,298	2,763	52.2	50.8-53.5	140	74	52.9	44.6-60.9
Activity Limitation	0.299	5,233	4,332	82.8	81.7-83.8	141	112	79.4	72.0-85.3

Abbreviations: SRH= self-rated health; GHQ = General Health Questionnaire; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Difference between those with and without multimorbidity, assessed by CHI squared test for association ** Not technically resilience given resilience is defined as the positive response in those with multimorbidity

Table 85: Enhanced ACONF 2001: Number of domains in which participants were resilient (n=139)

Number of domains in which resilient	**Number**	**%**	**95% CI**
None or one	10	7.4	4.0- 13.2
Two or three	20	14.7	9.6- 21.8
Four, five or six	106	77.9	70.1- 84.2
Total	136	100.0	

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

The prevalence of resilience to a negative mood state was 43% (95% CI 35% - 52%) and the prevalence of resilience to low self-esteem was 53% (95% CI 45% - 61%). The prevalence of resilience to activity limitation was 80% (95% CI 72%-85%). The confidence intervals for resilience prevalence across the measures were wide reflecting the underlying small numbers and low power.

The number of domains in which individuals were classed as resilient is shown in Table 85. Categories were combined due to small numbers. Ten individuals (7% [95% CI 4% - 13%]) were resilient in zero or one domain and 108 individuals (78% [95% CI 70% - 84%]) were resilient in four, five or six domains.

10.6.2 Outcomes

Mortality

The mortality survival data for the 6 resilience measures is in Table 86.

Table 86: Enhanced ACONF 2001: Cox regression survival analysis of the association between resilience measures in 2001 and mortality by 2016

Resilience measure	p-value*	Hazard ratio	95% CI
Overall health and wellbeing- SRH (n=142)			
Expected	0.036	1 reference group	
Resilient		0.37	0.15-0.94
Enjoyment- Positive GHQ 1 (n=142)			
Expected	0.098	1 reference group	
Resilient		0.55	0.27-1.12
Positive mood state –Positive GHQ 2 (n=140)			
Expected	0.726	1 reference group	
Resilient		0.84	0.37-1.91
Negative mood state- Negative GHQ 1 (n=139)			
Expected	0.596	1 reference group	
Resilient		0.90	0.50-1.62
Low self-esteem – Negative GHQ 2 (n=138)			
Expected	0.681	1 reference group	
Resilient		1.17	0.65-2.10
Activity limitation (n=139)			
Expected	0.573	1 reference group	
Resilient		1.24	0.59-2.61

Abbreviations: SRH= self-rated health; GHQ = General Health Questionnaire; 95% CI = 95% confidence interval; ACONF, Aberdeen Children of the 1950s

*Association tested using CHI-squared test of association

The lack of precision due to low power is reflected by the width of the confidence intervals. The data indicate an association between SRH resilience and mortality rate, p=0.036. In relation to the reference group of "expected" the HR of mortality in the resilience group was 0.4 (95% CI 0.1-0.9). For all other measures there was no association.

The number at baseline, the number of person years at risk, the number of deaths and the death rate per 1,000 person years for SRH resilience is in Table 87. Out of 142 individuals, eight were in the "expected" category and of these, five had died. The confidence intervals for the hazard ratios were very wide. The death rate per 1,000 person years in those who were in the expected group was 61.6 (95% CI 25.6-148.0) and for those who were resilient it was 23.3 (95% CI 17.2-31.6). Due to the very low number of deaths in the expected group, the survival curve is not shown.

Table 87: Enhanced ACONF: number of deaths and mortality rate, by self-rated health resilience status, from 2001 to 2016

Overall health and wellbeing- SRH	Number at baseline	Person-years at risk	Deaths	Mortality rate/ 1,000 person years	95% CI
Expected	8	81	5	61.60	25.64-147.99
Resilient	134	1,759	41	23.31	17.16-31.65
Total	142	1,840	46	25.00	18.72-33.37

Abbreviations: SRH, self-rated health; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s

Admissions

The results of multiple failure survival analysis assessing the association between the resilience measures and the rate of hospital admission is in Table 88. I found no association between any of the resilience measures and hospitalisation rate for all resilience measures.

Table 88: Enhanced ACONF 2001: Association between resilience measures in 2001 and rate of hospital admission by 2016 using multiple failure survival analysis

Resilience measure	p-value*	Hazard ratio	95% CI
Overall health and wellbeing- SRH (n=97)			
Expected	0.951	1 reference group	
Resilient		1.01	0.68-1.51
Enjoyment- Positive GHQ 1 (n=96)			
Expected	0.626	1 reference group	
Resilient		0.90	0.60-1.36
Positive mood state –Positive GHQ 2 (n=94)			
Expected	0.204	1 reference group	
Resilient		0.80	0.58-1.13
Negative mood state- Negative GHQ 1 (n=94)			
Expected	0.183	1 reference group	
Resilient		0.85	0.68-1.08
Low self-esteem – Negative GHQ 2 (n=94)			
Expected	0.332	1 reference group	
Resilient		0.89	0.69-1.13
Activity limitation (n=95)			
Expected	0.111	1 reference group	
Resilient		1.35	0.93-1.94

Abbreviations: 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models assessed by CHI squared test for association

10.7 Discussion

10.7.1 Summary of findings

Of 8,438 individuals in 2001, the secondary care multimorbidity prevalence was 3%. Of 7,353 individuals in 2016 the prevalence was 10%. In both Enhanced study populations, I found there was no difference in secondary care multimorbidity prevalence by age or gender. There was a reduction in the prevalence of secondary care multimorbidity from the most deprived through to the least deprived SIMD quintiles. Other than this there was no evidence of a trend in association of secondary care multimorbidity prevalence with any other of the baseline variables.

I found no association between social class of an individual's father at the birth and the presence of secondary care multimorbidity in 2001 or in 2016. This remained when adjusting by a variety of potential mediating and confounding factors.

There was a strong association between secondary care multimorbidity in 2001 and secondary care multimorbidity in 2016 and with the mortality rate. There was no association with the hospital admission rate.

There was no difference in the prevalence of the "resilient response" in those with secondary care multimorbidity compared to those without. The prevalence of resilience was highest in the SRH measure, the two positively worded GHQ measures (enjoyment and positive mood) and the activity limitation measure. It was lowest in the two negatively worded GHQ measures (negative mood and low self-esteem). The vast majority of individuals were resilient in between four and all six of the measures. There was a slightly lower mortality rate in those with SRH resilience. There was no association with mortality for any of the other measures. There was no association between any of the measures and hospital admissions.

10.7.2 Interpretation of findings

Secondary care multimorbidity

A first finding of note is that less individuals had no conditions in the 2016 population compared to the 2001 population and the prevalence of secondary care multimorbidity was higher. This is consistent with the accepted evidence that the number of health conditions increases as individuals age.[26,31] Given that external factors (such a recommendations for which conditions coders should look for) influence coding practice over time, prevalence changes should not be over-interpreted. However, broadly, the changes in the prevalence of conditions between 2001 and 2016 are in line with expected age related changes. For example, the prevalence of chronic conditions associated with older age such as hypertension, cancer, coronary heart disease and COPD are higher.[337] Some age-related conditions such as dementia are still rare in 2016. However, given that the population are in early older age this is not unexpected.

At the time of writing, no-one had studied the prevalence of multimorbidity in secondary care administrative data using the Barnett conditions. I have thus compared and contrasted my findings to those of Barnett themselves in their original paper. Although Barnett used a

primary care population, they did use administrative data and a Scottish population making contrasting the findings useful.[2] The prevalence of multimorbidity in the original Barnett paper was 30% in those aged 45-64 (the age range quoted in the study which is most comparable to this study).[2] The fact the Barnett prevalence estimate is higher may reflect the nature of the conditions included and the organisation of healthcare services in Scotland. I will describe these factors further here.

The five most common conditions in the original Barnett study were: hypertension (13%), depression (8%) and pain (7%), asthma (6%) and coronary heart disease (5%). The least common included Parkinson's disease, multiple sclerosis and chronic liver disease (all less than 0.3%).[2] I did not have the breakdown of these conditions by age. Depression is less than 0.5% in both my populations. Depression is known to be most commonly treated in primary care. Indeed, mental health conditions such as depression and anxiety only reach secondary care rarely and this indicates a severe end of the spectrum of the disease.[284] The low number of these conditions is why I did not study the role of mental health conditions in detail as I did in Diamond.

The healthcare system will also affect the prevalence of secondary care multimorbidity. In Scotland and the UK there is a strong universal primary care system in which GPs and other professionals provide high quality care. Primary care not only provides a "gate-keeping" role, but can provide care for many acute and chronic conditions which may in other countries, or historically in the UK, have required hospital admission.[338] This means that individuals will likely have a number of diagnosed health conditions which are not recorded in secondary care data. Coders can look at GP referral letters when coding but do not have to.

Evidence shows that as individuals age the likelihood they will develop conditions severe enough to warrant admission will increase.[339] Therefore, the prevalence of multimorbidity as measured in a secondary care population may become more comparable with that measured in a primary care population over time.

A further finding of note is that pain was the most prevalent condition in both the 2001 and 2016 populations (and also the third commonest condition in the original Barnett primary care study). This is an interesting finding given that I would have anticipated that non-specific diagnoses such as this would be less present in secondary care.[131]

As the Original and Enhanced ACONF populations are not identical (and only around 65% of the Enhanced populations had responded to the questionnaire) I am careful about comparing findings directly in this section. However, given my findings in ACONF and Diamond and my reviews of the literature in Chapter 1, the lack of association between social class at birth with secondary care multimorbidity is surprising. There was also no association between adult social class and secondary care multimorbidity. However, this again may be related to what is described above regarding the organisation and delivery of primary and secondary care services in Scotland. The cohort members may still be young enough to have the majority of their health conditions managed in primary care. It may be that any SES patterned healthcare usage would only be visible in primary care services.[338] The data I used did not include Accident and Emergency healthcare. It is possible that emergency healthcare use, which is accessed often without primary care referral, could produce relationships as seen in the previous chapter.

I did however, find that those living in more deprived areas (measured by the SIMD) had a higher prevalence of secondary care multimorbidity. This is consistent with the findings of the Barnett study and is a notable finding.[2] It is important to be aware that area based measures of deprivation and individual SES measures are different. This relates to the concept of "ecological fallacy" which refers to treating data collected at an area level as applying to an individual living in that area.[340] For example, a study by Davey Smith *et al*, in a Scottish population, showed that both area-based deprivation and individual social class were associated with poorer cardiovascular risk factors and outcomes.[341] However, these measures made independent contributions and the authors state the importance of considering both the characteristics of individuals living in an area as well as the characteristics of the area in which they live when aiming to reduce inequalities in health.[341] For example, the SIMD incorporates a measure of "access" to services, including transport

time to General Practice.[75] Those with poorer ability to access primary care may be more likely to become ill enough to be admitted to secondary care.

Notably, the postcode information supplying the SIMD status was available for only those who were CHI seeded AND who had an admission during the five year look-back period. This measure therefore restricts the population to those accessing secondary care services. The finding illustrates that in those of the cohort who do use secondary care services, the individuals from more deprived areas are more likely to have multimorbidity.

Secondary care multimorbidity in 2001 was associated with secondary care multimorbidity in 2016 which, as described in the previous chapter, is consistent with the findings of others. A further reason is the nature of the coding systems. I described in Chapter 4 that coders use other sources of information to code comorbidities. Individuals who are classed as having secondary care multimorbidity in 2001 will, by the very nature of the measure, have had one or more admission. If admitted again, coders are likely to refer to previous discharge letters and the same sources of information. Furthermore, the majority of conditions in Barnett are chronic in nature and so would be expected to be present in further admissions.

The finding that secondary care multimorbidity is associated with mortality and that the rate is increasing over time is a notable finding. Individuals using secondary care services, particularly at a younger age where primary care may usually provide most of the management, are likely reflective of a population with more serious illness. This could make them at greater risk of early mortality. As for the Original ACONF, I found no association with hospital admission rate and discussed some reasons for this in the previous chapter. However, given individuals need to have had an admission to be coded as having multimorbidity in the Enhanced ACONF, and on the assumption that those who have had an admission are more likely to have a further admission,[252] this is unexpected. It is possible that the follow-up period of 15 years is too short to observe this association if it does exist.

Resilience

The lack of a difference between those with and those without secondary care multimorbidity in the prevalence of the "resilient" response across all six measures in this chapter is not expected based upon my findings in Diamond and the Original ACONF. There are a number of potential reasons for this. Firstly, it may be that those with secondary care multimorbidity but who are not resilient to its effects were less likely to respond to the questionnaire. Additionally, those whose conditions are not severe or active, but who are still classified as multimorbid may have been more likely to respond than those with more serious conditions.

Additionally, the measure of secondary care multimorbidity was not drawn from the same source (the questionnaire) as the measures of resilience. This has the advantage that individuals are not "prompted" to report poorer wellbeing or function as a result of having being asked about health conditions. However, these measures may not be useful or appropriate when assessing resilience in a secondary care population. I discuss this with my recommendations in the next chapter.

In Chapter 9, I hypothesised that the self-reported multimorbidity measure is reflecting resilience to disease in that individuals who have greater resiliency are less likely to report two or more conditions. It could be argued that the use of health services also reflects resilience levels, whereby resilient individuals are more likely to self-manage than seek healthcare intervention.

The examination of outcomes in those with resilience (SRH, enjoyment, positive mood, negative mood, low self-esteem and activity limitation) was severely limited by power. I could not show results for the relationship to secondary care multimorbidity in 2016. For mortality, the SRH measure once again was associated with mortality and I have discussed reasons for this in the previous chapter. However, the number of deaths was small and the death rate confidence intervals were very wide.

10.7.3 Strengths and limitations

The key strength of this chapter is that I applied and tested the novel ICD-coded Barnett measure in a large study population. This paves the way for further study of Barnett multimorbidity in populations with healthcare systems which use the ICD (a commonly used coding measure globally). Given the high profile nature of the Barnett measure, this is an important step forward in generating consensus regarding the definition and measurement of multimorbidity. My analysis subsequent to the assessment of prevalence allowed me to apply this novel measure to a number of scenarios. However, selection bias and low power are a significant issues in this chapter and I have therefore been cautious about over-interpreting my findings.

Given that I was assessing both the prevalence of secondary care multimorbidity and its association with a number of different outcomes I used a disease count instead of a weighted measure based on the rationale outlined in Chapter 3. For the same reason I did not conduct analysis using more than one iteration of the Barnett measure. A study by Payne *et al* examined the relationship between multimorbidity measured using the Barnett measure in the same primary care population as the Barnett study, and the outcome of unplanned or potentially preventable admissions to hospital.[64] In this paper there was a distinction made between physical and mental health conditions as well as sensitivity analysis which included classifying the conditions as being "serious" or "not serious" based on what was described as "expert clinical opinion". However, this study was looking at one form of outcome as the main focus of the paper which is not what I was doing and so I did not adopt these approaches.

Conditions appearing in secondary care records will likely reflect a more serious burden of illness than those which would appear in primary care records. However, as described previously, not all conditions coded on discharge are active and may also have been sourced from primary care records. Although I have presented the conditions as measures of "prevalence" this will be impacted by changes in coding practice over time. Additionally, due to attrition, the population in 2016 is not the exact same population as in 2001.

Therefore examining and interpreting the "prevalence" of conditions must be taken with care. I have deliberately made broad conclusions rather than look at specific values.

The prevalence of multimorbidity is inevitably affected by the length of the look-back period. I set this at five years based upon the best available evidence, however there is no consensus on the time period. I did not aim to test the impact of different look-back period lengths, but acknowledge that changing the length could impact on the prevalence of secondary care multimorbidity and potentially on the findings of the other analyses. This latter point is the reason I fixed the look-back period *a priori*. It is surprising that there is not better consensus on look-back periods for either comorbidity or multimorbidity measures using administrative data. This is an important area of future research to which the findings of my thesis can contribute. A further area of recommended research is whether individual conditions should have different look-back periods within one measure.

Whilst I did not find the same association between social class at birth and multimorbidity in this chapter, I did find an association with the SIMD. This is consistent with the Barnett paper and so provides some support that missing data is not the sole reason for my findings. It is also a key and important finding in itself.

Confidence intervals were wide across the six resilience measures (SRH, enjoyment, positive mood, negative mood, low self-esteem and activity limitation). This reflects the underlying low power. When combined with selection bias related to differences between those with and without questionnaire data, findings in this section must be tested in other populations with greater power.

In the thesis I have measured resilience cross-sectionally. In the Original ACONF this was straightforward, as for each individual the data for the measurement of multimorbidity and that for the measurement of resilience were sourced from the questionnaire and thus at the same point in time. However, as the questionnaire was sent and returned over a year-long period, this is not true for the Enhanced ACONF. The data are therefore not truly cross-sectional. I selected the 30th September 2001 as the index date in which to measure secondary care multimorbidity as this was comparable with the end of the follow-up period

(30th September 2016). This is a further limitation in interpreting the prevalence of resilience across the six measures (SRH, enjoyment, positive mood, negative mood, low self-esteem and activity limitation) in this population and indeed the relationship between other questionnaire variables with multimorbidity. Future researchers could request access to the date of questionnaire return for each individual and make this the index date. This was not information I had access to.

Part four: Discussion and recommendations

11 Discussion

11.1 Structure of chapter

Throughout the thesis I have provided a detailed discussion on my findings at the end of each of the results chapters. In this chapter I summarise the key findings. I then describe key strengths and limitations and follow this with a discussion of important new developments in the literature. I finish with recommendations for future interventions, action and research.

11.2 Key findings

11.2.1 Objective one

Objective one was to determine how multimorbidity and resilience to multimorbidity should be defined and measured in Public Health research. I was the first to conduct a systematic review of relevant systematic reviews to seek evidence for consensus definitions and measures within the multimorbidity literature. From this, I defined multimorbidity as the co-existence of multiple conditions within an individual and found that a cut-off of two or more conditions was most commonly used by researchers in the field. Where a measure has been validated for a particular outcome of interest it should be used. Where there are no outcomes being considered or there are multiple outcomes then a disease count is appropriate.

Given there is no consensus disease count measure for use in the study of multimorbidity, utilising the Barnett measure is appropriate given its high profile nature. This paper has now been cited over 1,900 times indicating its ongoing influence in the multimorbidity field.

I was the first to adapt this measure for use in secondary care administrative databases (and indeed any database with ICD coding). I demonstrated the practical application of this measure in a large cohort and so have paved the way for this to be used by others in order to improve consensus in methodological approach between studies.

Drawing together the findings of my multimorbidity literature review with the implementation of the measures in Diamond and ACONF, I conclude that the following elements must be reported when conducting multimorbidity research:

1. The definition of multimorbidity
2. The name of the measure used
3. The list of conditions included
4. The data source
5. The look-back period if applicable
6. The reason for choosing the definition and measure

The work I conducted in Chapter 5 of this thesis was the first to focus upon clarifying the definition and measurement of resilience for use in studies of disease and illness. This is a highly important step forward given that research into resilience is increasing and there will be similar difficulties as encountered in the multimorbidity field if consensus approaches are not adopted. I applied novel resilience measures to multimorbidity populations. This paves the way for the development of this form of research in other study populations and scenarios. I studied resilience on the basis of positive outcomes *despite* disease which is important as not all disease can be prevented.

When conducting research into resilience to multimorbidity or to any other health condition, I recommend the following be reported:

1. Definition (I recommend using that set out by Windle[84], as described in Chapter 1)
2. The nature of the adversity
3. The measurement tool and which domain of resilience it represents
4. The measurement approach:

a. For cross-sectional studies I have demonstrated the utility of using positive responses to self-reported measures despite the adversity
b. For longitudinal studies of resilience, more research is needed into suitable approaches, but this could include examining the difference in prevalence before and after the adversity.

11.2.2 Objective two

Objective two was to assess the prevalence of multimorbidity and resilience to multimorbidity using the measures identified in objective one. These findings are summarised in Table 89.

Table 89: Discussion: summary of the prevalence of multimorbidity and of resilience in Diamond, the Original ACONF and the Enhanced ACONF populations

Cohort	Population description	Multimorbidity prevalence	Resilience prevalence
Diamond	Those who had seen a GP in the previous year and responded to a questionnaire	Primary care: 38.3%	SRH: 95.1%
			Activity limitation: 52.2%
Original ACONF	Responders to a postal questionnaire in 2001 Not selected on the basis of healthcare use	Self-reported: 5.4%	SRH: 60.4%
			Enjoyment- Positive GHQ 1: 53.4%
			Positive mood state- Positive GHQ 2: 66.0%
			Negative mood state- Negative GHQ 1: 18.8%
			Low self-esteem- Negative GHQ 2: 26.6%
Enhanced ACONF 2001	Members of ACONF who were alive, CHI seeded and resident in Scotland at the index date (1st September 2001)	Secondary care: 3.0%	SRH: 94.4%
			Enjoyment- Positive GHQ 1: 87.5%
			Positive mood state- Positive GHQ 2: 86.6%
			Negative mood state- Negative GHQ 1: 43.3%
			Low self-esteem- Negative GHQ 2: 52.9%
			Activity limitation: 79.4%
Enhanced ACONF 2016	Members of ACONF who were alive, CHI seeded and resident in Scotland at the index date (1st September 2016)	Secondary care: 10.0%	N/A

Abbreviations: GP, General Practitioner; SRH, Self-rated health; ACONF, Aberdeen Children of the 1950s; UK, United Kingdom; GHQ, General Health Questionnaire; CHI, Community Health Index

These measures are distinct, with different profiles of included conditions and different data sources and study populations. Given this, the prevalence findings should not be

directly compared. However, a number of observations can be made, which I outline in the following two sections. The strengths and weaknesses of my approach are described in more detail later in the chapter.

Multimorbidity

The three measures of multimorbidity provided contrasting assessment of prevalence. The prevalence of multimorbidity in an Australian primary care population aged between 18 to 75 who were asked if they had experienced any of 14 selected health conditions in the previous 12 months, was 38%. The prevalence of self-reported multimorbidity in a Scottish population aged between 45 to 51 years was 5%. The prevalence of multimorbidity in the same Scottish population measured using secondary care administrative data on the basis of 40 conditions was 3%. The prevalence measured in the same way when the population were aged between 60 to 66 years was 10%.

The Diamond study population was the only population out of the three which had been selected on the basis of recent healthcare use (having seen a general practitioner in the previous 12 months). It is reasonable to assume they are more likely to have at least one health condition compared to populations not selected on the basis of healthcare use. Therefore, the prevalence of multimorbidity being higher than in the two ACONF populations is consistent. Even though the Enhanced ACONF multimorbidity measure is drawn from secondary care data, the sample includes those who have been CHI seeded but have not accessed secondary care. Furthermore, given differences between primary care and secondary care systems in terms of use (particularly for adults not in very old age) as described in the discussion for Chapter 10, the prevalence in secondary care would be expected to be lower than that of a primary care setting.

The secondary care multimorbidity prevalence in ACONF in 2001 being slightly lower than the self-reported prevalence in 2001 may be explained by the age of the cohort. Individuals could have health conditions in middle age which are not yet sufficiently serious to lead to hospital admission, but are felt to be of high-burden to individuals themselves. The higher prevalence of secondary care multimorbidity in the ACONF in 2016 compared to 2001 is

entirely consistent with the fact that the number of morbidities an individual has increases with age and that the severity of conditions tends to increase with age.[26,31] This is mirrored in Diamond where the prevalence of multimorbidity increased with increasing age (as illustrated in Chapter 7).

The prevalence figures also need to be considered in terms of the disease count measures used. The primary care multimorbidity measure in Diamond consisted of 14 eligible conditions whilst that in the self-reported measure allowed recording of up to six and the secondary care measure contained 40. In general, an increasing number of eligible conditions in a measure leads to a higher prevalence of multimorbidity.[26] Given this, the prevalence figures are contrary to what might be expected but this may be explained by differences in the source of the data for the multimorbidity measures as described above.

The measures are not fully heterogeneous and there were some conditions and condition categories common to all. These included stroke, hypertension, cancer, various forms of heart disease, diabetes mellitus, various forms of skin disease, asthma, various forms of arthritis and mental illness.

Resilience

Comparing the prevalence of resilience across the different measures *within* each study has been discussed in the results chapter for that study. Here I compare the prevalence of resilience *across* the studies. Once again, it must be recalled that the nature of the adversity differs in each study, and that the Diamond and ACONF populations have different characteristics. Therefore, the prevalence of resilience, even by the same measure, would not be expected to be the same.

The prevalence of resilience across all five measures (SRH, enjoyment, positive mood, negative mood and low self-esteem) in the Original ACONF was lower than that of the Enhanced ACONF. Differences in prevalence between the Original and Enhanced ACONF populations may be because the measure of multimorbidity in the Original ACONF came from the same questionnaire as the measures of resilience, whilst secondary care multimorbidity was not sourced from the questionnaire. Thus, in the Original ACONF those

who self-report morbidities may be more likely to be prompted to respond less favourably to the SRH and GHQ questions (common methods bias as described in Chapter 7).

A further reason why the prevalence of resilience (across all five measures) in the Original ACONF was lower than that of the Enhanced ACONF could be that the self-reported multimorbidity measure in the Original ACONF was specifically related to conditions which were considered high burden by the respondent. As a result, the adversity may be more severe in the Original ACONF study compared to the Enhanced ACONF (where conditions contributing to the secondary care multimorbidity measure may not necessarily be active). The prevalence of SRH resilience in the Original ACONF was also lower than that of the Diamond and this could likewise be explained by differences in the multimorbidity measure, whereby conditions selected by Diamond respondents may not necessarily be active or high burden.

In the discussion for the Diamond study (Chapter 7) I described that the activity limitation question may be more subject to common methods bias than the SRH question because it specifically asks about a health condition. Therefore, those with multimorbidity may be more likely to select a less favourable response to the activity limitation question compared to the SRH question. This may explain why the prevalence of activity limitation resilience was higher in the Enhanced ACONF (79%) compared to Diamond (52%) despite the prevalence of SRH resilience being similar between the two. However, the lack of difference between the "resilient" responses in those with secondary care multimorbidity compared to those without it in the Enhanced ACONF, raises some concerns over the measurement of resilience in this population. I return to this later in the chapter.

11.2.3 Objective three

Objective three was to assess the role of mental health conditions and childhood SES in the occurrence of multimorbidity and resilience to multimorbidity.

In the Diamond study, I found that mental health conditions were associated with an increased prevalence of physical condition primary care multimorbidity. Additionally, the presence of mental health conditions slightly reduced the prevalence of SRH resilience.

Given this, mental health conditions should be explicitly included in multimorbidity measures and studies of resilience.

I found that an individual's social class, measured contemporaneously at birth, was associated with self-reported multimorbidity in middle age, but that this was partially mediated by educational attainment. I am the first to conduct such a study in a large longitudinal cohort and this finding has implications with regards to tackling health inequalities. This association did not hold true when multimorbidity was measured using secondary care data and this is an important area for more detailed research. However, secondary care multimorbidity was associated with area-based deprivation and provides ongoing support for Public Health action targeting the impact of deprivation.

In Diamond, I found a cross-sectional relationship between primary care multimorbidity and socio-economic factors (educational attainment and employment status) as well as smoking status. I found the same patterns in the determinants of SRH and activity limitation resilience to multimorbidity. My analysis of the determinants of resilience to multimorbidity was a novel approach.

Given the findings in both ACONF and Diamond regarding the influence of socio-economic factors, these are important considerations when designing approaches for preventing and managing multimorbidity and promoting resilience to multimorbidity.

11.2.4 Objective four

Objective four was to assess the impact of multimorbidity, and resilience to multimorbidity, on long-term outcomes. The analysis in this section was limited by missing data and low power (discussed later in this chapter).

There was an association between secondary care multimorbidity in middle age and mortality rate over 15 years follow-up. There was no association when using self-reported multimorbidity in middle age. There was a strong association between secondary care multimorbidity in 2001 and secondary care multimorbidity in 2016 but no relationship with

admission rate. There was no association between self-reported multimorbidity in 2001 and the hospital admission rate or the presence of secondary care multimorbidity in 2016.

As I described above, a weighted measure validated for a single outcome of interest should be used where a study focusses on that one outcome, whilst disease counts are more appropriate for studies such as mine which examine the prevalence of multimorbidity as well as examining multiple outcomes. The findings in this section may therefore change if studied using a weighted measure (for example the Charlson comorbidity index for mortality).[35] This falls outside of the aim and objectives of the thesis but is an interesting future research step.

I found that SRH resilience to both self-reported and secondary care data multimorbidity was associated with mortality. However, numbers of deaths were low and this must be tested in other populations where the proportion of missing outcome data is less.

11.3 Strengths and limitations

11.3.1 General

There were a number of strengths in the approaches taken in my thesis. Throughout I have been guided in the reporting of the results by relevant checklists. For the systematic reviews I used the PRISMA 2009 checklist, for the Diamond and ACONF analysis I used STROBE and for describing the linkage of administrative data I used the RECORD statement. Utilising these tools ensured I followed the required steps to allow others to interpret and replicate my research.

Using systematic reviews of the multimorbidity and resilience literature in order to set the definitions and measures for my thesis was a strength. This enables transparency and reproducibility. A further strength is the *a priori* setting of the definition and measurement of multimorbidity and resilience. This avoids the temptation of returning to the measures and trying other formulations (for example measuring multimorbidity as three or more conditions rather than two or more) in order to provide more statistically significant results.

I used two complementary study populations to meet the objectives. This allowed the study of multimorbidity prevalence from three perspectives and the testing of six novel measures of resilience to multimorbidity. The Diamond study enabled investigation of the impact of mental health conditions. The ACONF allowed longitudinal assessment of childhood and adult determinants of multimorbidity and this also addressed the need for large, long-term longitudinal cohort studies of multimorbidity.

However, whilst assessing multimorbidity and resilience by a number of approaches can be a strength in terms of reflecting that neither concept is homogenous, it also led to an important limitation. Specifically, it was more difficult to explain differences in the results across the three studies. My discussion above, where I compared the findings across the studies, was limited by the caveat that the data sources and measures are not homogenous. This meant interpretation of the meaning behind differences between studies and within studies was challenging. I describe some of these limitations in more detail in the following sections along with the complexities these factors bring when generalising the findings to other populations.

11.3.2 Measurement of multimorbidity and resilience

Multimorbidity

I described in Chapter 3 the rationale for using a disease count and the fact there are multiple disease counts being used in the literature with no evidence that any single count is superior. I have previously given the rationale for each of the measures I have used. Nonetheless, all multimorbidity measures may be subject to debate regarding which conditions are included. All measures could be analysed in a multitude of different ways (for example, sub-analysis of the effect of removing some conditions or splitting what may be described as acute conditions from chronic conditions). For the Diamond measure I did assess the impact of mental health conditions separately from the physical conditions. I did not do this for the ACONF analyses due to power limitations as described previously. I did not try any sub-analyses in the other measures given that I was describing the burden and, in ACONF, assessing the relationship between multimorbidity and a number of outcomes.

Indeed, multimorbidity is a heterogeneous entity in that the combination of co-existing conditions, the time since the onset of conditions and the severity of conditions may vary between individuals. This means, that for each of the three studies, the burden of multimorbidity was not the same across all members of the study. I describe this in more detail now.

In all three studies, I did not have access to an accurate onset date for morbidities. In Diamond, individuals were asked to consider the past 12 months when recording morbidity, however the time of first diagnosis could still be prior to the 12-month period. In the Original ACONF we know the condition was currently considered high-burden but respondents were not asked to indicate the onset date of these. Whilst the date a condition from the secondary care multimorbidity measure appears is recorded, the previously described issues with how discharges are coded does not make this simple. For example, a condition may have been diagnosed in the past in General Practice but not appear as a cause of admission until years later. This is not the incidence date. The changing guidance to coders over time also influences when conditions are recorded.

Accounting for the time since disease onset could be achieved in a self-reported measure by asking for conditions which have been diagnosed or which have manifested during a specified time point. In administrative data measures, primary care data may provide a more accurate representation of clinical onset as individuals are more likely to attend a GP when they first notice symptoms of a new condition.[22] As described later this might not be practical or feasible depending on the nature of administrative data sources. For example it is not currently possible to link to primary care data in Scotland.

With regards to disease severity, in the Original ACONF respondents were specifically asked to consider conditions which were high-burden in some way and this accounts for severity from the perspective of the individuals themselves. The primary care multimorbidity measure only includes conditions which have been experienced in the previous 12 months but this does not differentiate between those which have had a severe impact and those which have been relatively minor. The secondary care multimorbidity measure in the Enhanced ACONF may contain individuals with less severe forms of multimorbidity, for

example those whose multimorbidity status is based upon conditions which are not currently active but which have been recorded as supplementary conditions by coders.

Accounting for disease severity could be achieved by using a weighted measure such as the Charlson comorbidity index.[35] However, although weighted measures may account for severity, this will be in relation to the outcome or outcomes for which they have been validated and another weighted score could produce different findings. Using weighted measures relies on having sufficient data on relevant conditions and this was not available for the Diamond and Original ACONF.

In the secondary care multimorbidity measure, a different approach could be to limit the assessment of multimorbidity to only those conditions appearing as the main diagnosis (i.e. the condition which led to the admission). The prevalence of multimorbidity would thus be lower and it would change the nature of the measure from a description of the total multimorbidity burden of that individual to a description of "active condition" secondary care multimorbidity. Researchers wishing to do so would need to consider the aim of their work and whether the loss of information on other underlying morbidities is appropriate for their purpose.

Resilience

Given the vast heterogeneity of resilience research in the context of disease, I applied a number of restrictions to my systematic review of resilience in order to meet its aim of identifying consensus definitions and measures. In particular, I did not include mental health conditions as disease entities. Nonetheless, there were studies included in the systematic review which assessed mental health conditions or symptoms as determinants or measures of resilience. For example, Taylor et al found that depression was a significant determinant of a lack of resilience,[170] whilst Bonanno et al (2007) measured resilience on the basis of the presence of post-traumatic stress disorder symptoms.[160] In this thesis I considered mental health as part of the measure of primary care multimorbidity (the adversity) but also examined its impact upon the prevalence of resilience to physical disease multimorbidity in primary care. Mental health conditions also formed part of the

morbidities making up the self-reported multimorbidity measure in the Original ACONF and the secondary care multimorbidity measure in the Enhanced ACONF.

As my approach to measuring resilience was novel, there was little background literature to inform the manner in which to categorise the resilience measures. The activity limitation measures were identical in Diamond and the Enhanced ACONF. The question was binary and so was straightforwardly categorised for the purposes of measuring resilience. For the SRH measure I drew upon a study by Cairns *et al*, which had categorised SRH responses for the measurement of resilience.[183] There was a slight difference in the SRH measures used in Diamond and the ACONF. The measure in Diamond did not ask the individual to consider a time period whilst in the ACONF individuals were asked to consider the previous 12 months.

The categorisation of the GHQ measures was more complex than that of the SRH and activity limitation measures due to the lack of consensus on the scoring method for the positive and negatively phrased items. Resilience prevalence in both ACONF studies was lower in the two negatively phrased items compared to the positive. Whilst this may reflect a true lower prevalence of resilience in these domains (resilience to a negative mood state and low self-esteem) the fact that the prevalence of resilience as evidenced by a *positive mood state* was higher than the prevalence as evidenced by the *lack of a negative mood state* raises questions over this.

The activity limitation measure warrants further discussion. As I described earlier in the chapter, it differs from the other measures as it asks about high impact conditions whereas the others do not refer specifically to health problems. This measure therefore refers to the presence of an adversity directly. I described above that the finding of activity limitation resilience being lower than SRH resilience in Diamond may be due to the fact that the question refers explicitly to a health condition. Furthermore, the self-reported multimorbidity measure in the Original ACONF was developed from a similar question and this is why I did not measure activity limitation resilience in this population. However, the fact activity limitation can be used as a measure of morbidity does not mean it cannot be used as a measure of resilience to multimorbidity. The question distinguishes between

those who feel they have a condition which limits daily activity and those who do not. In other words, given the definition of resilience used in this thesis (demonstrating positive outcomes *despite* disease), it acts as a measure of resilience.

Relationship between multimorbidity and resilience

As described above, multimorbidity is a heterogeneous entity. In terms of studying resilience to multimorbidity, this means that the adversity may not be similar across all members of the study. This is in addition to the fact that in my thesis the measure of multimorbidity differed in each of the three studies. Where an adversity is more homogenous in nature, for example a single disease common to all individuals, the interpretation of differences in characteristics between resilient and non-resilient groups may be more straightforward. However even in single conditions, there will be differences across individuals with regards to factors such as disease severity and the length of time since diagnosis, and so this is not necessarily an issue limited to the study of multimorbidity.

Taking steps to make the measure of multimorbidity more homogenous, as described above, could assist with this. For example, if the Charlson comorbidity index was used, the score of multimorbidity burden could be summarised as a number of categories indicating increasing severity, and resilience prevalence could be compared across each category.

The timing of the onset of an adversity in relation to the timing of the measurement of resilience will affect the prevalence of resilience. In my systematic review I found studies which measured resilience cross-sectionally,[160,164,165,167-169,171] providing support for my approach. However, the longitudinal research included in the review[161-163,166] highlighted that the response to an adversity may change over time. For example, Bonanno et al (2008), in their study of psychological function after hospitalisation for SARS, identified four trajectories of response.[161] Individuals may have a reasonably good outcome immediately following the adversity but then follow declining trajectories or indeed improve over time.

The SRH and activity limitation resilience measures do not focus on a specific short-term time-point and thus allow somewhat for the fact that the specific onset date of multimorbidity is not known. The GHQ measures however, asked individuals to consider

the *past few weeks* when making their response. Asking individuals to consider a shorter period of time may also be less reflective of the overall level of resilience and more reflective of time-limited events impacting mood and function (for example short periods of illness, and positive and negative experiences at work or in home-life). This leads me to conclude that the GHQ questions are not ideal measures for use in the cross-sectional assessment of resilience. However, whilst it was not the aim of this thesis to measure resilience longitudinally, it is worth considering that the GHQ measure may be a suitable measure in longitudinal research. Its reference to the *past few weeks* mean that changes in response to the adversity over time can be mapped and trajectories identified. The structure of the GHQ questions is similar to the Short-Form 12 generic health status questionnaire (which includes questions relating to the "past 4 weeks").[344] This measure was used by Bonanno et al (2008)[161] to map trajectories.

It must be recalled that there was no significant difference in the prevalence of the "resilient" response (for all six measures) between those with, and those without, multimorbidity in the Enhanced ACONF (illustrated in section 10.6 of Chapter 10). In the Original ACONF and Diamond, the "resilient" response for all included measures was higher in those without multimorbidity, which is the expected direction (although I acknowledge the difference in the prevalence of the "resilient" responses for the SRH measure in Diamond was small). The measures of resilience in the Enhanced ACONF were from a different source as to that of the measure of multimorbidity. Whilst this can be seen as an advantage (by minimising common methods bias) the disconnect in timing between the completion of the questionnaire and the hospital admissions which recorded multimorbidity, may be too great to truly measure resilience in this population by this approach.

Furthermore, given that conditions contributing to the secondary care multimorbidity measure included those which were supplementary to the main diagnosis and therefore may not be active, it could be that the severity of the "adversity" of multimorbidity is insufficiently different from the experience of those without multimorbidity to measure resilience in this population. This could be explored further by using measures of

multimorbidity which better account for its severity (such as a weighted index or limiting the secondary care measure to only those conditions recorded as the reason for admission as described earlier). In addition, using a shorter look-back period (for example one year) could capture conditions which are more likely to be active.

Other measures of resilience could be considered for those wishing to identify populations with resilience to secondary care multimorbidity and develop interventions specific to that population. A measure based on identifying those with fewer or shorter hospital admissions despite multimorbidity or those with a lower mortality rate despite multimorbidity may be more helpful. This highlights the dynamic nature of resilience and that there needs to be careful consideration of the domain of resilience which is being measured and the reason resilience is being measured.

In general, I argue that the complexity regarding both multimorbidity and resilience to multimorbidity do not negate the worth of studying these. The approaches and findings in my thesis begin to disentangle some of these issues. However, the challenges I have highlighted must also be considered in both the interpretation of findings and the design of future studies.

11.3.3 Design of Diamond and ACONF studies

General

Using existing data (rather than designing and conducting a new study) means there is little control over the nature of the available variables and of the power of study (particularly in relation to its sample size). After setting the aim and objectives for this work in the design stage, I examined previous research in both Diamond and ACONF before selecting them for use, in order to ensure they were appropriate.

As discussed previously, those with more severe illness may not have been physically able to participate, or may not have been invited to participate, in both the Diamond and the ACONF. Related to this, those with lower resilience may have been less likely to participate. The prevalence of multimorbidity (in the Diamond and Original ACONF) may therefore be

under-estimated and the prevalence of resilience (in all the study populations) may therefore be over-estimated.

Diamond study

The Diamond was a cross-sectional study and its strengths were the detailed level of data on measures of multimorbidity, resilience and important determinants, as well as the low proportion of missing data across the included variables. The limitation of this study design was that it is difficult to show that cause preceded effect. Additionally, the initial response rate when participants were recruited was fairly low. Despite this, the Diamond cohort is reasonably representative of the Australian primary care population from which they were sourced.[202]

In considering the generalisability of the findings in the Diamond study to a UK population it is important to consider the similarities and differences between the health systems. As described in Chapter 4 and in Chapter 6, the NHS in Scotland and the rest of the UK is a nationally funded universal care system, whilst the Australian system is delivered via a combination of public and private mechanisms.[133,134,206] The systems have been assessed to be of similar quality in the most recent Commonwealth Fund report (which compared the performance of the healthcare systems of 11 high-income countries). The UK NHS (the data were sourced from England) was the top performing health care system and Australia was second.[345]

Within this overall assessment, the authors studied sub-domains of quality. Here, the two systems differed more. The Australian system ranked first for health-care outcomes whilst the UK ranked tenth, and whilst the UK ranked highest for equity, Australia ranked seventh.[345] Despite these differences, the countries have a similar overall healthy life expectancy (71.4 years for the UK and 71.9 years for Australia in 2015).[346] Healthy life expectancy describes the number of years lived in good health rather than simply all years lived and it is argued to better reflect inequalities by including morbidity with mortality.[347] The prevalence of multimorbidity overall may be similar therefore if the study was replicated in a UK primary care population.

Another important consideration is differences between the UK and Australia with regards to ethnic diversity. As described in Chapter 6, 96% of the Grampian area were white Scottish or white British in 2001.[219] This is the same proportion as Scotland as a whole.[219] Australia is more ethnically diverse. Around 70% of those living in the state of Victoria were born in Australia, with people born in the UK, New Zealand, Italy, China and Vietnam making up the majority of those not born in Australia.[205] Different ethnic groups may have different patterns of disease due to genetic predisposition or different cultural and environmental exposures and this could affect the both prevalence of multimorbidity and of resilience to multimorbidity. In Diamond, 83% of respondents were born in Australia[202] however, the ethnic groups represented were not recorded. Therefore, the impact of the ethnic differences between this population and the UK population upon the prevalence of multimorbidity and resilience to multimorbidity is unclear.

A final point about generalising the results of the Diamond to the UK population is to recall how the Diamond study population were selected (they had seen a GP in the previous 12 months). As discussed earlier, these individuals are therefore more likely to have morbidities and so the prevalence of primary care multimorbidity measured in this way would be expected to be higher than if considering all primary care patients. The finding that the prevalence of multimorbidity in the Barnett study (which included all registered primary care patients in Scotland) is lower than that of Diamond is therefore unsurprising, despite the fact the Barnett measure contained more eligible conditions (40 compared to 14).

ACONF study

The ACONF is a longitudinal cohort study. This study design has the advantage of being able to show cause preceded effect. For example, social class at birth was measured before the measurement of the occurrence of multimorbidity. It could be argued that individuals may be born with two or more health conditions (for example congenital heart disease)[348] and so the outcome has already occurred. However, it would not be logical to argue that the relationship is the other way round (i.e. that multimorbidity at birth causes lower paternal social class at an individual's birth).

Cohort studies can be affected by bias due to loss to follow-up and I described where this may affect the ACONF study results earlier in the thesis. An additional consideration is that all findings of long-term longitudinal cohorts need to be placed in the context in which participants grew and developed. Some important changes occurring since the 1950s are the improvement in social and economic material circumstances for all and changes in risk factor patterns such as declining smoking prevalence.[18,305] However, as described earlier in the thesis, it is the relative difference in social and economic resources between groups which drive inequalities in health and health outcomes rather than the absolute levels of these factors.[316] Therefore, the findings are still applicable to current populations as it is known that relative differences still exist.[18]

A further factor affecting generalisability to current populations is the lack of ethnic diversity in the ACONF likely leading to different patterns of multimorbidity and resilience to multimorbidity if the study is conducted in other populations. Additionally, the relative stability in terms of movement from Aberdeen or Scotland of the cohort may lead to a higher prevalence of resilience. Communities such as this may have greater cohesion leading to higher collective levels of resilience which manifest as higher personal resilience.[349]

11.3.4 Using administrative data

Administrative data are increasingly used in research and bring a number of advantages and disadvantages as I discussed in Chapter 1 and in Chapter 4.

In this study, I used ICD-9 and ICD-10 codes from secondary care administrative data in a universal, free at the point of use healthcare system. Generalising these findings to other populations must therefore take into account a number of factors. Firstly, ICD codes may be available for more than just secondary care settings. For instance, in Scotland, reasons for outpatient attendances are also coded with ICD.[350] These were not included in my study as my aim was to concentrate upon secondary care multimorbidity. Incorporating a greater number of data sources will likely increase the prevalence of multimorbidity. For example, a study by Tonelli *et al* applied an administrative data ICD multimorbidity measure to a

Canadian population-based administrative dataset which contained ICD codes from a range of sources.[351] This study found that the prevalence of multimorbidity was 8% when using only hospital data and 24% when incorporating insurance claims with hospitalisations.[351]

The healthcare system and mechanisms by which hospitals and practitioners are funded will influence matters. For example, a study in the USA found that where individuals had no, or limited, insurance coverage they were more likely to be discharged home in an unhealthy state, whilst those with more generous insurance coverage received an increased volume of healthcare provision.[352] This may lead to a lower recorded prevalence of administrative data multimorbidity in deprived populations. Where practitioners receive a fee based on services provided (fee-for-service) it is linked to inappropriate and inefficient provision of care and over-diagnosis.[353] It is possible that the prevalence of multimorbidity will be higher overall when measuring it using data from these healthcare systems compared to the UK.

The other factors to consider are:

- Whether national incentives exist for diagnosis and treatment of particular conditions (for example the QOF system of the UK General Practice contract gives financial incentives to measure factors such as blood pressure)[354]
- The robustness of quality assessment procedures for coding
- Whether coders are given specific conditions to look for (such as the list of comorbidities given to coders in Scotland)

An important point, which is not unique to Scottish healthcare data, is that the time of coding of a condition does not necessarily reflect the incidence of that condition or show that it is currently active. In my study, the strong association I found between 2001 secondary care multimorbidity and 2016 secondary care multimorbidity will be at least partly due to coders using the same sources of information on co-morbidities to code discharges from one admission to the next. This, plus changes in coding practice over time, means that studying how disease patterns develop (for example trajectories of multimorbidity) may not be appropriate using these data. Despite this, my approach to

assessing multimorbidity prevalence is consistent with others and this is also why I used a five year look-back to capture the burden rather than a single time point.

In Chapter 1, I described that morbidities may be sourced from various data sources and I made a distinction between case-note review and administrative data. However, this line is blurring as case-notes become increasingly electronic. It is possible that computerised techniques could be designed to search the text within records. This could balance the benefits of case-note review (the availability of more detailed information) with the benefits of administrative data as described previously.

In the ACONF study, I was able to access the secondary care healthcare record data and mortality data for the Scottish residents with CHI numbers. This did provide a large sample size but a crucial issue was that it was not available for those outside of Scotland. Whilst linkage to participants outside of Scotland is not currently being explored for ACONF (source: email correspondence with Heather Clark, ACONF study coordinator, December 2017) it is a recommended next step. Other parts of the UK have healthcare record linkage systems and so the capability to do so exists.[355]

It is not yet possible to link study participants to primary care records in Scotland. The assessment of the impact of mental health conditions in ACONF could be improved with linkage to these records. As described previously, at their current age primary care may still be acting as the predominant source of healthcare for ACONF members, and so social class patterns of secondary care multimorbidity may not yet be observable. However, it would be possible to utilise existing linkage systems to measure multimorbidity using Accident and Emergency department data, and assess if the patterns are visible in emergency care.

There are ongoing efforts in Scotland and the UK to make use of wider sources of administrative data, such as that from education, social care and the census (which is conducted every ten years). The Farr Institute and the Administrative Data Research Network (with funding from the Economic and Social Research Council) are at the forefront of this.[356-358] This would provide important opportunities for research and a richer evidence base for studying determinants and outcomes of health and disease.

11.3.5 Missing data and power

In my study protocol I acknowledged that the ACONF would have low power to study resilience to multimorbidity due to the small population with multimorbidity. I proceeded given my approach to measuring resilience was novel and there was a need to show proof of concept. However, I also ensured I was able to study resilience in a further study (Diamond) which had the power to study the prevalence and determinants of resilience.

The lack of regular status updates for the ACONF was a limitation as it meant assumptions were made as to whether individuals were alive or resident in Scotland between the updates. There were also missing administrative data for those who could not be CHI seeded. In managing missing data I applied two methods: Complete Case Analysis (CCA) and Multiple Imputation by Chained Equations (MICE). Both techniques have the potential to reduce or increase bias. Multiple imputation techniques are increasingly used but crucially, when not used appropriately can lead to highly misleading conclusions.[237]

The key to choosing MICE is justifying whether data are missing at random (MAR) and by including sufficient variables predictive of missing values. Additionally, if there are a lot of missing data then multiple imputation may increase bias.[240] Due to the extent of missing data with regards to the non-responders to the ACONF postal questionnaire, multiple imputation analysis was not appropriate. This approach is also consistent with other ACONF studies.[359] I did conduct MICE as a sensitivity analysis for missing data within the questionnaire responders. This did not affect the conclusions.

I did not conduct MICE on the Enhanced ACONF study populations as I could not argue that missing data regarding hospital admissions and mortality was MAR or that I had the required data available to inform imputations. Conducting a "sensitivity analysis" would not be helpful. If results are the same it does not add anything and if results were different I would not be able to justify using them.

11.3.6 Analysis in the Diamond and ACONF populations

I used a clear framework and step-wise approach to ensure I could explain the findings of my analyses. This included summarising the hypotheses as path diagrams in the longitudinal analysis in ACONF. I was also careful not to look for post-hoc associations when I found no relationship. Where exposure and outcome variables were measured cross-sectionally (for example in Diamond and for parts of the ACONF analysis) I did not conduct modelling analysis. The only exceptions to this were the educational attainment and secondary school type variables in ACONF which I have justified previously.

The analysis steps I adopted are important. If I treated educational attainment as a "confounder" I may conclude that there was little or no association between social class at birth and adult self-reported multimorbidity when adjusted by other variables. The lack of careful consideration as to what is adjusted for and what role variables have in the path of the relationship between exposure and outcome is a frequent concern.[360]

I concentrated on testing the relationship between social class at birth and multimorbidity to address a key evidence gap. It also allowed me show "proof of concept" of my choice of definition and measures of multimorbidity. Clearly, there will be an inter-relationship between the covariates included in my models. The finding of univariate relationships between school type and self-reported multimorbidity, and only those with the lowest cognition scores and multimorbidity also point to future areas of research. Variables not studied here but which warrant inclusion in future analysis are peri-natal factors such as birth weight. Lower parental SES has been shown to be associated with lower birth weight in a child and this has been linked to poorer early and later life health for that individual.[361]

The next steps would be to use the findings in my thesis to develop large scale explanatory models incorporating a larger volume of life-course variables and showing the relationship between these. There are modelling techniques which can simultaneously examine multiple effects and the relationships between variables in addition to their impact on the outcome, for example structural equation modelling (SEM).[362,363] Such large scale explanatory models are often used to study life-course determinants of health. When

developed with a robust underlying understanding of the relationships between variables they add crucial understanding to our knowledge of how different exposures over the life course influence the development of disease. I have illustrated key variables which should be considered in the next stages of multimorbidity research.

I argue that from a Public Health perspective, my approach allowed me to make specific and clear recommendations for future action. It is indeed likely I would find that variables such as school type, educational attainment, cognition and birth weight were inter-related in more detailed models. However, the overall conclusion that social class at birth determines later life self-reported multimorbidity and that educational attainment may mitigate this would not change. Both the negative impact of childhood SES and the ability to access education are factors which can inform actionable Public Health interventions.

I used survival analysis techniques for mortality and hospital admissions. For the latter, I adopted a more recently developed approach to measure multiple failures. This technique is becoming more widely used, however to illustrate the impact I also used single failure analysis in my first analysis. I found this had no effect on the overall conclusion.

11.4 Important new developments in the literature

My thesis was designed based upon the literature available up to the year 2014. In the discussion of the results of the Diamond and ACONF populations I have referred to updated literature. In this section I present an overview of other recent developments in the literature.

A review by Xu *et al*, published in August 2017, synthesised 53 systematic reviews of multimorbidity in order to assess the current evidence regarding multimorbidity.[364] This was not limited to those reviews which defined and measured multimorbidity as in my review. The authors found great heterogeneity in the definition of multimorbidity and that the prevalence ranged from 4% to 100%. They recommended the ongoing need for large

longitudinal studies to provide better evidence on prevalence, determinants and outcomes.[364] This provides further support for my work.

The National Institute for Health and Clinical Excellence (NICE) in the United Kingdom published its first clinical guideline on multimorbidity in 2016.[365] This was an important step forward given the concerns over polypharmacy and related issues with single condition guidelines.[112] Despite this, the guideline commented on the lack of consensus on what the definition of multimorbidity is.[365]

In the period since I developed codes for Barnett conditions, the study by Tonelli *et al* conducted similar work.[351] However, whilst the study used Barnett as a baseline for developing a multimorbidity measure, it did not aim to include all conditions. The authors searched for validated ICD-9/ICD-10 algorithms for most of the 40 conditions. Only algorithms with moderate to high validity (based upon a positive predictive value greater than or equal to 70%) were included and as a result the authors included 30 condition categories. The final list of Tonelli conditions was similar to, but did not match, the conditions within the Barnett measure. The differences included:

- Three algorithms were provided for cancer (lymphoma, metastatic and non-metastatic) whereas Barnett classes this as one category
- Only hepatitis B was included (instead of all viral hepatitis)
- Only hypothyroidism was included (instead of all thyroid disorders)
- Only myocardial infarction was included (instead of all coronary heart disease)
- Eczema is not included with psoriasis
- A full range of inflammatory poly-arthropathies were not included with rheumatoid arthritis
- "Other organic psychoses" and bipolar disorder were not included with Schizophrenia

It is not clear from the paper why these differences exist. The literature search conducted was non-systematic and the authors acknowledge their searches were not exhaustive. This means there may be further algorithms available which may allow inclusion of further

Barnett conditions. Additionally, the authors did not systemically evaluate the quality of the original studies.

However, this was a novel study which developed an administrative data multimorbidity measure which could be used across different settings. This could enable better comparison of results from different studies. As it was published since I developed my measure I did not make any changes to the analysis in the thesis. Nonetheless their approach to using validated algorithms for all conditions is one which could be used to fill in the gaps for the Barnett conditions where I used the ICD-10 data dictionary.

There are a number of recently published studies into resilience in chronic diseases. In 2016, Wister and colleagues published a descriptive paper based upon multimorbidity and resilience across the life-course.[366] The review describes resilience in terminology comparable to what I describe in the thesis- as a dynamic and adaptive process through which individuals can maintain wellbeing or quality of life despite poor health. The authors also describe the concept of a "resilience trajectory" where accumulated experiences and exposures across the life-course affect the development of resilience.[366] However, the authors also state there are gaps in our understanding as to which measures should be used to assess resilience.[366]

Other reviews published in the resilience to disease field are limited in being either poorly reported or having difficulties managing the lack of consensus definitions and measures of resilience.[367-369] Therefore, despite the increase in study of resilience to disease, it is apparent that consensus over definition and measurement is still not in place.

Multimorbidity research continues to evolve, with consideration of its role in ageing across the life-course being part of the recent WHO World Report on Ageing and Health.[370] Healthy ageing was defined as "*the process of developing and maintaining the functional ability that enables well-being in older age*".[370] The WHO called for research understanding the determinants of trajectories of healthy ageing across the life-course (not solely concentrating on older adults). This may be achieved by study of longitudinal cohorts and

by incorporating measures of multimorbidity with other important individual, social, environmental and political determinants of ageing.

11.5 Recommended future interventions, action and research

11.5.1 Interventions and action

From a Public Health point of view, the fact that individuals with lower birth social class are more likely to report having two or more conditions which limit them in middle age is extremely important. This is an inequality and, by nature of being avoidable and unfair, is a health inequity.[73] Support from early years is crucial, as is support in allowing access to education. For example, psychological and financial support for pregnant mothers, adequate paid parental leave, and access to pre-school education or childcare were recommended by the seminal Marmot review.[18] Selective schooling and the use of cognitive testing at a young age are policies which may widen the unequal impact of childhood SES status.

I also found that adult SES was associated with the prevalence of primary care multimorbidity and self-reported multimorbidity. Area-based deprivation was associated with secondary care multimorbidity. In Diamond I found that adult SES was associated with both SRH and activity limitation resilience to multimorbidity. Addressing the impact of lower SES in adults is important both for these individuals themselves and for reducing the impact of lower SES on children. Policies, for example on temporary contracts, could assist in providing adults with more secure employment and policies supporting higher quality housing could improve physical and mental wellbeing.[18,320]

Secondary care multimorbidity, as measured by Barnett conditions in administrative data in middle age, was associated with future mortality. This multimorbidity measure could be relatively easily assessed with access to hospital records, and could identify individuals at risk of early mortality. From this, action can be taken clinically, for example to target additional care or monitoring.

I found that mental health conditions were an important influence upon primary care multimorbidity and SRH resilience to primary care multimorbidity. Given the probability that mental health conditions are under-reported, this demonstrates the need for practitioners to actively ascertain mental health status in those with physical disease. This is particularly important for male patients where help is often sought late, or not at all.[104,105]

11.5.2 Future research

The ACONF has many advantages as a large cohort with extensive early and later life information. The cohort can be a rich source of information on ageing pathways as the participants move into older age. Examples of how this can be achieved are making use of administrative data (including linkage to a wider variety of databases as described earlier) and a further survey which includes more detailed measures of mental health and psychological factors. Ideally there would be regular waves of follow-up allowing the mapping of trajectories of ageing and its determinants.

My research into the impact of mental health conditions was cross-sectional and longitudinal study clarifying the direction of relationships is needed. This is particularly important for resilience to multimorbidity where this has not previously been studied. Gender differences need further consideration and studies should aim for methods which tackle the likely under-reporting of mental health conditions in men.

In this thesis, I used a systematic review to identify a definition of resilience and approaches towards measuring it. I used the findings to select the measures which I applied in Diamond and the ACONF. This approach showed proof of concept and also highlighted that the GHQ measures may not be suitable for cross-sectional research. Next steps in testing these new measures could involve assessing their validity. As described in the review of the multimorbidity literature in Chapter 3, validity describes whether an instrument is able to measure what it is intended to measure.[127] There are a number of approaches to assessing it. The lack of an accepted "gold-standard" measure of resilience to which I could compare my measures, makes assessing criterion validity difficult. Construct validity, where there is assessment of whether a measure performs in a manner which it expected given the

underlying theory,[127] could be tested by evaluating the performance of the measures in predicting longer-term outcomes. There is evidence showing that resilience improves outcomes such as healthcare utilisation, quality of life and mortality.[371-373] In the thesis, I tested the association between the resilience measures and outcomes, and found an association between SRH resilience and lower mortality. However, further study is needed in study populations with greater power to detect differences where they do exist.

In Diamond I showed that SRH and activity limitation resilience prevalence were associated with socio-economic factors. Longitudinal study of this is important to confirm the nature and direction of relationships. Tackling these research gaps can then inform research into resilience based interventions for disease. Life-course study can identify not only *which* factors determine resilience but also *when* in the life-course an intervention may be most effective.[366]

In my own future work, I plan to study trajectories and determinants of resilient ageing. This relates to the recommendations for research given in the WHO World report on ageing and health[370] and incorporates the findings in my thesis. I define resilient ageing as a trajectory of ageing whereby individuals maintain functional status despite declining physical capacity. I define functional status on the basis of individuals being able to do what is important to them. I plan to incorporate psychological, social and environmental determinants of health and wellbeing along with measures of multimorbidity.

The sourcing of views on what individuals define as being important to them may be influenced by individual expectations which have been shaped positively or negatively by a range of experiences. For example, “expectations regarding ageing” is a concept used to describe how well individuals believe they will maintain good health as they age.[374] Evidence has shown that individuals with negative expectations underestimate their capability to participate in factors such as physical activity and experience poorer outcomes as a result.[374] Alternatively, the views of other individuals, such as researchers and healthcare professionals, as to what individuals should be able to do, or want to do, as they age could be unrealistic or not relevant.[375] Therefore, what is measured as “resilience” may in fact not be reflective of the concept. This will need careful consideration in the design of

my future work. I am currently developing a protocol to run focus groups containing older people, researchers and healthcare practitioners in order to seek views on ageing. This will inform the design of my study into resilient ageing.

Frailty is a further aspect important in the study of ageing. Like the concepts of resilience and multimorbidity it has no consensus definition. The WHO describe it as an age related decline leading to reduced reserves of physical and mental health capacity, resulting in vulnerability to stressors and an increased risk of poor health outcomes.[370] Frailty and multimorbidity have been shown to be highly correlated.[376] Frailty may be the converse of resilient ageing or be a separate syndrome which results from a non-resilient ageing trajectory.[377] As part of my future work I will explore this.

11.6 Conclusion

The aim of this thesis was to define and measure the prevalence of multimorbidity and resilience to multimorbidity, to assess the role of mental health and childhood socio-economic status and to investigate the long-term outcomes, in order to inform Public Health research and action. By combining systematic reviews of the relevant literature with analysis of two study populations I have achieved this aim. I have summarised in this chapter the key findings and linked these to future Public Health interventions, action and research.

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13 Appendix 1: Literature review strategies

13.1 Review of cohort studies of multimorbidity

13.1.1 Literature review method

I searched Medline, Embase and the Cochrane database of systematic reviews from database inception to November 2013. The literature search terms were multimorbidity and its synonyms (such as "multiple coexisting diseases") combined by the Boolean operator "AND" with cohort and related words. Multimorbidity and its synonyms were searched in the title only, as an initial trial search found that widening this to the abstract or full text also significantly reduced the ability to detect relevant papers. "Cohort" and its synonyms were included as title or abstract words as well as MeSH terms. "Comorbidity" was included as a search term in the above strategy as it was possible that some papers including "comorbidity" in the title may go on to describe multimorbidity in the text.

The inclusion criteria were:

- Any prospective or retrospective cohort study
- Multimorbidity was either the main exposure or outcome variable
- Systematic reviews of cohort studies of multimorbidity (in order to extract references)

The exclusion criteria were:

- Multimorbidity, or a term very similar, was not used as a term in the paper
- Comorbidity without any reference to multimorbidity was used
- Study population was limited to adults aged 70 and over at the time of commencing follow-up
- Non-cohort study design (cross-sectional, non-systematic review, systematic review not focussed on cohort studies)

Titles and abstracts and then full texts were screened for relevance. I developed a data-extraction database to collect information regarding the cohort type, study size, follow-up time, exposure, outcome and study findings. I also collected data on the multimorbidity definition, the multimorbidity measures and data sources.

13.1.2 Literature review results

After removal of duplicates, 101 titles and abstracts were screened against the inclusion and exclusion criteria with 27 being eligible for full text screening. Of these, 14 were included.[57,59-70,72] There were also two systematic reviews[31,54] and after assessing their references and screening them against my study criteria I included one additional study.[71]

13.2 Childhood socio-economic status and multimorbidity

13.2.1 Literature review method

I searched Medline and Embase from database inception to 27th October 2014. The search terms were "multimorbidity" in the title or abstract combined with the Boolean operator AND with Social Class as a MeSH term along with its synonyms.

The inclusion criteria were:

- Quantitative studies
- Outcome measure is multimorbidity
- Childhood SES is the exposure variable (the childhood period defined as the pre-natal period to age 18).

The exclusion criteria were:

- Qualitative studies
- Non-systematic reviews
- Non peer reviewed work including online theses and opinion pieces
- Conference abstracts

- Studies not in the English language

I screened titles, abstracts and full-texts. I extracted data from included studies using the following headings: study aim, population characteristics, population size and follow-up, SES exposure, multimorbidity outcome measure and findings.

13.2.2 Literature review results

There were 125 references from Medline and 204 from Embase with 226 remaining once duplicates were removed. Following title and abstract screening there were 16 papers for full-text screening. There were three systematic reviews from which ten references were sourced.[31,51,54] Of these, six were duplicates of studies from the original search and four were not relevant following full-text screening. Three studies were included overall.[79-81]

13.3 Resilience and multimorbidity

13.3.1 Literature review method

I searched Medline and Embase from database inception to January 2014 using "multimorbidity" and its synonyms (such as "multiple coexisting diseases") in abstract or title combined by the BOOLEAN operator "AND" with "resilience" and its related concepts (for example hardiness and thriving). I included "comorbidity".

I searched for quantitative studies of adult populations where multimorbidity and resilience were considered as exposures or outcomes. I excluded studies of comorbidity which did not go on to describe multimorbidity. I did not include studies in which only the related concepts of resilience (such as hardiness) were studied or studies of other forms of resilience (for example organisational resilience and genomic/cellular resilience).

13.3.2 Literature review results

I retrieved 130 papers from Medline and 203 from Embase with 251 in total following removal of duplicates. Following screening, I found no relevant papers. Out of a number of qualitative studies, there was one which focussed on resilience and multimorbidity.[97]

13.4 Defining and measuring multimorbidity: a systematic review of systematic reviews

Table 90: Appendix one: search strategy for reviews of the multimorbidity literature (Medline search, adapted for other databases. For Cochrane, only "multimorbidity" and Cochrane selected word variations searched)

1	multimorbidity.m_titl.
2	(multimorbid$ or multi-morbid$).m_titl.
3	(multiple adj2 diseas$).m_titl.
4	(multiple adj2 diagnos$).m_titl.
5	(multiple adj2 illness$).m_titl.
6	(multiple adj2 condition).m_titl.
7	(multiple adj2 morbid$).m_titl.
8	(coexisting adj2 diseas$).m_titl.
9	(coexisting adj2 illness$).m_titl.
10	(coexisting adj2 diagnos$).m_titl.
11	(coexisting adj2 condition$).m_titl.
12	(coexisting adj2 morbid$).m_titl.
13	(co-existing adj2 diseas$).m_titl.
14	(co-existing adj2 illness$).m_titl.
15	(co-existing adj2 diagnos$).m_titl.
16	(co-existing adj2 morbid$).m_titl.
17	(concurrent adj2 diseas$).m_titl.
18	(concurrent adj2 illness$).m_titl.
19	(concurrent adj2 diagnos$).m_titl.
20	(concurrent adj2 condition$).m_titl.
21	(concurrent adj2 morbid$).m_titl.

22	(comorbid adj2 diseas$).m_titl.
23	(comorbid adj2 illness$).m_titl.
24	(comorbid adj2 diagnos$).m_titl.
25	(comorbid adj2 condition$).m_titl.
26	(comorbid adj2 morbid$).m_titl.
27	(co-morbid adj2 diseas$).m_titl.
28	(co-morbid adj2 illness$).m_titl.
29	(co-morbid adj2 diagnos$).m_titl.
30	(co-morbid adj2 condition$).m_titl.
31	(co-morbid adj2 morbid$).m_titl.
32	multiple comorbid$.m_titl.
33	multiple co-morbid$.m_titl.
34	case-mix$.m_titl.
35	casemix$.m_titl.
36	"comorbid*".m_titl.
37	co-morbid.m_titl.
38	"Health status indicator*".m_titl.
39	severity of illness index.m_titl.
40	diagnosis-related group.m_titl.
41	charlson.m_titl.
42	CIRS.m_titl.
43	cumulative illness rating scale.m_titl.
44	CIRS-G.m_titl.
45	cumulative illness rating scale-geriatric.m_titl.
46	"ACG*".m_titl.
47	Adjusted Clinical Group$.m_titl.
48	Ambulatory care group$.m_titl.
49	Disease count.m_titl.
50	DUSOI.m_titl.
51	Duke severity of illness.m_titl.
52	Duke case-mix system.m_titl.
53	DUMIX.m_titl.
54	ICED-DS.m_titl.
55	ICED-FS.m_titl.
56	Index of coexistent disease-disease severity.m_titl.
57	Cornoni-Huntley index.m_titl.

58	Liu index.m_titl.
59	Hurwitz index.m_titl.
60	Index of coexistent disease-functional severity.m_titl.
61	Hallstrom index.m_titl.
62	Incalzi index.m_titl.
63	Shwartz index.m_titl.
64	Kaplan index.m_titl.
65	Kaplan-Feinstein index.m_titl.
66	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67	review.m_titl.
68	66 and 67

Abbreviations: adj2; words adjacent within two words; m_title, title word

13.5 Sourcing codes for Barnett multimorbidity measure

Table 91: Appendix one: literature search strategy for sourcing codes for Barnett multimorbidity measure (Medline search, adapted for other databases)

1.	Comorbidity/*
2.	multimorbidity.m_titl.
3.	(multimorbid$ or multi-morbid$).m_titl.
4.	(multiple adj2 diseas$).m_titl.
5.	(multiple adj2 diagnos$).m_titl.
6.	(multiple adj2 illness$).m_titl.
7.	(multiple adj2 condition).m_titl.
8.	(multiple adj2 morbid$).m_titl.
9.	(coexisting adj2 diseas$).m_titl.
10.	(coexisting adj2 illness$).m_titl.

11.	(coexisting adj2 diagnos$).m_titl.
12.	(coexisting adj2 condition$).m_titl.
13.	(coexisting adj2 morbid$).m_titl.
14.	(co-existing adj2 diseas$).m_titl.
15.	(co-existing adj2 illness$).m_titl.
16.	(co-existing adj2 diagnos$).m_titl.
17.	(co-existing adj2 morbid$).m_titl.
18.	(concurrent adj2 diseas$).m_titl.
19.	(concurrent adj2 illness$).m_titl.
20.	(concurrent adj2 diagnos$).m_titl.
21.	(concurrent adj2 condition$).m_titl.
22.	(concurrent adj2 morbid$).m_titl.
23.	(comorbid adj2 diseas$).m_titl.
24.	(comorbid adj2 illness$).m_titl.
25.	(comorbid adj2 diagnos$).m_titl.
26.	(comorbid adj2 condition$).m_titl.
27.	(comorbid adj2 morbid$).m_titl.
28.	(co-morbid adj2 diseas$).m_titl.
29.	(co-morbid adj2 illness$).m_titl.
30.	(co-morbid adj2 diagnos$).m_titl.
31.	(co-morbid adj2 condition$).m_titl.
32.	(co-morbid adj2 morbid$).m_titl.
33.	multiple comorbid$.m_titl.
34.	multiple co-morbid$.m_titl.
35.	case-mix$.m_titl.
36.	casemix$.m_titl.
37.	"comorbid*".m_titl.
38.	co-morbid.m_titl.
39.	"Health status indicator*".m_titl.
40.	severity of illness index.m_titl.
41.	diagnosis-related group.m_titl.
42.	charlson.m_titl.
43.	CIRS.m_titl.

44.	cumulative illness rating scale.m_titl.
45.	CIRS-G.m_titl.
46.	cumulative illness rating scale-geriatric.m_titl.
47.	"ACG*".m_titl.
48.	Adjusted Clinical Group$.m_titl.
49.	Ambulatory care group$.m_titl.
50.	Disease count.m_titl.
51.	DUSOI.m_titl.
52.	Duke severity of illness.m_titl.
53.	Duke case-mix system.m_titl.
54.	DUMIX.m_titl.
55.	ICED-DS.m_titl.
56.	ICED-FS.m_titl.
57.	Index of coexistent disease-disease severity.m_titl.
58.	Cornoni-Huntley index.m_titl.
59.	Liu index.m_titl.
60.	Hurwitz index.m_titl.
61.	Index of coexistent disease-functional severity.m_titl.
62.	Hallstrom index.m_titl.
63.	Incalzi index.m_titl.
64.	Shwartz index.m_titl.
65.	Kaplan index.m_titl.
66.	Kaplan-Feinstein index.m_titl.
67.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66
68.	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66
69.	International Classification of Disease.tw

70.	ICD.tw
71.	administrative.m_titl.
72.	69 or 70 or 71
73.	68 and 72

Abbreviations: adj2; words adjacent within two words; tw, text word; m_title, title word
*MeSH term (of note, no MeSH term for multimorbidity)

13.6 Physical disease and resilient outcomes: a systematic review of resilience definitions and study methods

The following search terms were employed in Embase and Medline:

- Resilien* **(Title word or abstract)** AND
- ((Neoplasms OR Diabetes Mellitus OR Hypertension OR Kidney disease OR Asthma OR Chronic obstructive lung disease OR Cerebrovascular accident OR Stroke OR Cardiovascular disease OR Neurologic disease OR Nervous System Diseases OR Epilepsy OR Arthritis OR Communicable Diseases OR Chronic Disease OR Disease OR Acute Disease OR Aging) (**MeSH terms)** OR multimorbid* **(title, abstract)**).

14 Appendix 2: Additional Tables

14.1 List of conditions from Barnett *et al*

Table 92: Appendix two: conditions included in Barnett el al paper [2]

Condition name	Condition name
Hypertension	Atrial fibrillation
Depression	Peripheral vascular disease
Painful condition	Heart failure
Asthma	Prostate disorders
Coronary heart disease	Glaucoma
Treated dyspepsia	Epilepsy (currently treated)
Diabetes	Dementia
Thyroid disorders	Psoriasis or eczema
Rheumatoid arthritis, other inflammatory polyarthropathies & systematic connective tissue disorders	Schizophrenia (and related non-organic psychosis) or bipolar disorder
Hearing loss	Inflammatory bowel disease
Chronic obstructive pulmonary disease	Migraine
Anxiety & other neurotic, stress related & somatoform disorders	Blindness & low vision
Irritable bowel syndrome	Chronic sinusitis
New diagnosis of cancer in last five years	Learning disability
Alcohol problems	Anorexia or bulimia
Other psychoactive substance misuse	Bronchiectasis
Treated constipation	Parkinson's disease
Stroke & transient ischaemic attack	Multiple sclerosis
Chronic kidney disease	Viral Hepatitis
Diverticular disease of intestine	Chronic liver disease

14.2 Summary of process for selecting ICD-10 codes for Barnett multimorbidity measure

Table 93: Appendix two: summary of the findings of the process of selecting ICD-10 codes for Barnett multimorbidity conditions

Condition	Barnett definition	Quan 2005 ICD-10 code [157]	ISD LTC codes[149]	ISD comorbidity codes [142]	ICD-10 dictionary codes[10] and comments	Final List
Hypertension	**"Read code ever recorded" (applies to all grey shaded cells)**	I10.x –I15.x	I10.x –I15.x	I10X; I11.9; I12.x; I13.1; I13.9; I15.x		I10.x; I11.x – I13.x; I15.x (there is no I14)
Coronary heart disease		Nil	I20.x-I25.x; I48.x	I20.x; I25.x	Do not use I48 (used in AF below)	I20.x-I25.x
Diabetes		E10.x -E14.x	E10.x -E14.x	E10.x -E14.x	E10.x -E14.x	E10.x -E14.x
Thyroid disorders		E00.x–E03.x, E89.0 (hypothyroidism)	E00.x–E03.x (Hypothyroidism)	Nil	E00.x-E07.x "disorders of thyroid gland"	E00.x-E07.x
Hearing loss		Nil	Nil	Nil	H90.x: conductive, sensorineural; H91.x: other; H93.1: tinnitus	H90.x-H91.x, H93.1
Chronic obstructive pulmonary disease (COPD)		Included in "Chronic Pulmonary Disease" J40.x- J44.x	J41.x-J44.x, J47.x	J40.x- J44.x; J60.x-67.x	Do not include J60.x-67.x (lung disease due to external agents)	J40.x- J44.x
Rheumatoid arthritis, Inflammatory polyarthropathies Connective tissue disorders (contin. overleaf)		L94.0; L94.1; L94.3; M05.x; M06.x; M08.x; M12.0; M12.3, M30.x, M31.0–M31.3; M32.x–M35.x; M45.x; M46.1; M46.8; M46.9	M05.x, M06.x, M08.x, M45.x	Nil	M05-M14: Inflammatory polyarthropathies; M30- M36: Systematic connective tissue disorders; Do not use L94 as is localised skin diseases	M05.x-M14.x, M30.x-M36.x

Condition	Barnett definition	Quan 2005 ICD-10 code [157]	ISD LTC codes[149]	ISD comorbidity codes [142]	ICD-10 dictionary codes[10] and comments	Final List
Alcohol problems		F10; E52; G62.1; I42.6; K29.2; K70.0; K70.3; K70.9; T51.x; Z50.2; Z71.4; Z72.1	Nil	F10.x	Do not include E52.x (niacin deficiency) as it is non-specific to alcohol misuse	F10.x; G62.1; I42.6; K29.2; K70.0; K70.3; K70.9; T51.x; Z50.2; Z71.4; Z72.1
Psychoactive substance misuse		F11.x–F16.x; F18.x; F19.x; Z71.5; Z72.2	Ni	F11.x - F19.x	Do not include F17 (tobacco)	F11.x-F16.x; F18.x-F19.x
Stroke, transient ischaemic attack		G45.x; G46.x; H34.0; I60.x–I69.x	I60.x- I69.x	I65.x-I69.x		G45.x; G46.x; H34.0; I60.x–I69.x
Chronic kidney disease (CKD)		I12.0; I13.1; N18.x-N19.x; N25.0; Z49.0–Z49.2; Z94.0; Z99.2	N18.x; I12.x	Includes codes not CKD specific	Add N17.x (AKI)- as is potential sign of CKD	I12.0; I13.1; N17.x-N19.x; N25.0; Z49.0 – Z49.2; Z94.0; Z99.2
Diverticular disease		Nil	Nil	Nil	K57.x- Diverticular disease of the intestine	K57.x
Atrial fibrillation (AF)		I44.1–I44.3, I45.6, I45.9, I47.x–I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0	I48.x	I44.x - I45.x, I47.x-I49.x	Need to limit to only the AF code	I48.x
Peripheral vascular disease		I70.x- I71.x; I73.1; I73.8; I73.9; I77.1; I79.0; I79.2; K55.1; K55.8; K55.9; Z95.8; Z95.9	Nil	Nil		I70- I71.x; I73.1; I73.8; I73.9; I77.1; I79.0; I79.2; K55.1; K55.8; K55.9; Z95.8; Z95.9
Heart failure (HF)		I09.9; I11.0; I13.0; I13.2; I25.x; I42.0; I42.5–I42.9; I43.x; I50.x	I50.0; I50.1; I50.9	I11.0; I13.0-2; I42-I43.x I50.x; I51.7	Quan includes codes not specific to HF (e.g. I09.9 rheumatic heart disease)	I11.0; I13.0; I13.2; I42.x - I43.x; I50.x
Prostate disorders		Nil	Nil	Nil	N40: Hyperplasia; N41: Inflammatory diseases; N42: Other disorders of prostate	N40.x – N42.x
Glaucoma		Nil	Nil	Nil	H40-42: Glaucoma	H40-42
Dementia (contin. overleaf)		Nil	F00.x - F03.x	F00-F03.x; G30.x		F00.x - F03.x; G30.x

Condition	Barnett definition	Quan 2005 ICD-10 code [157]	ISD LTC codes[149]	ISD comorbidity codes [142]	ICD-10 dictionary codes[10] and comments	Final List
Inflammatory bowel disease		Nil	K50.x- K51.x	Nil		K50.x- K51.x
Blindness & low vision		Nil	Nil	Nil	H53.x-H54.x: Visual disturbance, blindness; H25.x-H26.x, H28.x: cataract	H25.x-H26.x; H28.x; H53.x-H54.x
Chronic sinusitis		Nil	Nil	Nil	J32.x: Chronic sinusitis	J32.x
Learning disability		Nil	Nil	Nil	F81.9: learning disability and learning disorder	F81.9
Anorexia, bulimia		Nil	Nil	Nil	F50.x: Eating disorders	F50.x
Bronchiectasis		J47. x	Nil	Nil		J47.x
Parkinson's disease		Nil	G20.x- G22.x	Nil		G20.x- G22.x
Multiple sclerosis		Nil	G35.x	Nil		G35.x
Viral Hepatitis		Nil	Nil	Nil	B15.x-B19.x- Viral hepatitis	B15.x-B19.x
Chronic liver disease		B18.x; I85.x; I86.4; I98.2; K70.x, K71.1, K71.3–71.5; K71.7, K72–K74.x; K76.0; K76.2–76.9; Z94.4	Nil	B18; I85; I86.4; I98.2; K70.x - K76.x	B18.x is included in viral hepatitis above	I85, I86.4, I98.2, K70 - K76, Z94.4
Depression (contin. overleaf)	Read code recorded in last 12m OR ≥4 anti-depressant prescriptions (excluding low dose tricyclics) in last 12m	F20.4; F31.3–F31.5; F32.x; F33.x; F34.1; F41.2; F43.2	F34.1	Nil	F20.4 (post schizophrenic depression) and F31.3–F31.5 (Bipolar with depression) are in Schizophrenia/Bipolar disorder below	F32.x, F33.x F34.1 F41.2, F43.2

Condition	Barnett definition	Quan 2005 ICD-10 code [157]	ISD LTC codes[149]	ISD comorbidity codes [142]	ICD-10 dictionary codes[10] and comments	Final List
Painful condition	≥4 prescription only medicine analgesic prescriptions in last 12m OR ≥4 specified anti-epileptics in the absence of an epilepsy Read code in last 12m	Nil	M54.5, M54.8, M54.9, F45.5 (back pain only)	Nil	R52.x: Pain, not classified; R10.x: abdomen; N64.4: breast; R07.0-4: throat, chest; H92.0: ear; H57.1: eye; M25.5: joint; M79.6: limb; R10.2: pelvic and perineal; F45.4: psychogenic; M75.8: shoulder; K14.6: tongue; K08.8: tooth; N23; renal colic	F45.4; 45.5; H57.1; 92.0; K14.6; K08.8; M25.5; M54x; 64.4; M75.8; M79.6; 23.x; R07.0- 07.4; R10x; R52.x
Asthma	Read code ever recorded AND prescription in last 12m	In "Chronic Pulmonary Disease". Disease specific codes for asthma selected.	J45 and J46	J45 and J46.		J45.x- J46.x
Treated dyspepsia	≥ 4 prescriptions in last 12m excluding antacids AND NOT (≥4 NSAIDS OR ≥4 aspirin/clopidogrel)	Nil	Nil	Nil	K30.x- dyspepsia	K30.x
Treated constipation	≥4 laxative prescription in last yr	Nil	Nil	Nil	K59.0: constipation	K59.0
Epilepsy (currently treated)	Read code ever recorded, anti-epileptic prescription in last 12m	Nil	G40.x- G41.x	Nil		G40.x- G41.x

(contin. overleaf)

Condition	Barnett definition	Quan 2005 ICD-10 code [157]	ISD LTC codes[149]	ISD comorbidity codes [142]	ICD-10 dictionary codes[10] and comments	Final List
Anxiety & other neurotic, stress related & somatoform disorders	Read code in last 12m OR ≥ 4 anxiolytic/ hypnotic prescriptions in last 12m OR ≥ 4 10/ 25mg amitriptyline in last 12m & not meet criteria for 'Pain'	Nil	Nil	Nil	F40.x: Phobic anxiety disorders F41.x: Generalised anxiety disorders	F40.x - F41.x
Irritable bowel syndrome	Read code ever recorded OR ≥ 4 antispasmodic prescription in last 12m	Nil	Nil	Nil	K58.x: Irritable bowel syndrome	K58.x
New diagnosis of cancer in last five years	Read code first recorded in last 5yrs	C00.x–C26.x; C30.x–C34.x; C37.x–C41.x; C43.x; C45.x–C58.x; C60.x–C85.x; C88.x; C90.0; C90.2; C96.x-C97.x	C00.x-C48.x	C00.x-C97.x		C00.x-C97.x
Schizophrenia (and non-organic psychosis) or bipolar disorder	Read code ever recorded/recorded in last 12m OR Lithium prescribed in last 168d	F20.x, F22.x–F25.x, F28.x, F29.x, F30.2, F31.2, F31.5	F29.x; F30.2; F31.2; F31.5	F20.x - F29.x; F31.x		F20.x- F29.x; F30.2; F31.x

(contin. overleaf)

Condition	Barnett definition	Quan 2005 ICD-10 code [157]	ISD LTC codes[149]	ISD comorbidity codes [142]	ICD-10 dictionary codes[10] and comments	Final List
Psoriasis or eczema	Read code ever recorded AND ≥ 4 related prescription in last 12m excl. simple emollients	Nil	Nil	Nil	L20.x-L30.x: Dermatitis and eczema; L40.x: Psoriasis	L20.x-L30.x; L40.x
Migraine	≥ 4 anti-migraine prescriptions in last year	Nil	Nil	Nil	G43.x: Migraine	G43.x

Abbreviations: ICD, International Classification of Disease; ISD, Information Services Division; LTC, long-term conditions

14.3 Baseline characteristics of Enhanced ACONF 2016 population

Table 94: Appendix two: Enhanced ACONF 2016: Characteristics of population, by gender (n=7,353)*

Characteristic	All n=7,353		Male n=3,700		Female n=3,653	
	Total	%	Total	%	Total	%
Total	7,353	100	-	-	-	-
Gender						
Male	3,700	50.3	-	-	-	-
Female	3,653	49.7	-	-	-	-
Responded to 2001 questionnaire	4,827	65.6	2,293	62.0	2,534	69.4
Mean age at September 2016	63.5	1.5	63.5	1.5	63.5	1.5
Social class of the father at birth of the participant						
I/II (Professional/ Managerial)	636	8.6	328	8.9	308	8.4
III (Skilled non-manual)	786	10.7	395	10.7	391	10.7
III (Skilled manual)	3,300	44.9	1,650	44.6	1,650	45.2
IV (Partly skilled)	1,045	14.2	550	14.9	495	13.5
V (Unskilled)	1,221	16.6	601	16.2	620	17.0
Unemployed/ unknown/disabled/dead	365	5.1	176	4.8	189	5.2
Mean cognition age 7	106.7 (SD 16.1)		106.4 (SD 16.0)		107.0 (SD 16.2)	
School Type						
Non-elite	3,309	45.0	1,553	41.97	1,756	48.07
Elite	1,310	17.8	641	17.32	669	18.31
Other	35	0.8	15	0.41	20	0.55
Missing	2,699	36.7	1,491	40.3	1,208	33.07
Educational attainment						
Tertiary (degree)	840	11.4	452	12.2	388	10.6
Tertiary (non-degree)	751	10.2	418	11.3	333	9.1
Advanced level	632	8.6	335	9.1	297	8.1
Ordinary level	1,356	18.4	537	14.5	819	22.4
School leaving/none	1,181	16.1	521	14.1	660	18.1
Missing	2,593	35.3	1,437	38.8	1,156	31.6
2001 adult Employment status						
Paid work	4,118	56.0	2,085	56.3	2,033	55.6
Unemployed	123	1.7	65	1.8	58	1.6
Permanently sick	260	3.5	106	2.9	154	4.2
Retired from paid work	32	0.4	16	0.4	16	0.4
Looking after family	230	3.1	7	0.2	223	6.1
Full time student	17	0.2	6	0.2	11	0.3
Missing	2,573	35.0	1,415	38.2	1,158	31.7
2001 adult social class						
I/II (Professional/ Managerial)	1,872	25.5	1,054	28.5	818	22.4
III (Skilled non-manual)	1,221	16.6	219	5.9	1,002	27.4
III (Skilled manual)	900	12.2	721	19.5	179	4.9
IV (Partly skilled)	496	6.7	185	5.0	311	8.5
V (Unskilled)	216	2.9	62	1.7	154	4.2
Missing	2,648	36.0	1,459	39.4	1,189	32.5

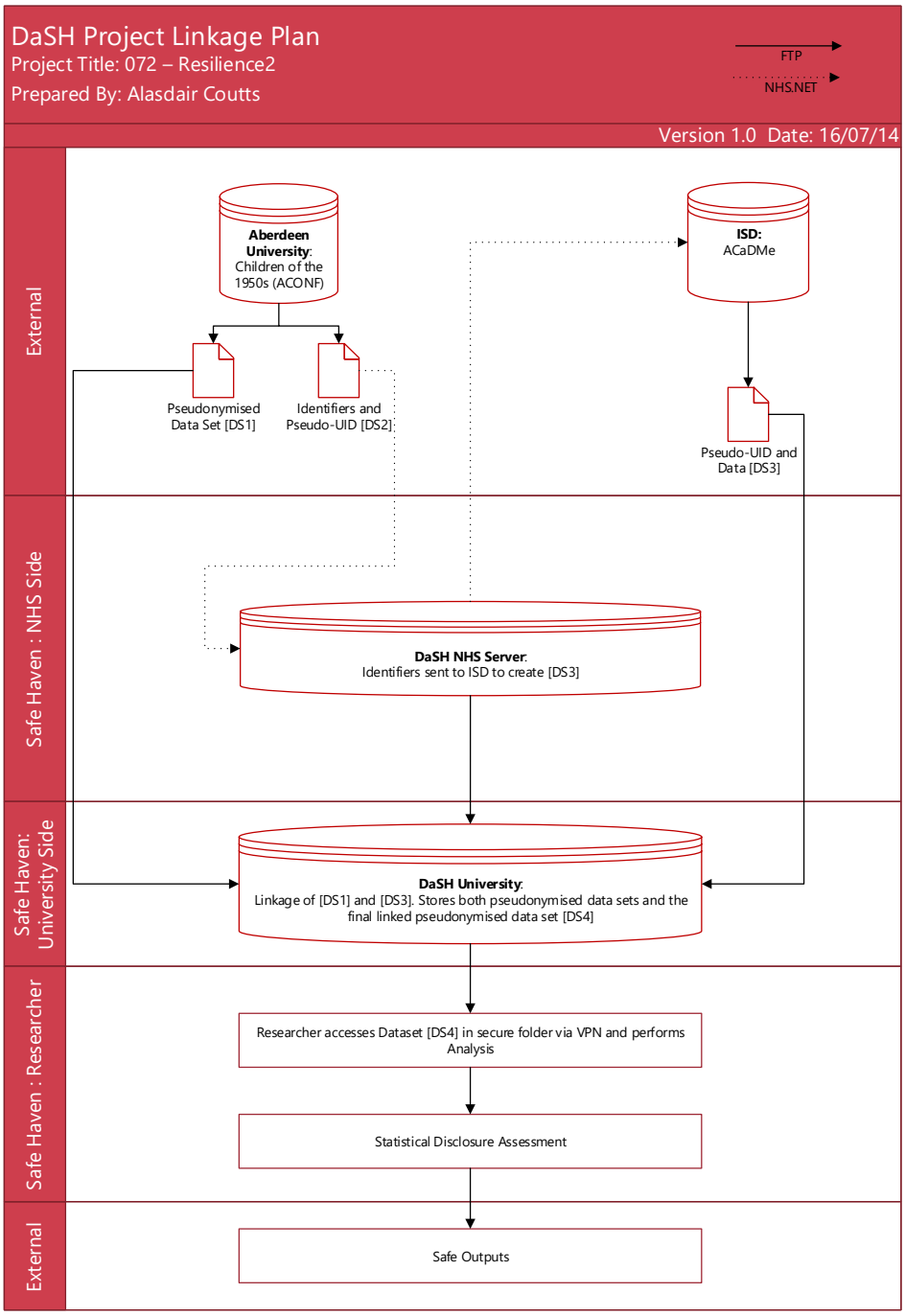
(contin. overleaf)

Characteristic	All n=7,353		Male n=3,700		Female n=3,653	
	Total	%	Total	%	Total	%
2001 adult annual income						
Less than £10,000	1,391	18.9	234	6.3	1,157	31.7
£10000 to £19,999	1,398	19.0	585	15.8	813	22.3
£20000 to £39999	1,332	18.1	922	24.9	410	11.2
£40000 or more	592	8.0	509	13.8	83	2.3
Missing	2,640	35.9	1,450	39.2	1,190	32.6
2001 mean adult body mass index	26.6 (SD 4.6)		26.8 (SD 3.9)		26.4 (SD 5.2)	
2001 adult body mass index categories						
Underweight (<18.5)	28	0.4	5	0.1	23	0.6
Normal (18.5-24.9)	1,859	25.3	730	19.7	1,129	30.9
Overweight (25-29.9)	1,745	23.7	959	25.9	786	21.5
Obese Class 1 (30-34.9)	612	8.3	321	8.7	291	8.0
Obese Class 2 (35-39.9)	173	2.4	49	1.3	124	3.4
Obese Class 3 (40+)	68	0.9	14	0.4	54	1.5
Missing	2,868	39.0	1,622	43.8	1,246	34.1
2001 adult smoking status						
Current smoker	1,257	17.1	593	16.0	664	18.2
Ex-smoker	1,206	16.4	625	16.8	581	15.9
Non-smoker	2,353	32	1,069	28.8	1,284	35.2
Missing	2,537	34.5	1,413	38.2	1,124	30.8
2001 adult alcohol related hangovers in past year						
At least once a week	104	1.4	76	2.0	28	0.8
1-3 times a month	537	7.3	378	10.2	159	4.3
Less than once a month	1,808	24.6	933	25.2	875	24.0
Not at all in the last year	2,088	28.4	816	22.0	1,272	34.8
Missing	2,816	38.3	1,497	40.5	1,319	36.1

Abbreviations: SD, standard deviation; ACONF, Aberdeen Children of the 1950s

*Figures presented are numbers and proportions unless stated otherwise

15 Appendix 3: Data Linkage Plan for ACONF analysis



16 Appendix 4: Multiple imputation analysis of Original ACONF

16.1 Overview

This appendix presents sensitivity analysis of the Multiple Imputation by Chained Equations (MICE) analysis of the Original ACONF. The aim was to test the effect of imputing missing values in the model analysing the association between social class at birth and self-reported multimorbidity and the impact of educational attainment and other covariates. I did not conduct imputation on the measurement of the association between social class at birth and the resilience measures as proportions of missing data were so small.

16.2 Background

There are two common approaches to conducting multiple imputation, these are MICE and a full multivariate model.[240,378] As a separate univariate regression model for each variable of interest can be generated, MICE allows for the inclusion of non-continuous variables. The multivariate model assumes a joint normal distribution of all variables in the imputation model and so does not allow for non-parametric and non-continuous variables.[240,378] The MICE approach is therefore more flexible and is more frequently used.[240,378]

In MICE, a series of regression models cycle through the variables with missing data and impute missing values. The values of missing data are predicted based upon the pattern of missing data and the values of the known data.[237,239] Any variables predictive of missing values and any variables which may influence the process causing the missing data should be included in the model.[237,379]

Multiple plausible values are generated for each missing value, and the analysis is performed on each of these imputed datasets. The estimates are pooled using Rubin's rules to form a single set of values.[237,240] As is conventionally recommended, 20 imputed datasets

were created for the analysis in this thesis (as using less may not be as effective in reducing sampling variability from the imputation process). [237]

Multiple imputation is not about replacing a missing value in a variable with a single new value which goes on to be treated like the rest of the observed data. Instead, multiple imputation techniques build in the uncertainty which is associated with the presence of missing data by including variability in the multiple imputed values. Therefore we do not know the "true value" of the missing data.[380]

16.3 Method

I conducted MICE for the model testing the association between social class at birth and self-reported multimorbidity and the role of educational attainment, cognition at age 7 and secondary school type. I firstly selected out the exposure and outcome variables and the covariates, along with other variables which I hypothesised would influence patterns of missingness. I then tested whether these latter variables influenced patterns of missingness in the key exposure, outcome and covariate variables. All variables influencing missingness were included in the imputation process.

All exposure, outcome, covariates and variables influencing patterns of missingness were entered using the STATA "multiple imputation for chained equations" command. For each variable I stated whether it was binary, categorical or continuous. Twenty imputed datasets were created. Once the process was over I conducted the regression analysis for the analysis as described in Chapter 9.

16.4 Results

The key variables are shown in Table 95. There were no missing data for the exposure, the outcome and for the confounder gender. There were missing data for the three mediators.

The variables I hypothesised to inform missing data patterns were social class in adulthood, BMI, smoking status and hangover frequency.

I started by examining the role of each of these variables upon the pattern of missing data in educational attainment. I found that hangover status did not play a role. However, there was an increasing prevalence of missing educational attainment data with increasing BMI, the prevalence was higher in smokers compared to non-smokers and it was higher in those with lower adult social class. These variables all must be included in the model.

I then checked whether hangover status played a role in the patterns of missing data in the other important covariates: cognition at age 7 and secondary school type. Hangover frequency did not influence cognition missing data but those with frequent hangovers had higher missing school type data. Therefore, all the variables in Table 95 were included in the imputation process.

Table 95: Appendix four: Original ACONF: assessment of missing data in key variables

Variable	Proportion of missing data (%)	Variable type	Role of variable
Gender	Nil	Binary	Confounder
Social class of father at birth	Nil	Ordinal categorical	Exposure
Self-reported multimorbidity	Nil	Binary	Outcome
Cognition at age 7	3.6	Ordinal categorical	Mediator
Secondary school type	4.7	Binary	Mediator
Educational attainment	1.4	Ordinal categorical	Mediator
Adult social class	2.3	Ordinal categorical	Hypothesised to inform missing data patterns in above variables
BMI	7.5		
Smoking status	0.3		
Hangover frequency	6.2		

Abbreviations: BMI, Body Mass Index; ACONF, Aberdeen Children of the 1950s

There were no missing data in the unadjusted association between social class at birth and self-reported multimorbidity. There were missing data in the analysis adjusted by the covariates. The CCA and the imputed analyses are compared in Table 96 for two models:

that adjusted by educational attainment and gender, and that adjusted by these plus cognition at age 7 and secondary school type.

In both models, imputed data led to no changes in the trends found in the CCA. For example, in the model adjusted by educational attainment and gender (with 100 missing observations), the OR of self-reported multimorbidity in those in social class category I/II at birth was 0.8 (95% CI 0.5-1.2) and in the same model with imputation of missing values the OR was also 0.8 (95% CI 0.5-1.2). Despite the slight increase in power, the width of confidence intervals did not markedly change.

16.5 Conclusion

The use of multiple imputation for missing data in this analysis has little impact. It does not change any conclusions.

Table 96: Appendix four: Original ACONF: Comparison of complete case analysis and multiple imputation by chained equations analysis in logistic regression analysis of the association between social class of the father at the birth of the participant and self-reported multimorbidity, adjusted by educational attainment and gender, and adjusted by educational attainment, gender, cognition at age 7 and school type

Social class of the father at birth of the participant	Number (unadjusted model, n=7,184)	Adjusted by educational attainment and gender				Adjusted by educational attainment, gender, cognition at age 7 and school type			
		CCA (n=7,084)*		MICE*		CCA (n=6,561)*		MICE*	
		Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
I/II (Professional/ Managerial)	789	0.80	0.51- 1.25	0.78	0.50-1.21	0.73	0.44-1.20	0.77	0.49-1.21
III (Skilled non-manual)	869	1.08	0.76-1.55	1.09	0.77-1.55	1.03	0.71-1.50	1.09	0.77-1.55
III (Skilled manual)	3,154	1 (reference group)							
IV (Partly skilled)	976	1.14	0.83-1.57	1.13	0.83-1.54	1.07	0.77-1.49	1.12	0.82-1.53
V (Unskilled)	1,048	1.28	0.95-1.72	1.24	0.93-1.66	1.24	0.91-1.70	1.21	0.90-1.62
Unemployed/ unknown/ disabled/ dead	348	1.66	1.08-2.55	1.68	1.11-2.54	1.74	1.11-2.72	1.63	1.07-2.47

Abbreviations: CCA, complete case analysis; MICE, multiple imputation by chained equations; 95% CI, 95% confidence interval; ACONF, Aberdeen Children of the 1950s
*Models statistically significant, p<0.001