SOCIAL ISOLATION IN RELATION TO VASCULAR DISEASE INCIDENCE AND MORTALITY AMONG ADULTS IN THE UK

A THESIS SUBMITTED FOR THE DEGREE OF

Doctor of Philosophy

Michaelmas 2019

Robert William Smith

Brasenose College

University of Oxford

SUPERVISORS

Dr. Sarah Floud and Dr. Isobel Barnes

Nuffield Department of Population Health

Abstract

Social Isolation in Relation to Vascular Disease Incidence and Mortality among Adults in the UK

Robert William Smith, Brasenose College, University of Oxford, DPhil, Michaelmas 2019

Social isolation has recently gained considerable attention as a potential modifiable risk factor for major causes of death and disability such as coronary heart disease and stroke (i.e. vascular disease), and all-cause mortality. However, previous studies have been limited by small sample sizes, reverse causation, and confounding bias. This thesis sought to address these limitations by examining social isolation in relation to vascular disease incidence, vascular disease mortality, and all-cause mortality among two large prospective cohorts of UK adults. To advance current conceptualisations of social isolation as a health risk factor, age, gender, and neighbourhood environments were examined as effect modifiers. Furthermore, independent and joint associations were examined for structural (i.e. social contact frequency and living alone), functional (i.e. social support), and perceived (i.e. loneliness and relationship satisfaction) dimensions of social isolation. Finally this thesis tested the popular claim that social isolation is as bad for health as smoking 15 cigarettes per day.

Generally healthy participants of the Million Women Study (N=326,169) and UK Biobank (N=296,913) were prospectively observed for six and seven years, respectively. An index of structural dimensions of isolation was used to measure social isolation. Associations between social isolation and vascular disease incidence and mortality outcomes were estimated using multivariable Cox regression. Analyses were adjusted for personal characteristics, health behaviours, and physiological factors. The percentage attenuation in the likelihood ratio chi-square test statistic indicated the degree to which these factors explained any associations with each outcome. Sub-group analyses and likelihood ratio tests of interaction were used to examine effect modification and interaction.

This thesis found evidence of strong associations between social isolation and mortality outcomes but only weak associations with vascular disease incidence. Compared to the least isolated Million Women Study and UK Biobank participants respectively, those who were most isolated had 80% (95% confidence interval: 41% - 131%) and 68% (28% to 121%) greater CHD mortality, 71% (34% to 118%) and 92% (32% to 181%) greater stroke mortality, and 32% (24% to 40%) and 38% (27% to 51%) greater all-cause mortality. Whereas compared to the least isolated participants, the most isolated had 7% (1% to 14%) greater and 6% lower (12% lower to 2% greater) CHD incidence, and 28% (19% to 38%) and 23% (9% to 40%) greater stroke incidence. Associations generally did not change according to age, gender, or neighbourhood socioeconomic deprivation, crime rates, distance to services, and greenspace availability. Health behaviours, namely smoking, explained the largest component of these associations. Among the constituent measures of structural isolation, living alone was more strongly and consistently associated with mortality. After adjusting for explanatory factors and structural isolation, lacking confiding support (i.e. functional isolation) was associated with 15% (6% to 24%) greater all-cause mortality. Perceived dimensions of social isolation were not independently associated with all-cause mortality. Associations between structural isolation and all-cause mortality also tended not to change if participants additionally lacked support or were lonely. Finally, associations between social isolation and all-cause mortality were 5-10-fold weaker than those for cigarette smoking.

In conclusion, there is stronger evidence to suggest that social isolation is independently associated with mortality versus vascular disease incidence. These associations did not vary by age, gender, neighbourhood factors, or functional and perceived isolation. Cigarette smoking had much stronger associations with mortality than social isolation. Further large-scale studies are needed to examine the role of delays in seeking care as a potential explanatory factor. Future research should also leverage lifecourse epidemiological methods to further examine the role of confounding in the associations observed.

Acknowledgments

This thesis was only possible because of the Million Women Study and UK Biobank participants. Thank you for sharing your time and information, and for your commitment to advancing human health. To those who founded and sustain these studies, I am equally grateful.

I am deeply indebted to my supervisors Dr. Sarah Floud and Dr. Isobel Barnes. Thank you for investing countless hours into carefully reading, re-reading, and re-re-reading my work. Thank you for always making yourselves available to me, for your detailed and thoughtful feedback, for sharing STATA- and epi-wisdom, and for your mentorship more broadly. This has been a tough but rewarding journey and I am grateful to have had your unabating support throughout. Also deserving of special thanks are those who acted as assessors at various stages of this research including Professor Robert Clarke, Professor Mika Kivimaki, Dr. Benjamin Cairns, and Professor Tim Key.

Over the past three years I am fortunate to have met incredible friends with whom I have had immeasurable fun, have expanded my mind, sought support, and have been inspired to continue striving for excellence in all aspects of life. I especially want to thank Jason Lacombe, Jessica Renzella, Lauren Bandy, and Rebecca Guerriero. Thanks also to the Nuffield Department of Population Health community, my friends in Office 5, and everyone working in the Cancer Epidemiology Unit, especially Dr. Karl Smith-Byrne, Dr. Seamus Kent, Dr. Ai Seon Kuan, Eleanor Watts, Dr. Mohammed Shadejur Rahman Shawon, and Tsz Wong. You've played pivotal roles getting me off the ground as an epidemiologist and you've made every day in the office enjoyable. I would also like to thank many other friends and colleagues who have helped make my Oxford experience indescribably meaningful including the Oxford University Ice Hockey Club community, Brasenose College Hulme Common Room community, and Brasenose College staff. To my friends back home, especially Ryan Gaio and Tanner Van Meer, thanks for your unrelenting support.

Mom and Dad, after my MSc thesis acknowledgements I am running out of ways to express my deep gratitude to you. Thank you sincerely for listening, advising, visiting, for your positive energy and interest, and constant moral support. Aiming high is much easier with a trusty net below. Thanks for enabling me to pursue the goals that drive me.

Finally, thanks to the Nuffield Department of Population Health Scholarship and Brasenose College for funding my studies, conference travel, and extracurriculars.

Table of Contents

List of Tables

List of Figures

List of Appendices

1 Introduction

1.1 Rationale

With older age comes increased risk of vascular diseases defined here as coronary heart disease and stroke. These vascular diseases represent the leading causes of death and disability globally (GBD 2013 Mortality and Causes of Death Collaborators, 2015). Similarly, as people age their network of social relationships evolves. Changing social networks can lead to social isolation, which a considerable body of literature suggests may also be detrimental to one's health (Holt-Lunstad, Smith and Layton, 2010; Holt-Lunstad *et al.*, 2015; Leigh-Hunt *et al.*, 2017). Social isolation is an experience generally characterised by a lack of social relationships and infrequent social contact (Berkman and Krishna, 2014). According to analyses of data from the English Longitudinal Study of Aging and UK Biobank, social isolation affects approximately 9.0% to 14.0% of adults over 40 years old in the UK (Beach and Bamford, 2014; Elovainio *et al.*, 2017).

For decades, health researchers have found associations between social isolation and all-cause mortality (House, Landis and Umberson, 1988; Holt-Lunstad *et al.*, 2010). Some researchers have compared the strength of these associations to that of smoking 15 cigarettes per day (Holt-Lunstad *et al.*, 2010). More recent meta-analyses have also linked social isolation to increased risk of developing and dying from vascular disease (Holt-Lunstad *et al.*, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). In light of these findings and the prevalence of social isolation, social isolation has become a public health concern in the UK (Public Health England, 2016). A more thorough understanding of any associations between social isolation, vascular disease, and mortality may assist public health and social care officials in the design of policies and programs to prevent vascular disease and premature death.

1.1.1 Research Aims

The primary aim of this thesis was to examine the prospective associations between social isolation, vascular disease incidence, vascular disease mortality, and all-cause mortality within the Million Women Study and UK Biobank cohorts. More specifically it aimed to address important limitations of previous research including reverse causation bias, to quantitatively assess the role of confounding or mediating factors, and to assess under what conditions any

associations may vary in strength. The general research questions addressed by this thesis are the following:

- After excluding people with pre-existing vascular disease, cancer, or of fair/poor self-rated health, is social isolation independently associated with vascular disease incidence, vascular disease mortality, or all-cause mortality?
- To what degree do personal characteristics, health behaviours, physiological factors, and psychological factors attenuate the strength of the associations of social isolation with each of the aforementioned disease outcomes?
- Do factors currently hypothesised to represent effect modifiers for social isolation, such as age, gender, and characteristics of people's neighbourhoods, moderate associations between social isolation and each disease outcome?
- Are associations between structural dimensions of social isolation (e.g. infrequent social contact, living alone) and mortality stronger among people who additionally experience functional (e.g. lacking social support) or perceived (e.g. loneliness) dimensions of social isolation?

Further details regarding the novelty and relevance of each research question are presented in section 1.6 and in the background sections for each chapter.

This introductory chapter will begin by describing the epidemiology of vascular disease (Section 1.2) and current approaches to defining and measuring social isolation (Section 1.3). Next, a conceptual model for how previous research suggests social isolation may affect vascular disease and mortality is presented (Section 1.4). Current approaches to intervening on social isolation will then be discussed (Section 1.5). The chapter concludes by outlining the overarching objectives of this Doctor of Philosophy thesis and the topics addressed in subsequent chapters (Section 1.6).

1.2 Vascular Disease in the United Kingdom

1.2.1 Prevalence, Incidence, and Mortality

Coronary heart disease (CHD) and cerebrovascular disease are the most prevalent forms of vascular disease, a broad class of diseases affecting blood vessels (British Heart Foundation, 2018a). CHD represents a group of diseases caused by fatty plaques (i.e. atheroma) which accumulate along blood vessel walls and impede blood flow to the heart muscle (British Heart Foundation, 2018a). CHD is defined in the International Classification of Diseases 10th Revision (ICD-10) as diagnosis codes I20 to I25 (World Health Organisation, 2010). These codes account for angina (I20), acute myocardial infarction (AMI, [I21]), subsequent myocardial infarction (I22), complications following AMI (I23), other acute ischaemic heart diseases (I24), and chronic ischaemic heart disease (I25) (World Health Organisation, 2010). The most common types of CHD are AMI and angina (British Heart Foundation, 2018a). While angina occurs during periods of inadequate blood flow to the heart, AMI occurs when portions of atheroma break off and become lodged in a vessel thus blocking blood flow (British Heart Foundation, 2018a).

Cerebrovascular diseases are caused by interrupted blood flow to the brain and are broadly defined by ICD-10 codes I60 to I69 (World Health Organisation, 2010). Two common acute sub-types of cerebrovascular disease (here forward referred to as stroke) are haemorrhagic (I60-61) and ischaemic (I63) stroke. Haemorrhagic strokes occur when blood vessels serving the brain rupture and cause bleeding (British Heart Foundation, 2018a). Ischaemic strokes occur after blood vessels in the brain become occluded by atheroma or haematoma. Other diseases classified under stroke include the following: other non-traumatic intracranial haemorrhage (I62), stroke not classified as haemorrhagic or ischaemic (I64), less acute conditions such as occlusion and stenosis of precerebral and cerebral arteries (I65-I66), other cerebrovascular diseases (I67), cerebrovascular disorders in diseases classified elsewhere (I68); and sequelae of stroke (I69) (World Health Organisation, 2010).

This thesis research focused on these broadly defined CHD and stroke outcomes to be consistent with previous research and with the British Heart Foundation CHD and stroke definitions (GBD 2013 Mortality and Causes of Death Collaborators, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016; British Heart Foundation, 2018a). It should be noted that previous studies examining social isolation and physical health outcomes also measure broader cardiovascular disease (CVD) outcomes which can additionally encompass the following diagnoses: chronic rheumatic heart disease (I05-I09), hypertensive diseases (I10-I15), other

heart disease (I26-I52), and diseases of the arteries, arterioles, and capillaries (I70-I79) (Holt-Lunstad *et al.*, 2015; Elovainio *et al.*, 2017; British Heart Foundation, 2018b).

As of 2017, over 2.2 million (3.3%) people in the UK had been diagnosed with CHD and 1.2 million (1.8%) with stroke (British Heart Foundation, 2018d). While these prevalence rates are not adjusted for age or other factors that may vary across countries within the UK, they tend to be lower in England (CHD: 3.2%; Stroke: 1.7%) compared to Scotland (CHD: 4.1%; Stroke: 2.2%), Wales (CHD: 3.7%; Stroke: 2.1%) and Northern Ireland (CHD: 3.8%; Stroke: 1.9%) (British Heart Foundation, 2018d). Every year in the UK, approximately 12 women and 31 men per 100,000 people are newly diagnosed with CHD, and ten women and 12 men per 100,000 people are newly diagnosed with stroke (British Heart Foundation, 2017).

CHD and stroke represent the first and third, respectively, most prevalent causes of years of life lost globally (GBD 2013 Mortality and Causes of Death Collaborators, 2015). As of 2016, CHD is the largest single cause of death in the UK, accounting for 8.5% of deaths among women and 13.8% of deaths among men (British Heart Foundation, 2018b). Approximately 7.1% of deaths among women and 5.5% of deaths among men were due to stroke (British Heart Foundation, 2018b).

CHD death rates have decreased substantially over the past 20 years. The magnitude of decreasing vascular disease mortality trends and trend differences according to gender are illustrated in Figure 1.1. Stroke mortality is lower than CHD mortality and has also decreased over time (Figure 1.1).

The age-standardised death rate for CHD in the UK was 114.1 per 100,000 people as of 2016 (British Heart Foundation, 2018c). CHD killed about half as many women than men in the UK (76.2 per 100,000 women and 162.6 per 100,000 men) (British Heart Foundation, 2018c). For stroke, the UK age-standardised death rate was 65.5 per 100,000 people as of 2016 (British Heart Foundation, 2018e). As of 2016, the age-adjusted death rates for stroke were 62.8 per 100,000 women and 68.1 per 100,000 men (British Heart Foundation, 2018e).

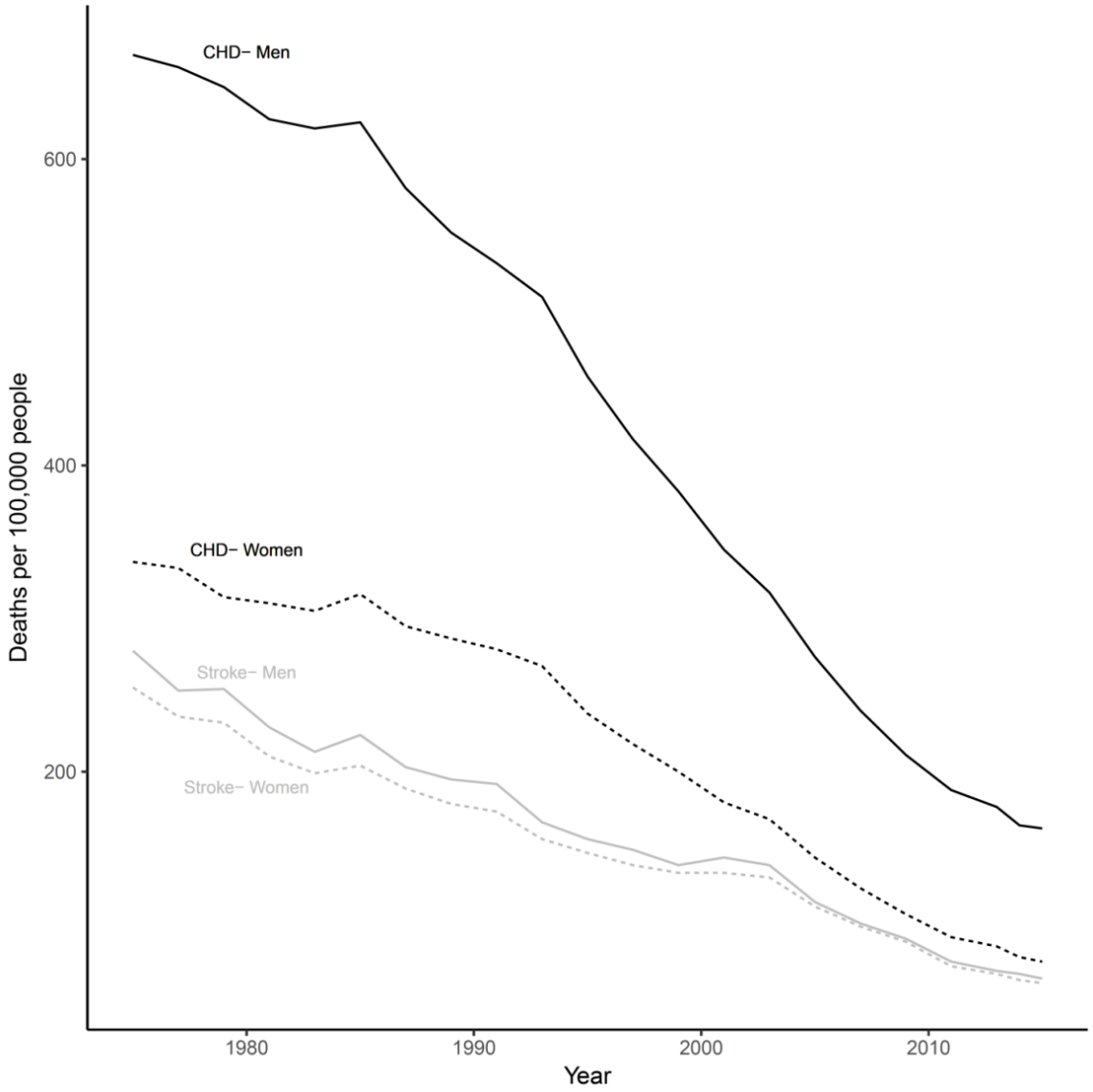


Figure 1.1.1. Age-standardised death rates due to coronary heart disease and stroke among UK women and men of all ages from 1975 to 2016 (British Heart Foundation, 2018d, 2018e).

1.2.2 Risk Factors for Vascular Disease

Contributing to the decreasing vascular disease mortality trends in the UK has been the identification of key risk factors, concerted public health interventions to address them, and advances in the treatment of vascular disease (Bhatnagar *et al.*, 2016). Vascular disease risk tends to increase according to non-modifiable factors such as older age and male sex (Palomeras Soler and Casado Ruiz, 2010). Modifiable risk factors for vascular disease incidence and mortality include smoking, hypertension (i.e. 140/80 mmHg or higher), diabetes mellitus, dyslipidemia, overweight and obesity (as indicated by body mass index [BMI] or waist-to-hip ratio), physical inactivity, and increased alcohol intake (Yusuf *et al.*, 2004;

Meschia *et al.*, 2014; O'Donnell *et al.*, 2016; Stewart, Manmathan and Wilkinson, 2017). Other modifiable and non-modifiable risk factors specific to stroke include atrial fibrillation, familial history of stroke, and previous CVD diagnoses (Meschia *et al.*, 2014; O'Donnell *et al.*, 2016). Due in part to challenges with reliable measurement, potentially modifiable dietary and psychosocial factors (e.g. depression and work, financial or life event related stress) are less consistently associated with vascular disease risk (Yusuf *et al.*, 2004; Meschia *et al.*, 2014; O'Donnell *et al.*, 2016; Stewart *et al.*, 2017). Recent meta-analytic reviews also suggest that characteristics of peoples' social relationships, particularly social isolation, represents a potentially modifiable risk factor for vascular disease (Holt-Lunstad *et al.*, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016).

1.3 Defining and Measuring Social Isolation

Through life, the number and nature of people's social relationships evolves. A social relationship is a state of interdependence between two or more people that is often characterised by mutual influence over one another's thoughts, feelings, and/or behaviours (Perlman and Vangelisti, 2006). A social network refers to the web of relationships within which someone is interconnected with others (Smith and Christakis, 2008). Experiences of social isolation can result from changes to an individual's social network. Social isolation is most often described in terms of lacking social relationships and infrequent contact with relatives, friends, or the broader community (Valtorta and Hanratty, 2012; Leigh-Hunt *et al.*, 2017). However, there remains no universal definition or gold-standard measurement tool for social isolation (Valtorta and Hanratty, 2012; Berkman and Krishna, 2014). There have also been recent calls for the concept of social isolation to be expanded beyond objective "structural" characteristics of people's social network to incorporate functional dimensions of isolation (e.g. lacking social support) and perceived dimensions of isolation (e.g. loneliness and relationship dissatisfaction) (Zavaleta, Samuel and Mills, 2017; Holt-Lunstad, 2018b).

Health researchers often opt for measurement tools which discern levels of isolation based on structural characteristics of people's relationships, frequency of contact, and/or living arrangements (Valtorta, Kanaan, Gilbody and Hanratty, 2016). Such measures range from unidimensional measures such as living alone, to multidimensional social relationship indices (Valtorta, Kanaan, Gilbody and Hanratty, 2016). Multidimensional indices are often summative and calculate social isolation scores based on the following measures: the number of and frequency of contact with relatives or friends; participation in faith-based groups and social groups or organisations; household occupancy; and marital status (Berkman and

Krishna, 2014; Valtorta, Kanaan, Gilbody and Hanratty, 2016). Such indices include the Berkman-Syme social network index (Berkman and Syme, 1979), social relationships and activity scale (House, Robbins and Metzner, 1982), the social network interaction index (Orth-Gomér and Johnson, 1987), and the social isolation index (Shankar *et al.*, 2011) .

The Berkman-Syme social network index was derived and validated within the Human Population Laboratory Survey cohort of residents from Alameda County, USA (Berkman, 1977). To calculate social network index scores, participants received one point if they were married, from one to five points for the number of and frequency of contact with close relatives and friends (i.e. five points representing larger social network and frequent contact), one point for membership in a church group, and one point for participation in other social organizations (Berkman, 1977). These points were summed, and participants were categorised into the following quartiles: Level I "low networks," Level II "medium networks," Level III "medium-high networks," and Level IV "high networks" (Berkman, 1977). Henceforth, participants in Level I were conceptualised as being among the most isolated, and those in Level IV were among the most integrated or least socially isolated. The Berkman-Syme social network index is often adapted according to the data available to researchers. A more recent adaptation assigned three points to participants who are married, and between one and three points if they had at least one close friend, participated in group activities at least one to two hours per week, and attended a religious service at least once per week (Chang *et al.*, 2017).

The more contemporary social isolation index was derived and validated within the English Longitudinal Study of Ageing cohort (Shankar *et al.*, 2011). To calculate social isolation index scores, study participants were assigned one point if they were not married or cohabiting with a partner, had less than monthly contact with children, other immediate relatives, and friends (one point for each), and if they participated in any religious, social, or recreational groups, organisations, or committees (one point total) (Shankar *et al.*, 2011). Points are summed and aggregated into categories from least isolated to most isolated. More recent adaptations of this index assigned one point to participants who live alone, or if they reported less than monthly contact with family or friends, or if they do not participate in at least weekly leisure/social group activities (Hakulinen *et al.*, 2018).

Based on early research by the RAND Corporation (Donaldson and Ware, 1982) and consistently reproduced associations between social isolation and mortality, multidimensional indices of social isolation like the social network index are believed to have good test-retest reliability and construct validity (Berkman and Krishna, 2014). An advantage of measuring

social isolation using such indices is that they account for different types of social relationships which may be associated with health independently and in combination. Studies using multidimensional social isolation indices are capable of comparing associations across constituent factors, and approximating which factors are more and less relevant to health. Research has yet to concurrently examine associations between structural, functional, and perceived dimensions of social isolation and mortality, in addition to the combination of these dimensions and their associations with mortality (Holt-Lunstad *et al.*, 2015).

Social support is generally described as a perceived resource available, or function carried out by someone, in order to assist another person (Umberson, Crosnoe and Reczek, 2010). These functions can be characterised as emotional, informational, and instrumental (Umberson *et al.*, 2010; Berkman and Krishna, 2014). Emotional support relates to demonstrations of empathy and compassion (e.g. confiding support provided by someone who is trusted) (Shor, Roelfs and Yogev, 2013; Berkman and Krishna, 2014). Emotional support was examined in this thesis because it has been studied widely in relation to health and was the only measure of social support available in the UK Biobank. While not examined in this thesis, instrumental and informational social support merit description.

Instrumental support relates to sharing material goods and assisting with activities (e.g. financial support, transportation to social programs or hospital) (Shor *et al.*, 2013; Berkman and Krishna, 2014). Informational support relates to sharing helpful information, appraisal, or advice (e.g. encouragement to quit smoking or seek healthcare) (Shor *et al.*, 2013). Informational support is closely related to the concept of social influence. Social influence is characterised by a person's thoughts and behaviours being altered by interaction with or comparison to others, and by what is generally accepted as normal within peoples' social network (e.g. peer-pressure affecting one's decision to quit smoking or take up exercise) (Christakis and Fowler, 2007, 2008; Berkman and Krishna, 2014).

Negative feelings accompanying social isolation are believed to be as relevant to health as the number of relationships someone shares with others (Holt-Lunstad *et al.*, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016; Wister *et al.*, 2019). Perceived isolation is often referred to as loneliness (Berkman and Krishna, 2014; Zavaleta *et al.*, 2017). Loneliness is defined as "a distressing feeling that accompanies the perception that one's social needs are not being met by the quantity or especially the quality of one's social relationships" (Hawkley and Cacioppo, 2010). While correlated, loneliness does not always accompany structural social isolation and vice versa (Hawkley and Cacioppo, 2010). Some suggest that structural isolation and loneliness

should be considered as independent constructs (Hughes *et al.*, 2004; Coyle and Dugan, 2012). Previous cross-sectional analyses of Health and Retirement Study participants found low to moderate correlations between structural measures of isolation and loneliness (Hughes *et al.*, 2004; Coyle and Dugan, 2012). In bivariate analyses, Coyle and Dugan (2012) also found associations between loneliness and increased likelihood of self-reported mental health problems but not general self-rated health, whereas structural isolation (measured using an index similar to the social isolation index) was associated with lower self-rated health but not mental health problems. Given that loneliness and structural isolation can co-occur and are conceptually related to the number and quality of social relationships one has, it was hypothesised that analysing structural and perceived isolation individually and as part of the same construct was reasonable (Wister *et al.*, 2019).

Another perceived dimension of isolation is satisfaction with relationships (Zavaleta *et al.*, 2017). Satisfaction with relationships in general has not been studied as widely as loneliness. However, along with related factors such as negative aspects of relationships (e.g. conflict) and marital satisfaction, the degree to which someone is satisfied with their relationships is believed to be relevant to the degree of distress caused by one's relationships (Berkman and Krishna, 2014; Robles *et al.*, 2014).

In an effort to develop coherence of terminology for research and policymaking, the Oxford Poverty and Human Development Initiative (OPHI) generated a definition and measurement framework for social isolation encompassing structural, functional, and perceived dimensions. The OPHI define social isolation as an experience characterised by inadequacy in the:

> *"...quality and quantity of social relations with other people at the different levels where human interaction takes place (individual, group, community, and the larger social environment)"* (Zavaleta et al. 2014, pp.5).

To assess the utility of including indicators of functional and perceived dimensions of isolation in multidimensional social isolation indices, Chapter 6 of this thesis examined social support, loneliness, and relationship satisfaction in relation to mortality both individually, and in combination with an index of structural isolation. Whilst acknowledging the novelty and comprehensiveness of the OPHI measurement framework for social isolation, analyses in Chapter 3, 4, and 5 were focussed on a multidimensional index of structural isolation. As detailed in Sections 3.2.2 and 4.2.2, social isolation was measured using an index similar to the social isolation index (Shankar *et al.*, 2011; Hakulinen *et al.*, 2018). It was hypothesised that this measure would increase the comparability of findings from this research with previous

studies and that the more objective nature of these constituent factors would be less vulnerable to measurement error.

1.3.1 Prevalence of Social Isolation

The diversity of methods for measuring social isolation makes precisely estimating the prevalence of social isolation in society challenging (Victor, 2005; Valtorta, Kanaan, Gilbody and Hanratty, 2016). Recently, social isolation was estimated to affect 9.0% of middle aged and older adults within the UK Biobank cohort (Elovainio *et al.*, 2017). Elovainio and colleagues (2017) categorised participants as socially isolated if they met at least two of the following criteria: they were living alone, had at most monthly contact with friends or relatives, and participated in social/leisure activities less than weekly. This study is relevant because it was the largest study to measure social isolation in the UK and the UK Biobank was the focus of Chapter 4 analyses. However, given that the UK Biobank cohort is not nationally representative, prevalence estimates may be biased. Analyses of the nationally representative English Longitudinal Study of Aging data estimate that social isolation affects 10.0% of women and 14.0% of men over 50 in England (Beach and Bamford, 2014). Beach and Bamford (2014) categorised participants as socially isolated if they met at least three of the following criteria: were not married or living with a partner, less than monthly contact with children, other family members or friends, and having no affiliation with a social organisation.

More data related to the individual factors constituting social isolation is available from national surveys such as the Census. According to the 2011 Census, approximately 43.0% adults 65 years old and older in England and Wales were not married or in a civil partnership (Office for National Statistics, 2013). Similar to the proportion of people living alone within the European Economic Area, 13.0% of all residents of England and Wales lived alone (Office for National Statistics, 2014). The proportion of adults who lived alone in the UK increased with age, ranging from 17.0% among those 50 to 64 years old, 38.0% among those aged 65 to 74 years, and 59.0% among those 85 years old and older (Office for National Statistics, 2014). With regard to social contact, according to data from the 2012 European Quality of Life Survey, approximately 42.0% of UK adults aged 45 to 64 years old reported meeting family, friends, or work colleagues less than weekly (Siegler, Njeru and Thomas, 2015). This proportion decreased to 25.0% among adults aged 75 years and older (Siegler *et al.*, 2015). Approximately 45.0% of UK adults over 45 years old were not involved in professional, religious, political or recreational organisations (Siegler *et al.*, 2015). Finally, most UK adults did not participate in voluntary service (Siegler *et al.*, 2015). At 76.0%, non-participation was lowest among those aged 65 to 74 years old and increased to 85.0% among those 75 and older (Siegler *et al.*, 2015).

Popular media outlets and scientific literature describe social isolation, and perceived isolation specifically, as growing concerns and "epidemic" in modern society (Kullar, 2016; Easton, 2018; Holt-Lunstad, 2018a). However, there is little evidence to suggest that the prevalence of social isolation has changed throughout the 20th and 21st centuries. Longitudinal research suggests that at least in the UK, the prevalence of perceived isolation has remained stable over the decades since World War II (Victor, 2005; Victor and Bowling, 2012). Some may argue that the rising number of single-occupant households (since the 1980s) within increasingly ageing populations in Europe and North America, is indicative of more isolated societies (Office for National Statistics, 2018b; Eurostat, 2019; Tang, Galbraith and Truong, 2019; U.S. Census Bureau, 2019). Caution is warranted when interpreting these statistics because without consideration for other constituent factors such as people's frequency of contact with family, friends or social groups, these statistics may not accurately represent social isolation. Furthermore, framing such statistics as indicating a problem is also challenged when it remains unclear to what degree people in these nations prefer to live alone in their homes. Further longitudinal research using multidimensional measures of social isolation is needed in order to understand whether the prevalence of social isolation in society is indeed changing. Whether or not prevalence is changing, increases in the absolute frequency of people experiencing isolation may still indicate a public health concern, particularly if social isolation does in fact influence risk of negative health outcomes and greater healthcare utilisation (Leigh-Hunt *et al.*, 2017; Valtorta, Collingridge Moore, *et al.*, 2018). To more effectively frame social isolation as a public health issue, a better understanding of exactly how social isolation may affect health is needed.

1.4 How Social Isolation Gets Under the Skin to Affect Health

This thesis drew upon Berkman and Krishna's model of social networks and health to conceptualise the processes through which social relationships are hypothesised to influence health (Appendix A, Figure A1.1, pp.219) (Berkman and Krishna, 2014). These processes are complex and not fully understood (Berkman and Krishna, 2014). Berkman and Krishna's model proposes a causal chain of factors from the social and physical living environments which shape people's social networks, to behavioural, physiological, and psychological factors that more directly influence health (Berkman and Krishna, 2014). To guide this thesis research, Berkman and Krishna's model was adapted to illustrate the processes by which social isolation may affect vascular disease and mortality, using the data available to examine explanations for any associations (Figure 1.2).

1.4.1 Neighbourhood Factors

The first construct presented in Figure 1.2 is “Neighbourhood Factors.” Social and physical characteristics of people’s living environments are believed to shape their social networks. Here forward referred to as neighbourhood factors, Berkman and Krishna (2014) propose that these factors influence people’s capacity to form and maintain relationships, and participate within communities. Neighbourhood factors include, but are not restricted to, socioeconomic deprivation, crime, and proximity to places where social interaction occurs (e.g. parks, shops, GP surgery). It is hypothesised that health effects of social isolation are in part moderated by neighbourhood factors, however, few studies have examined their influence (Berkman and Krishna, 2014). These social and physical factors may influence the number of people individuals have the opportunity to interact with, how often they interact with others, and the types of support available through these relationships (Berkman and Krishna, 2014).

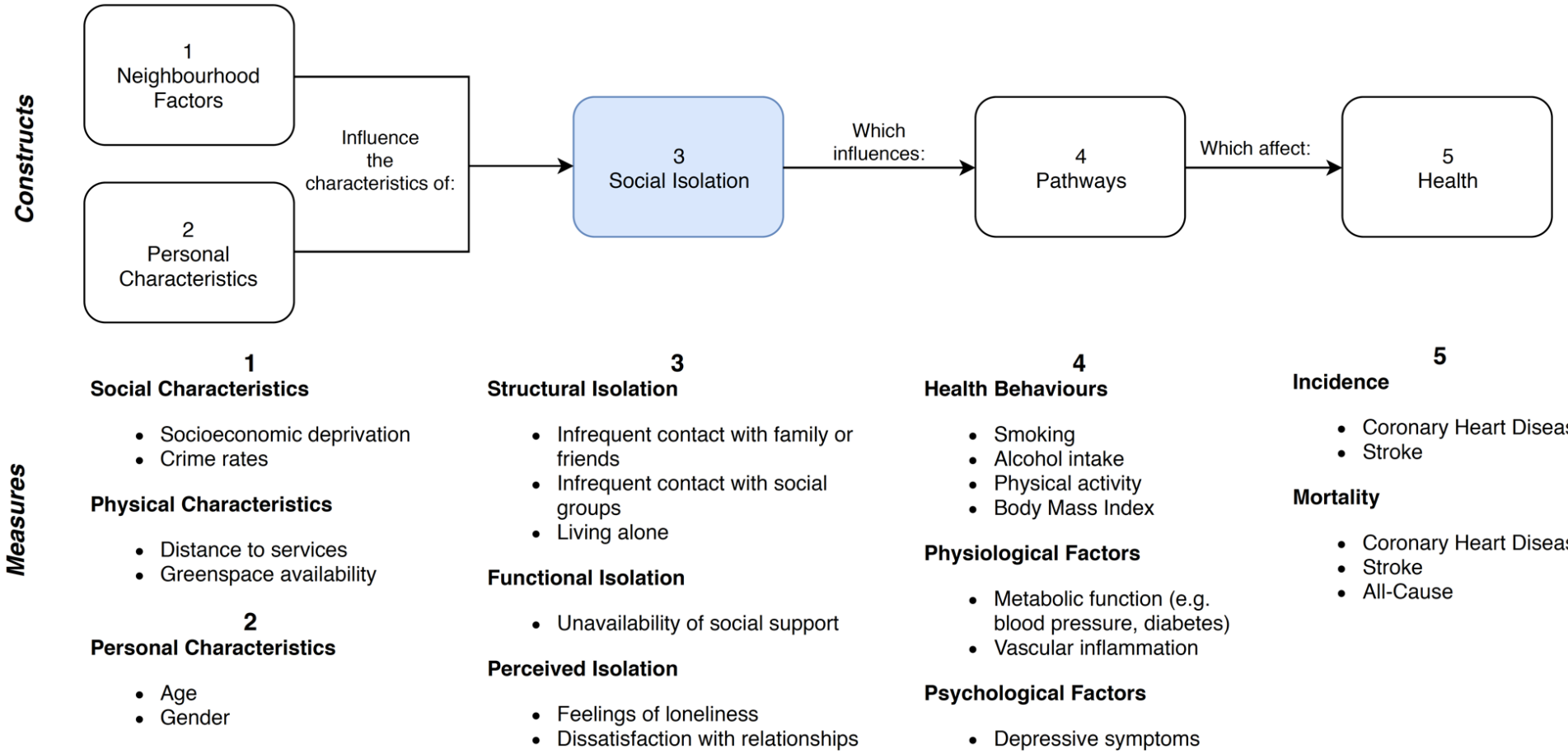


Figure 1.2. Conceptual model of the factors potentially modifying and mediating associations between social isolation, vascular disease and mortality, and the measures to be examined in this thesis.

1.4.2 Personal Characteristics

The second construct presented in Figure 1.2 is "Personal Characteristics." It is believed that people's social networks and behavioural responses to social isolation are influenced by personal characteristics such as age and gender (Kim and Kawachi, 2018). Personal characteristics may thus represent modifiers of associations between social isolation and health. As one ages, people may become isolated due to factors such as retirement, bereavement, migration of family members, and the development of illness and disability (Wilson *et al.*, 2010; Marit *et al.*, 2012). In these circumstances people may have limited access to emotional support, which may buffer any negative effects of distress from the perception of isolation (Hawkley and Cacioppo, 2010; Shor *et al.*, 2013; Berkman and Krishna, 2014; Holt-Lunstad, 2018b). Also, people may have limited access to instrumental support which may assist them in completing activities of daily living, accessing health services, or following therapeutic regimens (Shor *et al.*, 2013; Berkman and Krishna, 2014; Holt-Lunstad, 2018b). Social isolation may be more likely to influence health among younger adults through the adoption of deleterious health behaviours to cope with, for example, distress from the dissolution of marriage (Kim and Kawachi, 2018).

The degree to which personal characteristics modify associations between social isolation and health may be dependent on the cultural norms which tacitly dictate how people go about developing and behaving within social relationships (Kim and Kawachi, 2018). Social relationships may influence health differently due to gender-related differences in expectations for giving and receiving social support (Shor *et al.*, 2013; Yang *et al.*, 2013; Kim and Kawachi, 2018). Some hypothesise that when presented with a change in their social network (e.g. meeting someone new, being asked for help, or becoming more isolated), women are more likely to "tend-and-befriend" others (Yang *et al.*, 2013). Women may thus enjoy larger social networks and have greater access to emotional and instrumental social support than men (Shor *et al.*, 2013). Access to such support may buffer adverse physiological responses to the perception of isolation (Yang *et al.*, 2013). Gender differences may also be related to help-seeking behaviours. For example, compared to men, women may be more aware of and attentive to the symptoms of their partners and facilitate more timely help-seeking at the onset of a stroke (Madsen *et al.*, 2017).

Personal characteristics such as age and gender could however also represent confounding factors on associations between social isolation and health (Kim and Kawachi, 2018). As a confounder, age may influence both risk of becoming isolated, and of developing and dying from vascular disease (Palomeras Soler and Casado Ruiz, 2010; Nicholson, 2012; Holt-Lunstad, 2018b). It is important to note that sex refers to the genetic make-up of an individual, whereas gender represents how an individual identifies with and performs their femininity and masculinity. Therefore, while gender may influence one's risk of becoming isolated, biological sex is known to affect the pathophysiology of vascular disease (Turtzo and McCullough, 2008; Khamis, Ammari and Mikhail, 2016). For ease of explanation, here forward, gender will be used to refer to both biological sex and self-identified gender. This thesis examined age and gender as confounders and modifiers of associations.

1.4.3 Social Isolation

The third construct presented in Figure 1.2 is "Social Isolation." As discussed in Section 1.3, indices of structural isolation are commonly used to study associations between social isolation and health. Analyses within this thesis ascertained structural social isolation primarily according to frequency of contact with relatives or friends, frequency of contact with social groups, and whether participants lived alone. Functional and perceived dimensions of isolation were also examined, but only in relation to mortality, and the relevance of these dimensions were compared to that of structural isolation. Functional dimensions such as the availability of social support, and perceived dimensions such as loneliness and dissatisfaction with relationships were believed to be important factors which confer or buffer health risks potentially attributable to structural isolation (Berkman and Krishna, 2014). Structural, functional, and perceived dimensions of social isolation are believed to impact health by influencing people's health behaviours, physiological factors, and psychological factors that are more directly related to health outcomes (Berkman and Krishna, 2014).

1.4.4 Pathways

The fourth construct presented in Figure 1.2 is "Pathways." Behavioural, psychological and physiological pathways represent factors which are most directly related to the maintenance of health and onset of disease. More frequent contact with, social support from, and the social influence of relatives, friends, or groups may discourage smoking, encourage physical inactivity, and influence dietary choices (Christakis and Fowler, 2007, 2008; Umberson *et al.*, 2010; Berkman and Krishna, 2014). Structural and perceived dimensions of isolation have also been associated with decreased utilisation of preventative health service utilization, delays in

seeking timely medical attention, and modestly associated with lower participation in breast cancer screening (Keating *et al.*, 2011; Madsen *et al.*, 2017; Stafford *et al.*, 2018). The social influence of relationships on health behaviours may also be bidirectional. While noting the methodological limitations of modelling the spread of behaviours through social networks, Christakis and Fowler (2013) suggest that the social influence of close relatives and friends can promote and reinforce smoking and alcohol consumption behaviours, as well as obesity. Finally, unhealthy behaviours may also be used as a coping mechanism from distress related to perceived isolation (Umberson *et al.*, 2010). The health behaviours examined in this thesis include smoking, alcohol intake, physical activity, and BMI as a proxy measure for diet.

Previous studies examining potential physiological pathways have largely focused on hypertension, dyslipidemia, and diabetes, as well as immunological processes such as vascular inflammation (Berkman and Krishna, 2014; Kubzansky, Seeman and Glymour, 2014). For example, loneliness and negative social interactions are believed to trigger stress responses implicating the nervous, endocrine, and immune systems that promote vascular inflammation (Chiang *et al.*, 2012; Cacioppo *et al.*, 2015). Another perspective on the physiological effects of social networks is that chronic exposure to social isolation accelerates biological ageing (Berkman and Krishna, 2014). Epigenetic studies have found associations between marital status, social support, relationship quality and leukocyte telomere length (Kim and Kawachi, 2018). However, studies examining telomere length in relation to mortality have produced inconsistent results in the strength and statistical significance of associations (Kim and Kawachi, 2018). While few have examined this "accelerated ageing hypothesis" in relation to structural social isolation, studies examining composite measures of biological risk factors (e.g. studies measuring allostatic load) suggest that biological ageing is indeed sensitive to social relationships (Berkman and Krishna, 2014). The concept of allostatic load is closely related to the accelerated ageing hypothesis. Allostatic load is defined as the cumulative biological stress or "wear and tear" resulting from the body's adaptation to chronic physiological dysregulation across multiple organ systems (Kubzansky *et al.*, 2014). Constituent measures of structural social isolation have been associated with allostatic load, however previous studies tend to be small and the direction and magnitude of associations tend to be mixed (Seeman *et al.*, 2002, 2004; Brooks *et al.*, 2014). Among the original objectives of this thesis research was to examine cardiometabolic, inflammatory, and biological ageing related physiological pathways. However unfortunately, biomarker data did not become available until March 2019. This release date did not align with the proposed timelines for completion of the project. Therefore, measures for hypertension and diabetes that were available in both the Million Women Study and UK Biobank, and a proxy measure for dyslipidemia from the UK Biobank were examined.

Compared to health behaviours and physiological factors, less research has examined the role of psychological processes mediating associations between social isolation and health (Berkman and Krishna, 2014). One hypothesis is that social support helps promote self-efficacy and coping skills in response to illness, while buffering the psychological stress caused by social isolation (Berkman and Krishna, 2014; Holt-Lunstad, 2018a). Another hypothesis suggests that participation in social groups or activities may buffer psychological distress by reinforcing meaningful social roles and one's sense of identity and belonging (Berkman and Krishna, 2014; Jetten *et al.*, 2014). Social isolation may also negatively influence mood and emotion, and promote mental health conditions such as depression (Berkman and Krishna, 2014). Previous research suggests that depression may be more relevant in explaining associations between perceived isolation (i.e. loneliness) and health than structural and functional isolation (Uchino, Uno and Holt-Lunstad, 1999; Cacioppo, Hawkley and Thisted, 2010; Courtin and Knapp, 2017; Wang *et al.*, 2018).

It is difficult to establish the direction of association from previous research examining potential mediating pathways between social isolation and health. It is therefore important to note that whilst presented as potential mediators, health behavioural, physiological, and psychological factors may also represent confounders of any associations between social isolation, vascular disease, and mortality. This thesis referred to variables that may represent confounders or mediators as explanatory factors because when adjusted for, these factors were hypothesised to explain varying degrees of minimally adjusted associations between social isolation and the health outcomes of interest.

1.4.5 Health

The fifth and final construct presented in Figure 1.2 is "Health." Vascular disease incidence and mortality were chosen as outcomes for this thesis because these conditions represent major causes of death and disability worldwide, and social isolation research examining these outcomes is often used to help frame social isolation as a public health issue (Kullar, 2016; Campaign to End Loneliness, 2017; Department for Digital Culture Media and Sport, 2018a; Holt-Lunstad, 2018a). CHD and stroke-specific outcomes as opposed to aggregate CVD outcomes were chosen for this thesis research because while similar, each disease has unique pathophysiological traits. For example, strokes can result from the blockage (i.e. from blood clots and/or fatty plaque fragments) or rupture (i.e. from weakened vessel walls, hypertension, traumatic force) of cerebral arteries whereas CHD results from the progressive blockage of coronary arteries (British Heart Foundation, 2018a). As hypothesised by others (Yang *et al.*, 2013; Cacioppo *et al.*, 2015; Holt-Lunstad, 2018b), if social isolation induces psychological

stress which promotes vascular inflammation, and thus ischemic vascular disease, there may be differences in the strength of associations with CHD compared to stroke. CHD and stroke also have unique symptoms which may affect a person's recognition of symptoms and decision to seek help, and the likelihood of others encouraging help-seeking or preventative health behaviours before acute events. Henceforth, social isolation could have unique causal mechanisms leading to CHD and stroke. By examining CHD and stroke-specific incidence and mortality, this research may build upon current explanations for how social isolation may affect the physiology of vascular disease.

The CHD and stroke incidence outcomes combined fatal and non-fatal incident events to avoid underestimating any associations between social isolation and CHD or stroke incidence. To improve the comparability of findings from this thesis and previous studies focused on vascular disease mortality, CHD and stroke mortality outcomes counted CHD and stroke deaths regardless of whether they were preceded by a non-fatal incident event during the observation period. All-cause mortality was also chosen as an outcome because it is the most common outcome examined in relation to social isolation, and it is used in epidemiology as a general indicator of population health (Holt-Lunstad *et al.*, 2010; Shor *et al.*, 2013).

1.5 Implications for Intervention

Understanding if and how social isolation affects health is important, because if causal associations exist, social isolation interventions can be designed to prevent adverse health outcomes. Within the literature, it remains unclear which interventions are and are not effective for reducing social isolation and promoting mental and physical health (Cattan *et al.*, 2005; Dickens *et al.*, 2011; Courtin and Knapp, 2017). Current strategies aimed at reducing structural and perceived isolation tend to focus on identifying isolated older adults and improving access to social support interventions (Campaign to End Loneliness, 2014; National Seniors Council, 2014; Equal Opportunities Committee, 2015; Valtorta and Hanratty, 2016). Previous research has examined three general types of social isolation interventions. They are the following: one-to-one support services (e.g. in-person, telephone, or online befriending schemes, counselling); group support services (e.g. group counselling, therapy, and educational seminars); and services enabling community participation (e.g. outreach programs designed around shared interests such as physical activity, the arts, and socializing) (Cattan *et al.*, 2005; Dickens *et al.*, 2011; Jopling and Vasileiou, 2015). Individual and group-level interventions aim to ameliorate social isolation by helping individuals maintain existing social relationships, build new relationships, and adapt their ways of thinking about social connection in older age (e.g.

through cognitive behavioural therapy, mindfulness meditation) (Cattan *et al.*, 2005; Dickens *et al.*, 2011; Jopling and Vasileiou, 2015). Least attention has focused on population-based approaches to primary prevention of social isolation which address broader social determinants of health (Valtorta and Hanratty, 2016).

The lack of conclusive evidence on interventions appears to stem from small and or unrepresentative samples, inconsistent data reporting, high attrition, and study design weaknesses (Cattan *et al.*, 2005; Dickens *et al.*, 2011). Further, heterogeneity in the design of interventions and studied cohorts, makes general inferences about the effectiveness of types of interventions difficult (Cattan *et al.*, 2005; Dickens *et al.*, 2011). While considering these limitations, group-based support interventions which were co-designed by researchers and intervention recipients, tended to be the most effective (Cattan *et al.*, 2005; Dickens *et al.*, 2011). One-to-one interventions taking place in participants' homes tended not to be effective (Cattan *et al.*, 2005). More empirically rigorous research into individual and group-level interventions, as well as population-level interventions (e.g. intervening on neighbourhood factors) is needed (Cattan *et al.*, 2005; Dickens *et al.*, 2011; Valtorta and Hanratty, 2012). Such population-level approaches may include policies promoting the integration of older adults within the labour market, and municipal infrastructure and residential planning that promotes geographic mobility and safe communal space for individuals of all ages. However, before social isolation interventions can be effectively designed to reduce risk of vascular disease and mortality, further research is needed to understand if and how social isolation is associated with these outcomes.

1.6 Thesis Overview

In line with Berkman and Krishna's conceptual model, the model adapted for this thesis research assumes that associations between social isolation and health are causal. The objective of this research was not however to establish causation. This thesis aimed to more robustly estimate and describe any associations between social isolation, vascular disease, and mortality, and explore how measures of neighbourhood factors, personal characteristics, and each hypothesised pathway alter any associations. The background provided in subsequent chapters present further details regarding each construct included in Figure 1.2 and previous research examining relationships among them.

Chapter 2 presents a systematic review focused on previous epidemiological studies examining structural dimensions of social isolation in relation to vascular disease incidence, vascular disease mortality, and all-cause mortality.

Chapters 3 and 4 of this thesis examined structural social isolation in relation to vascular disease incidence, mortality, and all-cause mortality among two cohorts of over 500,000 adults from the Million Women Study and UK Biobank. These analyses additionally sought to quantify the degree to which personal characteristics, health behaviours, and physiological factors explain any associations between social isolation and the aforementioned outcomes. It should be noted that two of the studies reviewed in Chapter 2 examined social isolation in relation to similar outcomes within the UK Biobank (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Compared to previous UK Biobank analyses, the Chapter 4 analysis more thoroughly mitigated reverse causation bias by restricting the cohort to participants without previous vascular disease, cancer, and fair/poor self-rated health. By looking at two cohorts, findings from the UK Biobank could be compared with those from an older and more representative cohort of UK women participating in the Million Women Study. Chapter 4 also improves upon previous UK Biobank analyses by examining the role of gender as a modifier of associations, and associations between each constituent measure of social isolation and each outcome.

Altering the social and physical characteristics of people's neighbourhood environments is believed to be a promising approach to preventing social isolation and its potential health effects (Valtorta and Hanratty, 2016; Holt-Lunstad, 2018b). However, research evaluating interventions that address neighbourhood factors is scarce (Cattan *et al.*, 2005; Dickens *et al.*, 2011; Valtorta and Hanratty, 2016). This may be because little research has examined whether neighbourhood factors affect associations between social isolation and health (Marcus *et al.*, 2016). Chapter 5 of this thesis examined whether associations between structural social isolation and mortality vary according to characteristics of peoples' neighbourhoods such as socioeconomic deprivation, crime rates, geographic distance to services, and greenspace availability. These are the largest analyses to examine the role of neighbourhood socioeconomic deprivation in associations between social isolation and health, and also the first to examine the role of neighbourhood crime rates, geographic distance to services, and greenspace availability.

The first three analysis chapters of this thesis focussed on structural dimensions of social isolation. Some believe that structural conceptualisations of social isolation should be expanded to include broader functional and perceived dimensions of social isolation (Zavaleta *et al.*, 2017; Holt-Lunstad, 2018b; Wister *et al.*, 2019). In popular discourse, these dimensions are often conflated, and their associations with mortality are equated with that of smoking 15 cigarettes per day (Brody, 2013; National Health Service, 2015; AgeUK, 2017; CBC News, 2017; Tate, 2018; Coughlan, 2019; Mahder-Bashi and Savage, 2019). However, research has

yet to compare associations between each dimension and mortality individually, while also examining associations between all possible exposure combinations for two or more dimensions (Holt-Lunstad *et al.*, 2015). For example, it is hypothesised that when compared to those who are not exposed to either structural or perceived isolation, people who are exposed to both will have greater mortality than those who are singly exposed to either dimension of isolation (Holt-Lunstad *et al.*, 2015). Part 1 of Chapter 6 examined functional isolation (i.e. lacking confiding social support) and perceived isolation (e.g. loneliness and dissatisfaction with relationships) in relation to all-cause mortality. Using a similar approach as Chapters 3 and 4, these analyses quantified the degree to which personal characteristics, physiological factors, and depressive symptoms explained associations. Associations between combinations of functional and structural isolation and mortality were then examined. Likewise, associations between combinations of perceived and structural isolation were examined. Part 2 of Chapter 6 then investigated the claim that associations between structural, functional, and perceived isolation are equal to those of smoking and mortality. All Chapter 6 analyses were conducted using UK Biobank data. This thesis concludes with a summary of findings and further discussion of their implications for future research, policy, and intervention.

1.7 Role of the Author in the Preparation of this Thesis

The original idea of studying social isolation in relation to non-communicable disease within the Million Women Study and UK Biobank was conceived by Dr. Sarah Floud. As part of the Doctor of Philosophy program application and Transfer of Status processes and with advisory support from Dr. Sarah Floud and Dr. Isobel Barnes, Robert William Smith developed the proposal for the research presented in this thesis. Robert William Smith led all aspects of this thesis research including analysis planning, literature review, data analysis, data visualisation, interpretation of results, and write-up. Dr. Sarah Floud acted as Principle Investigator for the UK Biobank data application. Dr. Isobel Barnes supported data analysis by providing example code from related analyses, and by leading dataset acquisition for the UK Biobank analysis. The Million Women Study 12-year re-survey data was linked to NHS Digital records by Sau Wan Kan. All data were cleaned and maintained by Million Women Study and UK Biobank data support teams.

1.8 Publications from this Thesis

Results from Chapters 3 and 4 were presented at the Society for Social Medicine and Population Health conference in Glasgow, Scotland in 2018. In 2019, results from Chapter 6 were presented at the Society for Epidemiologic Research conference in Minneapolis, USA,

and the Society for Social Medicine and Population Health and European Congress of Epidemiology conference in Cork, Ireland. A manuscript presenting results from Chapters 3 and 4 will be submitted for publication in peer-reviewed journals in autumn 2019. Manuscripts for Chapters 2, 5, and 6 are being drafted for submission to peer-reviewed journals in 2020.

2 Systematic Review of Studies Examining Social Isolation, Vascular Disease, and Mortality

2.1 Background

Over the past four decades, epidemiological research has sought to understand if and how social isolation affects health (House *et al.*, 1988). Most recently, three meta-analyses have drawn considerable attention to social isolation as a potentially modifiable risk factor for developing vascular disease and for mortality (Holt-Lunstad *et al.*, 2010, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016).

Holt-Lunstad and colleagues (2010) synthesised the results of 148 studies examining structural, functional, and perceived dimensions of social isolation in relation to mortality. Across these dimensions, compared to those who were less isolated, greater social isolation was associated with 50% increased all-cause mortality (*OR*=1.50, *95% CI*: 1.42-1.59) (Holt-Lunstad *et al.*, 2010). In the twelve studies that examined cardiovascular disease mortality, no statistically significant associations were observed (*OR*=1.08, *95% CI*: 0.76-1.39, *p*=0.61, *n*=12) (Holt-Lunstad *et al.*, 2010). In a subsequent review, Holt-Lunstad and colleagues (2015) found greater structural and perceived isolation to be associated with a 30% increased all-cause mortality compared to those who were less isolated (*OR*=1.30, *95% CI*: 1.16-1.46, *n*=52). Among these studies, structural isolation specifically was associated with a 29% increased all-cause mortality (*OR*=1.29, *95% CI*: 1.06-1.56, *n*=14) (Holt-Lunstad *et al.*, 2015). No statistically significant differences in these associations were observed according to cause of death (Holt-Lunstad *et al.*, 2015). Most recently, Valtorta and colleagues' (2016) meta-analysis found structural and perceived isolation to be associated with 29% increased incidence of CHD (*RR*=1.29, *95% CI*: 1.04-1.59, *n*=11) and stroke (*RR*=1.32, *95% CI*: 1.04-1.68, *n*=7). Overall, these meta-analyses generally suggest that having less frequent social contact with fewer people, less access to social support, and feelings of loneliness are associated with increased risk of vascular disease and of mortality (Holt-Lunstad *et al.*, 2010, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). Only general inferences about associations between social isolation and health can be made from these reviews due to important methodological limitations.

Limitations of these reviews include heterogeneity in the populations studied, social isolation measures used, and the degree to which studies accounted for reverse causation and factors which may confound or mediate associations between social isolation and each outcome (Holt-Lunstad *et al.*, 2010, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). Indeed, after Valtorta and colleagues (2016) excluded studies at higher risk of measurement error and confounding bias, associations between social isolation and vascular disease incidence were attenuated and not statistically significant.

Reverse causation bias is a particularly important limitation of previous research. Reverse causation is a concern because poor health status (e.g. undiagnosed vascular disease) may reduce the amount of social contact a person has with others. Therefore, poor health may cause social isolation as opposed to social isolation causing poor health (Flanders *et al.*, 1992; Webb and Bain, 2010). Among the studies included in these reviews, baseline health status was often adjusted for using self-reported comorbidities or excluding those with a history of the disease of interest (Holt-Lunstad *et al.*, 2010, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). However, research beyond these reviews also suggests that poor or fair self-rated health is a useful indicator of sub-clinical disease or general illness that may impede social interaction (Floud *et al.*, 2015; Liu and Floud, 2017; Liu *et al.*, 2017). Unless baseline health status is carefully accounted for, reverse causation bias can obscure the validity and direction of associations between social isolation, vascular disease, and mortality.

In addition, the estimates of association calculated in these meta-analyses may be biased given that they were derived from the results of analyses which did and did not adjust for explanatory factors (Holt-Lunstad *et al.*, 2010, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). The strength of any association between social isolation and vascular disease or mortality remains uncertain due to heterogeneity in the explanatory factors measured in the reviewed studies.

The purpose of this chapter is to present a narrative review of prospective studies examining social isolation in relation to vascular disease incidence, vascular disease mortality, and all-cause mortality. This review describes the current state of knowledge and gaps warranting further investigation within a more methodologically similar collection of studies than previous reviews. Included in this review are some previously reviewed studies and others published since the aforementioned meta-analyses.

An electronic search strategy was used to identify peer-reviewed studies examining composite measures of social isolation in relation to vascular disease incidence and mortality, and all-cause mortality. This search strategy was executed within Ovid Medline (Table A2.1, pp.221).

Peer-reviewed articles were included if they met the following criteria: published in English; were observational and prospective in design; conducted among non-institutionalised, community-dwelling, adult populations; examined incidence or cause-specific mortality related to vascular disease, or all-cause mortality; and used composite measures of social isolation including living alone, marital status, frequency of contact with family or friends, and participation with social groups. A key objective of these inclusion criteria was to minimise heterogeneity in study design, particularly in the measurement of social isolation and identify studies at lower risk of reverse causation bias. Studies were included if they examined broadly defined CVD incidence or mortality outcomes because it was hypothesised that many studies would use these outcomes and that CHD and stroke would represent the largest proportions of cases and deaths measured by these outcomes. Reference list screening and manual searches within PubMed were also used and identified four additional studies. The initial search identified a total of 2,286 articles. Ultimately, 23 studies (Figure A2.1, pp.220) published between 1979 and 2018 were included. Details of the social isolation indices examined in these studies are presented in Table A2.2 (pp.222).

Unless otherwise specified, the risk ratios (e.g. relative risk [RR], hazard ratio [HR], odds ratio [OR]) presented and discussed in the following sections will be estimates from the most comprehensive multivariable regression models presented in each study reviewed. Risk ratios from analyses that compared the least isolated participants to the most isolated participants were inversed to facilitate ease of comparison across studies. Unless otherwise noted, the estimates of association plotted in Figures 2.1, 2.3, and 2.4 are for analyses using statistical methods and outcomes that most closely reflect those used in this thesis. Regression coefficients were exponentiated for studies that did not calculate risk ratios. Where standard error values were reported, 95% confidence intervals (CI) were calculated.

In the following sections, results pertaining to associations between social isolation and each outcome will be reported (Sections 2.2-2.4). Next, the results for analyses of constituent measures of isolation in relation to each outcome will be reported (Section 2.5). The review will then report how studies addressed reverse causation, adjusted for explanatory factors, and examined age and gender-related effect modification (Section 2.6, 2.7). The review will conclude with a summary of findings, discussion of limitations, and identify key areas for future research (Section 2.8, 2.9).

2.2 Social Isolation and Vascular Disease Incidence

2.2.1 CHD Incidence

Six studies examined social isolation in relation to CHD incidence (Reed *et al.*, 1983; Kawachi *et al.*, 1996; Eng *et al.*, 2002; Barefoot *et al.*, 2005; Chang *et al.*, 2017; Hakulinen *et al.*, 2018). To provide a summary of the magnitude of associations and to facilitate comparison across studies, the risk ratios from studies that used multivariable Cox regression or related analyses (e.g. discrete time survival analysis, pooled logistic regression with fixed follow-up) are presented in Figure 2.1. Details for each study are presented in Table 2.1. Only one study presented evidence of a statistically significant association between social isolation and CHD incidence (Barefoot *et al.*, 2005). Before and after adjustment for explanatory factors, and using a composite measure of the diversity of people's social contact, Barefoot and colleagues observed a statistically significant trend between decreased frequency of intimate social contact (i.e. relatives and friends) and increased CHD incidence (Most to least social contact, *HR range*: 1.08 [*95% CI*: 0.65-1.92] to 2.56 [*95% CI*: 0.94-7.14], *p for trend*=0.04) (Barefoot *et al.*, 2005). However, there were no statistically significant associations observed between decreased social contact with family, friends, neighbours, or work colleagues (i.e. the index more closely related to that used in the current thesis) and CHD incidence before and after adjustment for explanatory factors (Most isolated compared to least isolated, *HR*=1.49, *95% CI*: 0.72-3.03, *p for trend*=0.36) (Figure 2.1a). The five studies that did not report statistically significant associations used more conventional methods for measuring social isolation, such as modified Berkman-Syme social network indices and social isolation scales (Reed *et al.*, 1983; Kawachi *et al.*, 1996; Eng *et al.*, 2002; Chang *et al.*, 2017; Hakulinen *et al.*, 2018). Details of the social isolation indices used in each study are presented in Appendix A (Table A2.2, pp. 222).

The earliest study examined men of Japanese ancestry living in Hawaii, USA (Reed *et al.*, 1983). After adjusting for age, this study found statistically significant increases in non-fatal acute myocardial infarction (AMI) incidence among those who were more compared to least isolated (Least isolated, *incidence rate*=22 per 1,000 participants, Most isolated, *incidence*= 26 per 1,000 participants; *p for heterogeneity*=0.04). CHD incidence was lower among the most compared to least isolated (Least isolated, *incidence rate*: 58 per 1,000 participants, Most isolated *incidence rate*: 51 per 1,000 participants, *p for heterogeneity*=0.03). However, after adjustment for personal characteristics, health behaviours, and physiological factors, no statistically significant associations were observed between social isolation and CHD or non-fatal AMI incidence (Reed *et al.*, 1983). The covariates adjusted for in each study are presented

in Figure 2.2 (Note: this figure will be discussed in greater detail in Section 2.6). As discussed in Section 1.2.1, AMI is a prevalent subset of CHD diagnoses. It was therefore reasonable to compare analyses examining AMI outcomes with those examining broader CHD and CVD outcomes. Analyses of men in the Health Professionals Follow-up Study, did not observe statistically significant associations between social isolation and CHD incidence nor AMI incidence in minimally and fully adjusted analyses (Kawachi *et al.*, 1996; Eng *et al.*, 2002). Among women in the Nurses' Health Study, social isolation was associated with increased CHD and non-fatal AMI incidence in minimally-adjusted analyses but this association was attenuated and not statistically significant after adjusting for explanatory factors (Chang *et al.*, 2017). These minimally-adjusted associations were largely explained by health behavioural factors such as smoking and physical activity (Chang *et al.*, 2017). Similar results were found among over 479,000 women and men in the UK Biobank cohort (Hakulinen *et al.*, 2018).

2.2.2 Stroke Incidence

Two studies examined social isolation in relation to stroke incidence (Kawachi *et al.*, 1996; Hakulinen *et al.*, 2018) (Table 2.2; Figure 2.1b). These studies are mixed in their findings. In minimally adjusted analyses, Kawachi and colleagues (1996) observed statistically significant trends between increased isolation and increased stroke incidence. Adjustment for explanatory factors attenuated these associations but they remained statistically significant (Most isolated compared to least isolated, *relative risk* [*RR*]=2.02, *95% CI*: 1.00-4.08, *p for trend*<0.01) (Kawachi *et al.*, 1996). Within the UK Biobank cohort those who were socially isolated had increased risk of incident stroke in minimally adjusted analyses, however this association was attenuated and not statistically significant after adjusting for behavioural, psychological, and physiological factors (Most isolated compared to least isolated, *HR*=1.06, *95% CI*: 0.96-1.19, *p value*=0.26) (Hakulinen *et al.*, 2018).

2.2.3 CVD Incidence

One study examined CVD incidence. Valtorta and colleagues (2018) used a broader CVD outcome measure, in their study using English Longitudinal Study of Ageing data. This study was unique among those reviewed as it examined social isolation longitudinally and thus compared participants who were and were not isolated at least once over on average five years of observation period. They found that compared to participants who did not report social isolation, those who reported isolation at baseline and in at least one re-survey did not have increased odds of incident CVD in minimally or fully adjusted analyses (Valtorta, Kanaan, *et al.*, 2018). Therefore, there was no cumulative association of prolonged social isolation on fatal

or non-fatal incident CVD. They also showed that social isolation status tended to remain consistent over the observation period (Valtorta, Kanaan, *et al.*, 2018).

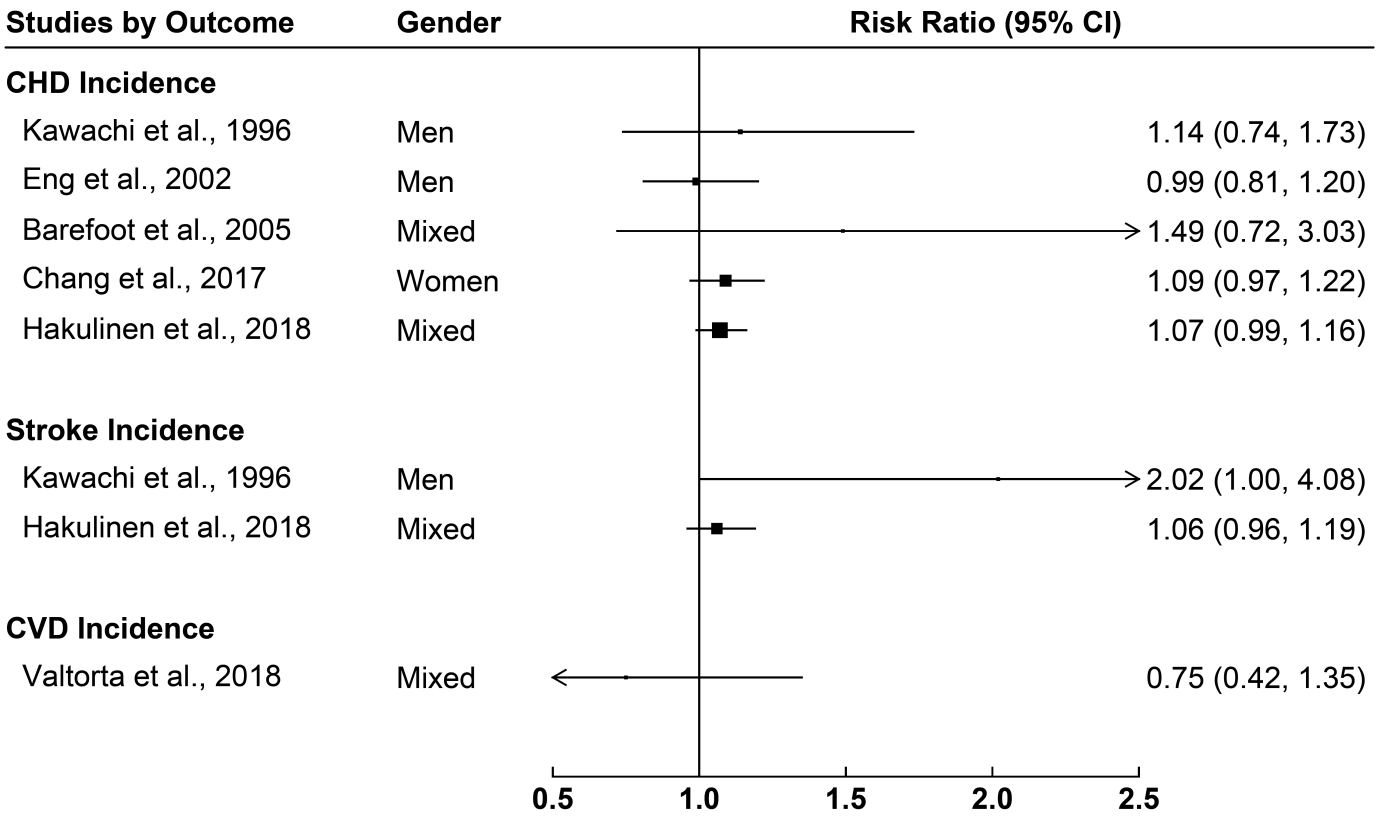


Figure 2.1. Adjusted risk ratios and 95% confidence intervals (CI) from analyses of social isolation and vascular disease incidence. Note: Fully adjusted estimates compare most isolated category to least isolated category; Hakulinen *et al.* 2018 examined AMI incidence. Box size is inversely proportional to standard error of the risk ratio estimate.

Table 2.1. Cohort studies published between 1979 and 2018 examining social isolation in relation to vascular disease incidence.

Study	Data Source (Years Sampled)	Age and Gender of Sample	No. of Cases/ Sample Size	Social Relationships Measure	Results *Risk presented for most isolated compared to least isolated participants unless indicated.*
Multivariable Cox Regression and Related Analyses					
Barefoot *et al*., 2005	Copenhagen City Heart Study, Denmark (1991-1994)	19-93 years; Women/Men	CHD: 427/9573	Social contact diversity index	Any social contact: *HR*=1.49, *95% CI*: 0.72-3.03, *p for trend*= 0.36 Intimate social contact: *HR*=2.56, *95% CI*: 0.94-7.14, *p for trend*= 0.04
Chang *et al*., 2017	Nurses' Health Study, USA (1992)	30-55 years; Women	CHD: 2372/76362 AMI: 1964/76362	Modified Berkman-Syme social network index	CHD: *HR*=1.09, *95% CI*: 0.97–1.22, *p for trend*=0.17 AMI: *HR*=1.03, *95% CI*: 0.91–1.18, *p for trend*=0.66
Eng *et al*., 2002	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	CHD: 1816/17769 AMI: 618/17769	Modified Berkman-Syme social network index	CHD: *RR*=0.99, *95% CI*: 0.81-1.20, *p for trend*= 0.14 AMI: *RR*=1.11, *95% CI*: 0.80-1.53, *p for trend*=0.61
Hakulinen *et al*., 2018	UK Biobank, UK (2007-2010)	40-69 years; Women/Men	AMI: 5731/479054	Social isolation scale	*HR*=1.07, *95% CI*: 0.99-1.16, *p for heterogeneity*=0.11
Kawachi *et al*., 1996	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	CHD: 403/32624 AMI: 275/32624	Berkman-Syme social network index	CHD: *HR*=1.14, *95% CI*: 0.74-1.73, *p for trend*=0.06 AMI: *HR*=1.00, *95% CI*: 0.58-1.71, *p for trend*=0.19
Valtorta *et al*., 2018	English Longitudinal Study of Ageing Waves 2-4, UK (1991-1994)	19-93 years; Women/Men	CVD: 571/5397	Social isolation scale	Isolated at one or more time points compared to never isolated: *OR*=0.75, *95% CI*: 0.42-1.35, *p heterogeneity*=NR
Logistic Regression and Related Analyses					
Reed *et al*., 1983	Honolulu Heart Program, USA (1971)	49-71 years; Men	CHD: 218/4653 AMI: 95/4653	Social network index	CHD: *OR*=1.05, *95% CI*: NR, *p for heterogeneity*>0.05 AMI: *OR*=0.80, *95% CI*: NR, *p for heterogeneity*>0.05

Notes: All studies were prospective cohort studies; HR= Hazard Ratio; RR= Relative Risk; OR= Odds Ratio; CI= Confidence Interval; NR= Not Reported

Table 2.2. Cohort studies published between 1979 and 2017 examining social isolation in relation to stroke incidence and mortality.

Study	Data Source (Years Sampled)	Age and Gender of Sample	No. of Cases/ Total Sample Size	How Measured: Social Relationships	Results *Risk presented for most isolated compared to least isolated participants unless indicated.*
Hakulinen *et al.*, 2018	UK Biobank, UK (2007-2010)	40-69 years; Women/Men	*Incidence* 3471/5397	Social isolation scale	*Incidence* *HR*=1.06, *95% CI*: 0.96-1.19, *p for heterogeneity*=0.26
Kawachi *et al.*, 1996	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	*Incidence* 104/32624 *Mortality* 13/32624	Berkman-Syme social network index	*Incidence* *HR*=2.02, *95% CI*: 1.00-4.08, *p for trend*<0.01 *Mortality* *HR*=3.64, *95% CI*: 0.78-16.9, *p for trend*=0.04

Notes: HR= Hazard Ratio; CI= Confidence Interval

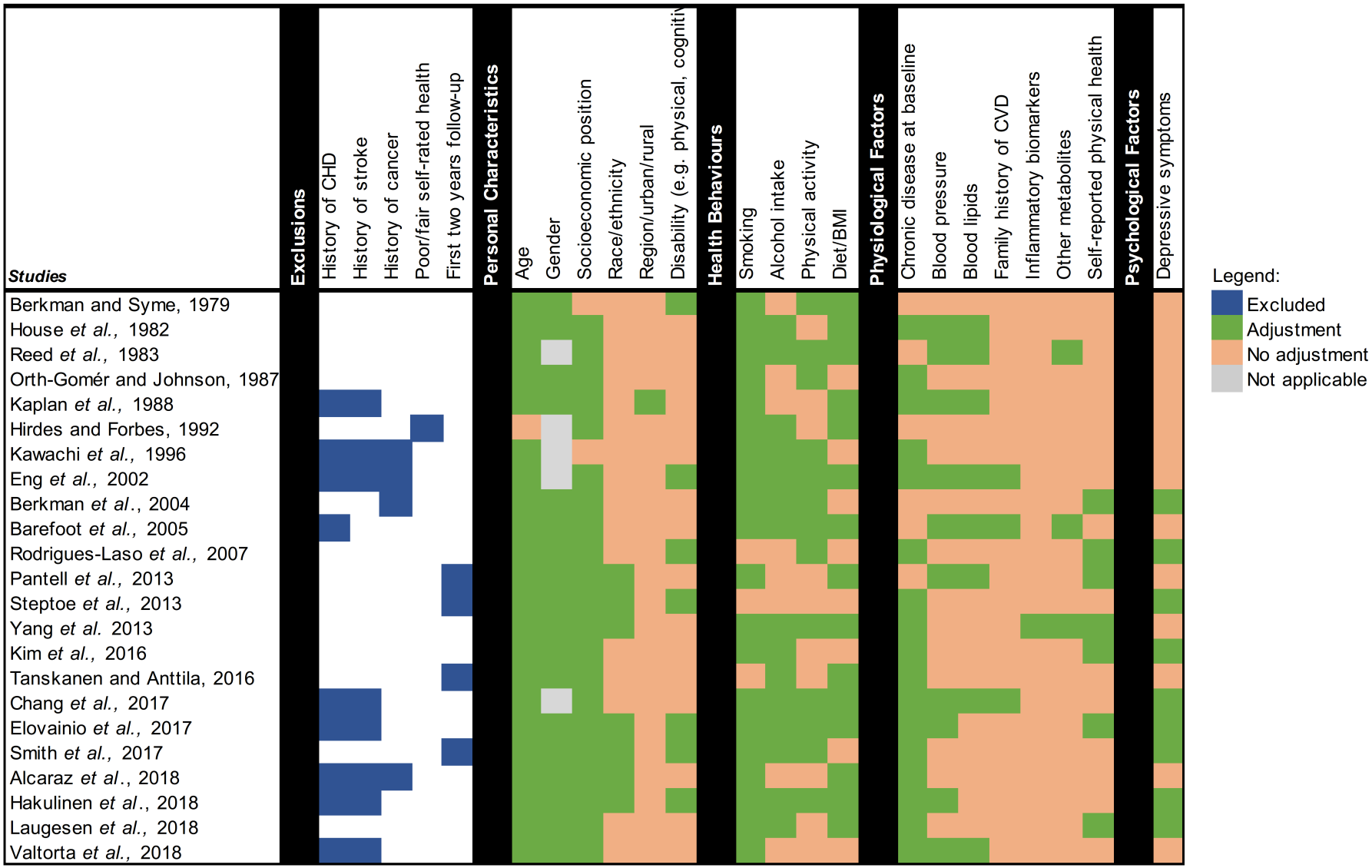


Figure 2.2. Matrix presenting cohort and follow-up exclusion criteria used and explanatory factors adjusted for in the studies reviewed.

2.3 Social Isolation and Vascular Disease Mortality

2.3.1 CHD Mortality

Four studies examined social isolation in relation to CHD mortality (Figure 2.3a). Only one found a statistically significant association between social isolation and CHD mortality (Chang *et al.*, 2017). Before and after adjusting for all explanatory factors, increased isolation was associated with increased risk of fatal incident AMI events among women (Table 2.3; Least compared to most isolated: *HR*=1.47, *95% CI*: 1.09–1.96, *p for trend*=0.02) (Chang *et al.*, 2017). AMI mortality also tended to be greater among the more compared to less isolated men, however these associations were not statistically significant (Kawachi *et al.*, 1996; Eng *et al.*, 2002) (Table 2.3). It should be noted that in the aforementioned analyses, participants were censored at the time of their first CHD event whether it was fatal or non-fatal. One study which counted fatal CHD events that may have been preceded by non-fatal incident events within the observation period found no statistically significant associations between social isolation and CHD mortality (Kaplan *et al.*, 1988). With the exception of Chang and colleagues (2017), low death frequency across levels of social isolation was a common characteristic of each of these studies (Kaplan *et al.*, 1988; Kawachi *et al.*, 1996; Eng *et al.*, 2002).

2.3.2 Stroke Mortality

One study examined social isolation in relation to stroke mortality (Figure 2.3b; Table 2.2). In this study only 13 stroke deaths were observed (Kawachi et al., 1996). While Kawachi and colleagues (1996) found a statistically significant trend (*p for trend*=0.04) across levels of social isolation, there were too few cases to derive reliable estimates of association (Figure 2.3b; Table 2.2).

2.3.3 Cardiovascular Disease Mortality

Eight studies examined aggregated CVD mortality outcomes inclusive of CHD and stroke deaths (Figure 2.3c). Four observed statistically significant associations between social isolation and CVD mortality (Kawachi et al., 1996; Yang et al., 2013; Elovainio et al., 2017; Alcaraz et al., 2018) and four did not observe statistically significant associations (Orth-Gomér and Johnson, 1987; Kaplan et al., 1988; Eng et al., 2002; Berkman et al., 2004) (Table 2.3). Estimates of association for the most compared to least isolated participants ranged from *HR*=1.24 (*95% CI*: 1.17–1.31) to *HR*=1.76 (*95% CI*: 0.97–3.16, *p for trend*=0.02) (Kawachi *et al.*, 1996; Elovainio *et al.*, 2017). Within the Cancer Prevention Study-II, Alcaraz and colleagues' (2018) reported lower magnitude associations between social isolation and CVD

mortality among white men (*HR*=1.29, *95% CI*: 1.21-1.38, *p for trend*<0.0001). Associations tended to be stronger among women and black men (Table 2.3; *HR range*: 1.47 [*95% CI*: 1.21–1.38] to *HR*=1.51 [*95% CI*: 1.16–1.97], *p for trend for each sub-group* ≤ 0.02) (Alcaraz et al., 2018). Differences in these associations according to race were not statistically significant (Alcaraz et al., 2018). In the studies that presented unadjusted or minimally adjusted and fully adjusted regression models, the adjustment for explanatory factors attenuated associations between social isolation and CVD mortality (Kawachi et al., 1996; Yang et al., 2013; Elovainio et al., 2017). Before adjustment for explanatory factors, two studies found statistically significant associations which were attenuated and not statistically significant after adjustment (Orth-Gomér and Johnson, 1987; Eng et al., 2002). Berkman and colleagues (2004) found no association between social isolation and CVD among men in the GAZEL cohort before and after adjustment for explanatory factors. Kaplan and colleagues (1998) did not present results from minimally adjusted analyses, however, the fully adjusted association was not statistically significant.

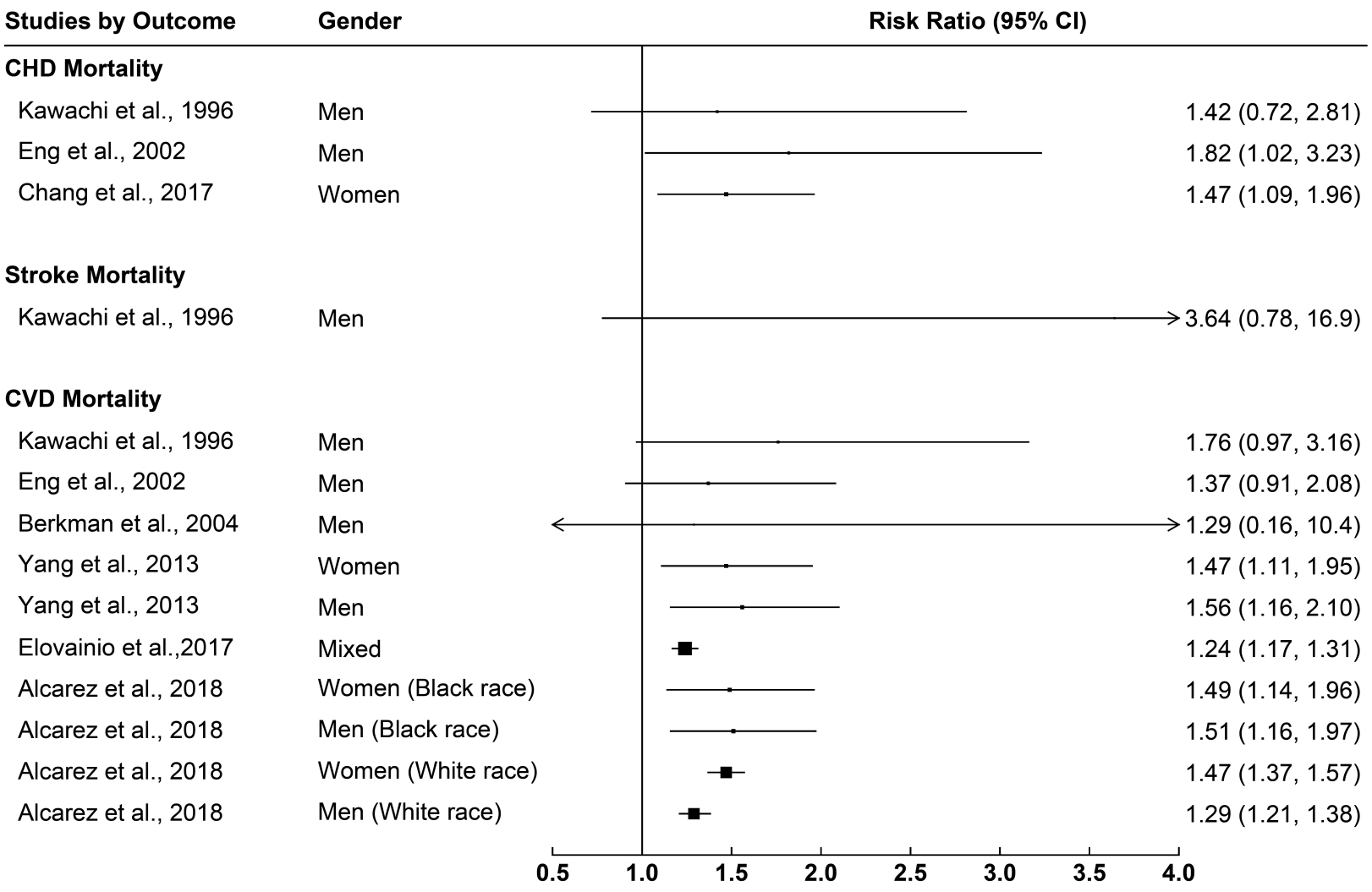


Figure 2.3. Adjusted risk ratios and 95% CI from analyses of social isolation and vascular disease mortality. Note: Fully adjusted estimates compare most isolated category to least isolated category; Chang *et al.* 2017, Eng *et al.* 2002, and Kawachi *et al.* 1996 examined fatal incident AMI; Box size is inversely proportional to standard error of the risk ratio estimate.

Table 2.3. Cohort studies published between 1979 and 2018 examining social isolation in relation to vascular disease mortality.

Study	Data Source (Years Sampled)	Age and Gender of Sample	No. of Deaths/ Sample Size	Social Relationships Measure	Results *Risk presented for most isolated compared to least isolated participants unless indicated.*
Multivariable Cox Regression and Related Analyses					
Alcaraz *et al.,* 2018	Cancer Prevention Study-II, USA (1982)	30-90 years; Women/Men	CVD: 33365/580182	Modified Berkman-Syme social network index	Black Women: *HR*=1.49, *95% CI*: 1.14-1.96, *p for trend*<0.001 Black Men: *HR*=1.51, *95% CI*: 1.16-1.97, *p for trend*=0.02 White Women *HR*=1.47, *95% CI*: 1.37-1.57, *p for trend*<0.0001 White Men *HR*=1.29, *95% CI*: 1.21-1.38, *p for trend*<0.0001
Berkman *et al.*, 2004	Electricity of France-Gas France cohort, France (1991)	35-50 years; Women/Men	CVD - Men: 47/17253	Modified Berkman-Syme social network index	*HR*=1.29, *95% CI*: 0.16-10.41, *p for trend*=0.75
Chang *et al.*, 2017	Nurses' Health Study, USA (1992)	30-55 years; Women	AMI: 408/76362	Modified Berkman-Syme social network index	*HR*=1.47, *95% CI*: 1.09–1.96, *p for trend*=0.02
Elovainio *et al.*, 2017	UK Biobank, UK (2007-2010)	40-69 years; Women/Men	CVD: 2032/466901	Social isolation scale	*HR*=1.24, *95% CI*: 1.17–1.31, *p for heterogeneity*=NR
Eng *et al.*, 2002	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	CVD: 320/17769 AMI: 142/17769	Modified Berkman-Syme social network index	CVD *RR*=1.37, *95% CI*: 0.91-2.08, *p for trend*=0.11 AMI: *RR*=1.82, *95% CI*: 1.02-3.23, *p for trend*=0.10
Kawachi *et al.*, 1996	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	CVD: 153/32624 AMI: 128/32624	Berkman-Syme social network index	CVD: *HR*=1.76, *95% CI*: 0.97-3.16, *p for trend*=0.02 AMI: *HR*=1.42, *95% CI*:0.72-2.81, *p for trend*=0.13
Yang *et al.*, 2013	Third National Health and Nutrition Examination Survey, USA (1988-1994)	47 years and older; Women/Men	CVD – Women: 626/3647 CVD – Men: 648/3082	Modified Berkman-Syme social network index	Women: *HR*=1.47, *95% CI*: 1.11–1.95, *p for heterogeneity*<0.01 Men: *HR*=1.56, *95% CI*: 1.16–2.10, *p for heterogeneity*<0.01
Logistic Regression and Related Analyses					
Kaplan *et al*., 1988	Eastern Finland study, Finland (1972-1977)	39-59 years; Women/Men	CVD: 297/13301 CHD: 223/13301	Social connections index	CVD – Men: *OR*=1.80, *95% CI*: 0.87-3.70, *p for heterogeneity*=NR CHD – Men: *OR*=1.72, *95% CI*: 0.77-3.84, *p for heterogeneity*=NR

Orth-Gomér and Johnson, 1987	Swedish National Survey of Living Conditions, Sweden (1976-1977)	29-74 years; Women/Men	CVD: 414/17433	Social network interaction index	*OR*=1.37*, 95% CI*: 0.97-1.96, *p for heterogeneity*=0.08

Notes: All studies were prospective cohort studies; RR= Relative Risk; OR= Odds Ratio; CI= Confidence Interval; NR= Not Reported

2.4 Social Isolation and All-Cause Mortality

Social isolation was statistically significantly associated with all-cause mortality in 18 of 19 studies (Table 2.4) (Berkman and Syme, 1979; House *et al.*, 1982; Orth-Gomér and Johnson, 1987; Kaplan *et al.*, 1988; Hirdes and Forbes, 1992; Eng *et al.*, 2002; Berkman *et al.*, 2004; Rodriguez-Laso, Zunzunegui and Otero, 2007; Pantell *et al.*, 2013; Steptoe *et al.*, 2013; Yang *et al.*, 2013; Tanskanen and Anttila, 2016; Kim *et al.*, 2016; Alcaraz *et al.*, 2018; Smith *et al.*, 2018; Laugesen *et al.*, 2018). The strength of associations between social isolation and all-cause mortality varied widely (Figure 2.4). Even among larger and more recent studies, after adjustment, compared to the least isolated participants, the most isolated had 26% to 80% greater risk of all-cause mortality (Figure 2.4; Table 2.4) (Pantell *et al.*, 2013; Steptoe *et al.*, 2013; Yang *et al.*, 2013; Kim *et al.*, 2016; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018; Smith *et al.*, 2018). However, only two studies presented findings which were not consistent with other studies (Kawachi *et al.*, 1996; Barefoot *et al.*, 2005). Similar to their findings for CHD incidence, Barefoot and colleagues (2005) found statistically significant associations between intimate social contact, but not any social contact, and all-cause mortality. Also, whilst using the Berkman-Syme social network index, Kawachi and colleagues (1996) found no statistically significant associations between increased isolation and all-cause mortality after adjustment for personal characteristics, health behaviours, and physiological factors.

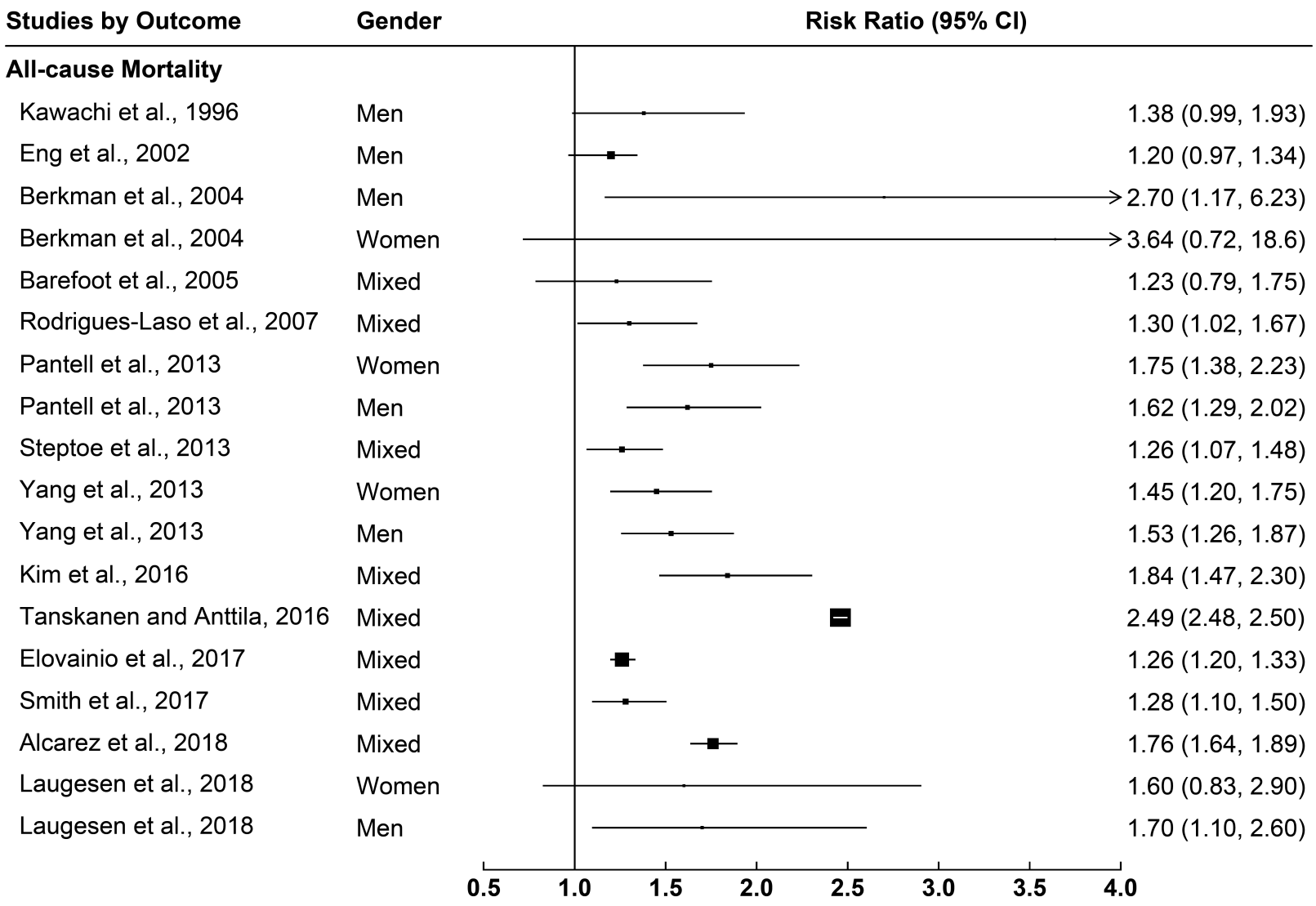


Figure 2.4. Adjusted risk ratios and 95% CIs from analyses of social isolation and all-cause mortality. Note: Fully adjusted estimates compare most isolated category to least isolated category; Box size is inversely proportional to standard error of the risk ratio estimate.

Table 2.4. Cohort studies published between 1979 and 2018 examining social isolation in relation to all-cause mortality.

Study	Data Source (Years Sampled)	Age and Gender of Sample	No. of Deaths/ Sample Size	Social Relationships Measure	Results *Risk presented for most isolated compared to the least isolated participants unless indicated.*
Multivariable Cox Regression and Related Analyses					
Alcaraz *et al*., 2018	Cancer Prevention Study-II, USA (1982)	30-90 years; Women/Men	83798/580182	Modified Berkman-Syme social network index	Full Sample: *HR*=1.76, *95% CI*: 1.64-1.89, *p for trend* <0.0001 Black Women: *HR*=2.13, *95% CI*: 1.44-3.15, *p for trend* <0.0001 Black Men: *HR*=2.34, *95% CI*: 1.58-3.46, *p for trend* <0.01 White Women: *HR*=1.84, *95% CI*: 1.68-2.01, *p for trend* <0.0001 White Men: *HR*=1.60, *95% CI*: 1.41-1.82, *p for trend* <0.0001
Barefoot *et al*., 2005	Copenhagen City Heart Study, Denmark (1991-1994)	19-93 years; Women/Men	1089/9573	Social contact diversity index	Any social contact: *HR*=1.23, *95% CI*: 0.79-1.75, *p trend* =0.37 Intimate social contact: *HR*=0.46, *95% CI*: 0.25-0.85, *p trend* =0.01
Berkman *et al*., 2004	Electricity of France-Gas France cohort, France (1991)	35-50 years; Women/Men	Women: 29/4352 Men: 228/12347	Modified Berkman-Syme social network index	Women: *HR*=3.64, *95% CI*: 0.72-18.58, *p for trend* =0.01 Men: *HR*=2.70, *95% CI*: 1.17-6.23, *p for trend* <0.001
Elovainio *et al.,* 2017	UK Biobank, UK (2007-2010)	40-69 years; Women/Men	11593/466901	Social isolation scale	*HR*=1.26, *95% CI*: 1.20–1.33, *p for heterogeneity* =NR
Eng *et al*., 2002	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	1365/17769	Berkman-Syme social network index	*RR*=1.20, *95% CI*: 0.97-1.34, *p for trend* =0.01
Kawachi *et al*., 1996	Health Professionals Follow-up Study, USA (1988)	42-77 years; Men	511/32624	Berkman-Syme social network index	*HR*=1.38, *95% CI*: 0.99–1.93, *p for trend* =0.06
Kim *et al*., 2016	Korean Longitudinal Study of Ageing, Korea (2006)	45 years and older; Women/Men	754/8234	Social engagement index	*HR*=1.84, *95% CI*: 1.47–2.30, *p for trend* <0.001
Laugesen *et al*., 2018	*How are you?* Survey, Denmark (2006)	25-79 years; Women/Men	NR/21,604	Modified Berkman-Syme social network index	Women: *HR*=1.60, *95% CI*=0.83-2.90, *p value* =NR Men: *HR*=1.70, *95% CI*=1.10-2.60, *p value* =NR

Pantell *et al*., 2013	Third National Health and Nutrition Examination Survey, USA (1988-1994)	47 years and older; Women/Men	NR/16,849	Modified Berkman-Syme social network index	Women: *HR*=1.75, *95% CI*: 1.38-2.23, *p for heterogeneity* <0.001 Men: *HR*=1.62, *95% CI*: 1.29-2.02, *p for heterogeneity* <0.001
Rodriguez-Laso *et al*., 2007	Ageing in Leganes Study, Spain (1993)	65 years and older; Women/Men	352/1174	Family ties index	*HR*=1.30, *95% CI*: 1.02–1.67, *p value* =NR
Smith *et al*., 2017	English Longitudinal Study of Ageing, UK (2004-2005)	50 years and older; Women/Men	1261/7731	Social isolation index	*HR*=1.28, *95% CI*: 1.10-1.50, *p value* =NR
Steptoe *et al*., 2013	English Longitudinal Study of Ageing, UK (2004-2005)	50 years and older; Women/Men	918/6500	Social isolation index	*HR*=1.26, *95% CI*: 1.07-1.48, *p for heterogeneity* <0.01
Tanskanen and Anttila, 2016	Living Conditions Survey, Finland (1994)	16-93 years; Women/Men	1472/8650	Social isolation index	*HR*=2.49, *95% CI*: 2.48-2.50, *p value* =NR
Yang *et al*., 2013	Third National Health and Nutrition Examination Survey, USA (1988-1994)	47 years and older; Women/Men	Women: 1340/3647 Men: 1434/3082	Modified Berkman-Syme social network index	Women: *HR*=1.45, *95% CI*: 1.20–1.75, *p for heterogeneity* <0.001 Men: *HR*=1.53, *95% CI*: 1.26–1.87, *p for heterogeneity* <0.001
Logistic Regression and Related Analyses					
Berkman and Syme, 1979	Human Population Laboratory survey, Alameda County, USA (1965)	30-69 years; Women/Men	Women: 160/2496 Men: 211/2229	Berkman-Syme social network index	Women: *RR*=4.60, *95% CI*: NR, *p for heterogeneity* <0.001 Men: *RR*=2.50, *95% CI*: NR, *p for heterogeneity* <0.001
Hirdes and Forbes, 1992	Ontario Longitudinal Study of Ageing, Canada (1959-1978)	45 years; Men	NR/751	Social relationships index	*OR*=3.33, *95% CI*: 1.20-9.09, *p for heterogeneity* <0.05
House *et al*., 1982	Tecumseh Community Health Study, USA (1967-1969)	35-69 years; Women/Men	Women: 87/1431 Men: 172/1323	Social integration index	Women *OR*=1.25, *95% CI*: NR, *p for heterogeneity* >0.05 Men *OR*=1.51, *95% CI*: NR, *p for heterogeneity* <0.03
Kaplan *et al*., 1988	Eastern Finland study, Finland (1972-1977)	39-59 years; Women/Men	598/13301	Social connections index	Men *OR*=2.00, *95% CI*: 1.18-3.39, *p for heterogeneity* =NR
Orth-Gomér and Johnson, 1987	Swedish National Survey of Living Conditions, Sweden (1976-1977)	29-74 years; Women/Men	841/17433	Social network interaction index	*OR*=1.34, *95% CI*: 1.06-1.69, *p for heterogeneity* =0.02

Notes: All studies were prospective cohort studies; HR= Hazard Ratio; RR= Relative Risk; OR= Odds Ratio; CI= Confidence Interval; NR= Not Reported

2.5 Constituent Measures of Social Isolation Indices

Eight studies further examined associations between constituent measures of social isolation and CHD incidence and mortality, CVD mortality, and all-cause mortality (Table 2.5) (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Berkman *et al.*, 2004; Barefoot *et al.*, 2005; Pantell *et al.*, 2013; Chang *et al.*, 2017; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018).

For CHD Incidence, only two studies examined constituent measures in relation to CHD incidence and their findings are mixed (Barefoot *et al.*, 2005; Chang *et al.*, 2017). One study found that those with more frequent contact with their parents had 27% reduced risk of CHD, but did not study any other constituent variables (Barefoot *et al.*, 2005). The other study found at least weekly religious service attendance associated with approximately 15% decreased risk of incident CHD, but no other associations (Chang *et al.*, 2017). No study examined each constituent measure of isolation in relation to stroke incidence and mortality.

For CHD, CVD and all-cause mortality, being unmarried or not living with a partner was most consistently and strongly associated with increased risk (Table 2.5). Unmarried people tended to have approximately 20% to 50% increased risk of CVD and all-cause mortality (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Pantell *et al.*, 2013; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018). Greater variation in the strength of these associations was observed for CHD mortality (Berkman *et al.*, 2004; Chang *et al.*, 2017). No other associations were observed between constituent measures of isolation and CHD mortality (Berkman *et al.*, 2004; Chang *et al.*, 2017).

There was little evidence of statistically significant associations between less frequent contact with family or friends and CVD and all-cause mortality outcomes (Table 2.5). Only one study found women who had infrequent contact with family or friends to be at 25% increased risk of all-cause mortality, however, there was no association among men (Pantell *et al.*, 2013). Another observed weak inverse associations between number of close friends and CVD and all-cause mortality (Alcaraz *et al.*, 2018). Three studies did not find associations between contact with family or friends and CVD or all-cause mortality (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Laugesen *et al.*, 2018).

Studies of frequency of contact or affiliation with social groups present mixed findings in relation to mortality outcomes. For frequency of social group participation, inverse associations with CVD mortality were found in one study (Alcaraz *et al.*, 2018) but not in two others (Kawachi *et al.*, 1996; Eng *et al.*, 2002). Inverse associations were also observed in relation to

all-cause mortality in two studies (Eng *et al.*, 2002; Alcaraz *et al.*, 2018) but not in two others (Kawachi *et al.*, 1996; Laugesen *et al.*, 2018). In another study, club or social group membership was associated with all-cause mortality among men but not women (Pantell *et al.*, 2013).

Findings for church membership and religious service attendance in relation to CVD mortality were mixed but more consistently associated with all-cause mortality (Table 2.5). Alcaraz and colleagues (2018) found those who attended services less than monthly to have 5% increased risk of CVD mortality. However, two other studies did not find any associations with CVD mortality (Kawachi *et al.*, 1996; Eng *et al.*, 2002). Infrequent service attendance was associated with 9% to 35% increased risk of all-cause mortality in three of four studies (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Alcaraz *et al.*, 2018). Further, those who did not belong to a church had a 42% increased risk of all-cause mortality in one study (Kawachi *et al.*, 1996).

Table 2.5. Associations between social isolation constituent measures and each outcome.

	Marital status	Contact with family or friends	Number of close relatives or friends	Contact or affiliation with social groups	Religious service attendance or affiliation
CHD Incidence	No association[d]	*At least monthly contact with parents*: *HR*=0.63, *95% CI*: 0.42-0.95[b]	No association[d]	No association[d]	*At least weekly attendance*: *HR*=0.82, *95% CI*: 0.72–0.93[d]
CHD Mortality	*Unmarried*: *HR*=1.28, *95% CI*: 1.11-1.59 [d] *Unmarried, women*: *HR*=3.56, *95% CI*: 1.62-7.84[c] *Unmarried, men*: *RR*=1.74, *95% CI*: 1.18-2.56[c]		No association[d]	No association[d]	No association[d]
CVD Mortality	No association[e] *Unmarried*: *HR*=1.25, *95% CI*: 1.22-1.29[a] *HR*=1.44, *95% CI*: 0.88-2.38[f]	No association[e]	No association[e] *Less than seven*: *HR*=1.04, *95% CI*: 1.01-1.07[a]	No association[e] *Less than monthly*: *HR*=1.15, *95% CI*: 1.13-1.18[a]	No association[e] *Less than monthly*: *HR*=1.05, *95% CI*: 1.02-1.08[a]
All-cause Mortality	*Unmarried*: *HR*=1.17, *95% CI*: 1.15-1.19[a] *RR*=1.27, *95% CI*: 1.07-1.50[e] *HR*=1.41, *95% CI*: 1.07-1.87[f] *Unmarried, women*: *HR*=1.19, *95% CI*: 1.03-1.37[h] *HR*=1.70, *95% CI*: 1.20-2.40 [g] *Unmarried, men*: *HR*=1.23, *95% CI*: 1.08-1.40[h] *HR*=1.50, *95% CI*: 1.20-2.10 [g]	No association[e f g] *At most three times per week, women*: *HR*=1.25, *95% CI*: 1.04-1.50[h] *At most three times per week,* men: No association[h]	No association[e] *Less than seven*: *HR*=1.05, *95% CI*: 1.03-1.06[a]	No association[f g] *Less than monthly*: *HR*=1.13, *95% CI*: 1.12-1.15[a] *At most 10 hours per week*: *RR*=1.56, *95% CI*: 1.04-2.34[e] *Do not belong to club or organisation*, women: No association[h] *Do not belong to club or organisation*, men: *HR*=1.15, *95% CI*: 1.02-1.31[h]	No association[g] *Less than monthly*: *HR*=1.09, *95% CI*: 1.07-1.11[a] *Less than monthly, women* *HR*=1.35, *95% CI*: 1.17-1.56[h] *Less than monthly,* men *HR*=1.27, *95% CI*: 1.13-1.42[h] *Rarely/never attend*: *RR*=1.15, *95% CI*: 1.02-1.30[e] *Not belonging to a church*: *HR*=1.42, *95% CI*: 1.19-1.70[f]

Legend: [a] Alcaraz *et al*., 2018 [b] Barefoot *et al*., 2005 [c] Berkman *et al*., 2004 [d] Chang *et al*., 2017 [e] Eng *et al*., 2002 [f] Kawachi *et al*., 1996 [g] Laugesen *et al*. 2018 [h] Pantell *et al*., 2013

2.6 Bias Analysis and Explanatory Factors

To assess the quality of each study, the Cochrane Collaboration's generic Risk of Bias assessment tool was used (McGuinness, 2019). Overall, there was some concern of bias, primarily due to reverse causation or confounding, for most of the reviewed studies (Figure 2.5). Almost all studies were at low risk of bias due to measurement error in the exposure (e.g. indices of social isolation with at most two constituent measures) or in the outcome (e.g. unspecified data source used to ascertain outcomes) (Figure 2.5). There was at least some concern of confounding bias in most studies and reverse causation bias in each study (Figure 2.5).

Studies were judged as having high risk of reverse causation bias if the cohort exclusion criteria did not include vascular disease, or if outcomes occurring within two years of follow-up were not censored and models did not adjust for baseline health status. Studies were judged as having some concern of bias if their exclusion criteria did not include vascular disease, cancer and poor/fair self-rated. The reviewed studies varied in their approaches to addressing reverse causation (Figure 2.2). All studies The most common approach to addressing reverse causation bias was excluding participants with vascular disease at baseline (Kaplan *et al.*, 1988; Kawachi *et al.*, 1996; Eng *et al.*, 2002; Berkman *et al.*, 2004; Barefoot *et al.*, 2005; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018; Hakulinen *et al.*, 2018; Valtorta, Kanaan, *et al.*, 2018). Four studies which did not exclude participants based on prevalent disease, censored vascular disease events or deaths occurring within two years of baseline (Pantell *et al.*, 2013; Steptoe *et al.*, 2013; Tanskanen and Anttila, 2016; Smith *et al.*, 2018). Eight studies did not exclude participants with these characteristics or censor events occurring within two years of baseline (Berkman and Syme, 1979; House *et al.*, 1982; Reed *et al.*, 1983; Orth-Gomer and Johnson, 1987; Rodriguez-Laso *et al.*, 2007; Yang *et al.*, 2013; Kim *et al.*, 2016; Laugesen *et al.*, 2018). These studies tended to account for baseline health by adjusting regression analyses for self-reported chronic diseases at baseline.

Heterogeneity was also observed in the explanatory factors adjusted for in the reviewed studies (Figure 2.2). More recent studies tended to have low risk of bias due to confounding (Figure 2.5). However, at least some concern of confounding was observed in most studies (Figure 2.5). High risk of confounding was judged if the study did not adjust for smoking. Some concern of bias was judged if models were adjusted for at most two health behavioural factors (as listed in Figure 2.2) but they were not also adjusted for personal characteristics like socioeconomic position or disability or physiological factors. Almost every study adjusted their

analyses for personal characteristics including age, gender, and socioeconomic position. Eleven studies additionally adjusted for race and ethnicity, geographic region, and/or disability (Berkman and Syme, 1979; Kaplan *et al.*, 1988; Eng *et al.*, 2002; Rodriguez-Laso *et al.*, 2007; Steptoe *et al.*, 2013; Yang *et al.*, 2013; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018; Hakulinen *et al.*, 2018). With the exception of Steptoe and colleagues (2013), all studies adjusted for at least one health behavioural factor such as smoking, alcohol intake, physical activity, and diet or body mass index. Seven studies adjusted for each of these health behaviours (Reed *et al.*, 1983; Eng *et al.*, 2002; Barefoot *et al.*, 2005; Yang *et al.*, 2013; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). The most commonly examined physiological factors were related to chronic conditions reported at baseline (e.g. cardiovascular diseases, diabetes). Ten studies examined blood pressure and lipids (House *et al.*, 1982; Reed *et al.*, 1983; Kaplan *et al.*, 1988; Eng *et al.*, 2002; Barefoot *et al.*, 2005; Pantell *et al.*, 2013; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018; Valtorta, Kanaan, *et al.*, 2018). Seven studies adjusted for self-reported physical health (Berkman *et al.*, 2004; Rodriguez-Laso *et al.*, 2007; Pantell *et al.*, 2013; Yang *et al.*, 2013; Kim *et al.*, 2016; Elovainio *et al.*, 2017; Laugesen *et al.*, 2018). Only three studies examined inflammatory biomarkers such as c-reactive protein and/or other metabolites such as serum glucose and albumin (Reed *et al.*, 1983; Barefoot *et al.*, 2005; Yang *et al.*, 2013). Nine studies adjusted for depressive symptoms to account for psychological factors (Berkman *et al.*, 2004; Rodriguez-Laso *et al.*, 2007; Steptoe *et al.*, 2013; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018; Laugesen *et al.*, 2018; Smith *et al.*, 2018). This was the only psychological factor examined in the reviewed studies.

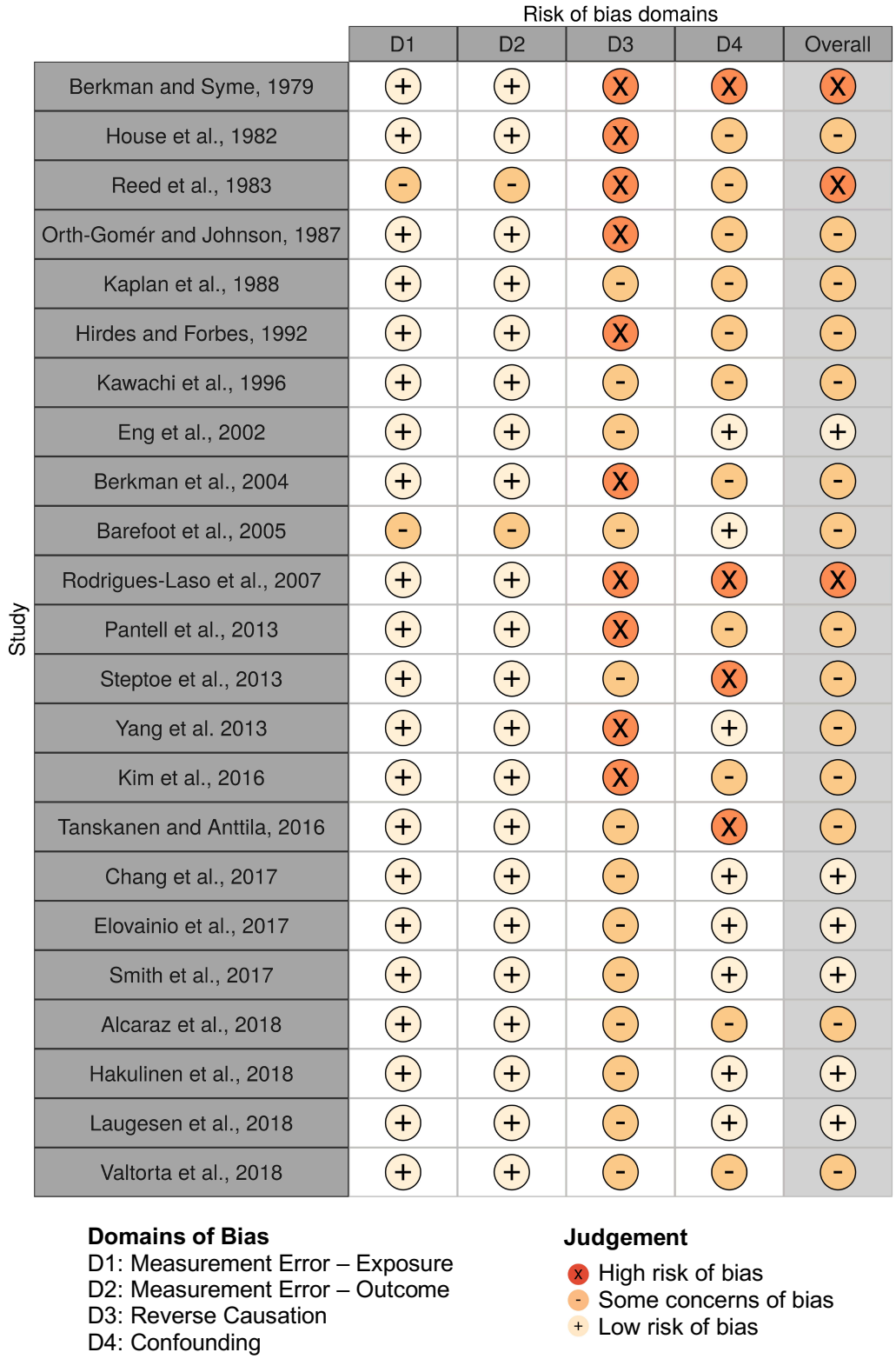


Figure 2.5. Risk of bias assessment for each reviewed study.

Three of the reviewed studies quantitatively assessed the degree to which specific explanatory factors confounded or mediated associations between social isolation and vascular disease or mortality. Previous analyses of UK Biobank data compared risk ratios from models that were minimally adjusted for age, gender, and ethnicity, and additionally adjusted for each group of explanatory factors (i.e. personal characteristics, health behaviours, physiological factors, and psychological factors) (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). To calculate a percentage of excess risk mediated (PERM), the difference between minimally and explanatory factor adjusted models was divided by the difference between the minimally adjusted model and the value one (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Chang and colleagues calculated a similar measure of mediation however they assessed change in risk ratios (per one standard deviation increase in social integration index score) between models that adjusted for age, gender, education, income, physiological factors, and depressive symptoms, and models that additionally adjusted for health behaviours (Chang *et al.*, 2017). These studies generated similar findings.

Health behaviours, particularly smoking, explained approximately 50% of excess vascular disease incidence associated with social isolation (Chang *et al.*, 2017; Hakulinen *et al.*, 2018). Compared to vascular disease incidence, health behaviours explained lower proportions of associations between social isolation and vascular disease mortality (CVD, *PERM*=35%; AMI, *percent mediated*=18%) and all-cause mortality (*PERM*=34%), but still tended to explain the largest proportions of excess mortality (Chang *et al.*, 2017; Elovainio *et al.*, 2017). Only the UK Biobank analyses examined multiple groups of explanatory factors. Compared to health behaviours, socioeconomic position and self-rated health explained similar proportions of associations with mortality (i.e. 31% to 35%) (Elovainio *et al.*, 2017). Socioeconomic position also explained similar proportions of excess vascular disease incidence (i.e. AMI, *PERM*=48% and stroke, *PERM*=55%) (Hakulinen *et al.*, 2018). Physiological and psychological factors tended to explain the lowest proportions of associations with vascular disease incidence and mortality (i.e. 4% to 28%) (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). After adjusting for all explanatory factors, minimally adjusted associations were attenuated by 83% and 84% for AMI and stroke incidence, and 64% for CVD and all-cause mortality (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018).

2.7 Effect Modification

2.7.1 Age Differences

To address confounding due to age-related factors, all studies adjusted their analyses for participant age at baseline (Tables 2.6 and 2.7). To assess modification of associations by age, some studies additionally conducted sub-group analyses to compare associations between social isolation and vascular disease incidence (Hakulinen *et al.*, 2018), CVD mortality (Yang *et al.*, 2013), and all-cause mortality (Berkman and Syme, 1979; Yang *et al.*, 2013; Elovainio *et al.*, 2017) across age groups. Overall, it is unclear from these studies whether social isolation is more or less strongly associated with vascular disease and mortality among younger versus older adults. Berkman and Syme (1979) found that associations between social isolation and all-cause mortality tended to be stronger among men 30 to 59 years old than those who were 60 to 69 years old (Table 2.4). Among women, these associations were strongest among those aged 30 to 49 and 60 to 69 years old compared to women aged 50 to 59 years old (Table 2.4). In unadjusted sensitivity analyses, Elovainio and colleagues (2017) found that associations with all-cause mortality were similar among those aged 37 to 60 years, and weaker among those 61 to 73 years of age. A similar pattern was observed for CHD incidence in another study using UK Biobank data (Hakulinen *et al.*, 2018). However, associations between social isolation and stroke incidence tended to be strongest among those aged 61 to 73 years, and weaker among those 37 to 60 years old (Hakulinen *et al.*, 2018). Finally, Yang and colleagues (2013) did not observe a statistically significant association between social isolation and CVD mortality and all-cause mortality among those 40 to 64 years old but did observe associations among those 65 years and older. A limitation of these studies is that none tested whether any variation in associations between social isolation and vascular disease or mortality across age groups was statistically significant.

2.7.2 Gender Differences

To address confounding, all studies examining mixed gender cohorts adjusted their analyses for gender or completed their analyses in women and men separately (Tables 2.6 and 2.7). It remains unclear from the reviewed studies whether associations between social isolation and vascular disease or mortality vary by gender. Only Hakulinen and colleagues (2018) compared associations between social isolation and vascular disease incidence across men and women. Stronger associations were observed among men compared to women in minimally adjusted sensitivity analyses (Hakulinen *et al.*, 2018). Six studies examined associations between social isolation and mortality outcomes (Pantell *et al.*, 2013; Yang *et al.*, 2013; Kim *et al.*, 2016; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018). Two observed stronger

associations between social isolation and CVD and all-cause mortality among men compared to women (Yang *et al.*, 2013; Elovainio *et al.*, 2017). Among studies focused on all-cause mortality, one found increased all-cause mortality among isolated men but not women (Laugesen *et al.*, 2018). Another observed stronger associations between social isolation and all-cause mortality among men than women (Kim *et al.*, 2016), and another observed stronger associations among women than men (Pantell *et al.*, 2013). However, none of the aforementioned studies tested the statistical significance of differences in these associations by gender. Among those that did, Alcaraz and colleagues (2018) found statistically significant differences according to gender among white, but not black, women and men. Within this study, the most isolated women had statistically significantly greater risk of CVD mortality (Women: *HR*=1.47, *95% CI*: 1.37-1.57; Men: *HR*=1.29, *95% CI*: 1.21-1.38; *p for interaction*<0.0001) and all-cause mortality (Women: *HR*=1.84, *95% CI*: 1.68-2.01; Men: *HR*=1.60, *95% CI*: 1.41-1.82; *p for interaction*<0.0001) than the most isolated men. In contrast, Steptoe and colleagues (2013) found no statistically significant differences in associations between social isolation and all-cause mortality by gender.

2.8 Summary

This review of 23 studies examining multidimensional indices of structural isolation within general adult populations found stronger evidence of associations between social isolation and vascular disease mortality and all-cause mortality than vascular disease incidence. Explanatory factors, particularly health behaviours, tended to explain associations between social isolation and CHD incidence. After adjustment for explanatory factors, minimally adjusted associations with vascular disease and all-cause mortality were attenuated but remained statistically significant. In the few studies that examined social isolation in relation to stroke incidence and mortality, associations were generally inconsistent in magnitude. Marital status and living alone tended to be more consistently and strongly associated with CVD and all-cause mortality compared to other constituent measures of social isolation indices. There was also some evidence to suggest that infrequent contact with social groups or religious service attendance was associated with increased all-cause mortality. Few studies formally tested whether statistically significant differences by age and gender exist in associations between social isolation and vascular disease or mortality. It thus remains unclear whether age and gender represent modifiers of associations. Further research on large prospective cohorts is warranted to generate more robust estimates of any associations between social isolation, vascular disease, and mortality, to examine potential explanatory pathways, and to assess whether any associations are sensitive to modification by age and gender.

Contrary to Valtorta and colleagues' (2016) meta-analysis, the reviewed studies present little evidence of associations between social isolation and vascular disease incidence. This contrast may be due in part to the conflation of structural and perceived isolation measures within the analysis by Valtorta and colleagues (2016), and the consistency of structural isolation measures assessed within the current review. Further research is needed among large cohorts to examine associations between social isolation and stroke incidence. Among the two studies that examined stroke incidence, one was underpowered to generate reliable associations, and the other found no association after adjustment for explanatory factors. While many previous studies have individually examined social contact, group participation, and living alone in relation to vascular disease incidence and all-cause mortality (Floud *et al.*, 2015; Holt-Lunstad *et al.*, 2015; Shor and Roelfs, 2015), among the reviewed studies, few compared multiple constituent measures of social isolation in relation to vascular disease incidence. Among constituent measures there was only weak evidence of associations between increased frequency of contact with family members and religious service attendance and decreased CHD incidence (Barefoot *et al.*, 2005; Chang *et al.*, 2017).

There was stronger evidence suggesting that social isolation is associated with increased vascular disease mortality. While only a quarter of the studies examining CHD-specific mortality found statistically significant associations, those that did not may have been underpowered to detect associations. Studies observing statistically significant associations tended to be larger than those which did not find statistically significant associations. The only study examining stroke-specific mortality found a statistically significant association, however, this study observed very few stroke deaths. Half of the studies examining aggregated CVD mortality measures found statistically significant associations. The strength of associations between CHD and CVD varied considerably from 20% to 76% increased mortality among the most isolated participants compared to the least isolated. Such variation may be explained by differences in the measurement of social isolation (e.g. different constituent measures examined) and outcomes (e.g. differences in the amount of follow-up time and breadth of diagnoses included within the outcome measure). Due to sparse data bias, studies examining multi-category social isolation indices with smaller sample sizes may also have overestimated associations (Greenland, Mansournia and Altman, 2016). Indeed, larger prospective analyses found the most isolated participants to have 20% to 30% greater vascular disease mortality than the least isolated (Chang *et al.*, 2017; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018). This estimate is consistent with Holt-Lunstad and colleagues' meta-analysis (2015a). There was some evidence to suggest that isolated women may have greater risk of vascular disease mortality than isolated men (Alcaraz *et al.*, 2018). No studies assessed the statistical significance of any

effect modification according to age. Among constituent measures of social isolation, being unmarried or living without a partner was most consistently and strongly associated with increased risk of vascular disease mortality. Patterns of associations with vascular disease mortality were not apparent among other constituent measures.

Greater social isolation was consistently associated with increased all-cause mortality. The strength of these associations varied considerably, ranging from 26% to 80% greater mortality among the most isolated compared to least isolated participants. While varied, these estimates are more consistent than those observed in previous meta-analyses which included studies that were and were not restricted to general community-based adult populations (Holt-Lunstad *et al.*, 2010, 2015). It remains unclear whether gender-differences exist in associations between social isolation and all-cause mortality as two studies presented contrasting evidence of effect modification by gender (Steptoe *et al.*, 2013; Alcaraz *et al.*, 2018). No studies formally assessed effect modification by age. Among the constituent measures, again marital status was most consistently associated with mortality. Infrequent social group participation and religious service attendance also tended to be associated with increased all-cause mortality, however these associations were weaker than those for marital status and living alone.

Many reviewed studies made some attempt to minimise reverse causation bias, most often by excluding participants with a history of vascular disease, and/or by adjusting regression models for chronic conditions at baseline. However, reverse causation bias remains an important limitation of the reviewed studies because these exclusions and adjustments do not account for sub-clinical vascular disease. Therefore, future research should use more thorough approaches to minimising reverse causation bias such as excluding participants with a history of vascular disease *and* those reporting fair or poor self-rated health at baseline.

Generally, the reviewed studies appropriately adjusted for several important personal characteristics, health behavioural, physiological, and psychological explanatory factors. Potentially contributing to variation in the magnitude of associations between social isolation and mortality outcomes was heterogeneity in the types of variables adjusted for and the distribution of these explanatory factors within the analysed samples. If causal inferences are to be made about social isolation in relation to vascular disease and mortality, it is important for future research to quantify the degree to which associations can be explained by potential confounders and mediators. In particular, a stronger understanding is needed of the degree to which physiological factors explain any associations.

2.9 Conclusions

It remains unclear whether social isolation is associated with incident vascular disease. There is greater evidence for associations with vascular disease mortality and all-cause mortality. However, even among methodologically similar studies, there is still considerable variation in the magnitude of associations. Confounding and reverse causation remain important limitations of this evidence. Few studies have investigated whether there are age or gender differences in any associations between social isolation, vascular disease, and mortality. Further prospective research on large healthy cohorts of general adult populations is needed to more robustly estimate the aforementioned associations, examine which factors explain any associations, and to test whether any associations vary by age, gender, or other factors. The analyses presented in Chapter 3 analyses were aimed at addressing these limitations of previous research.

3 Social Isolation in Relation to Vascular Disease and Mortality within the Million Women Study

3.1 Introduction

3.1.1 Background

Previous research suggests that social isolation is associated with increased risk of developing and dying from vascular disease and all-cause mortality (Holt-Lunstad *et al.*, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016; Elovainio *et al.*, 2017). There are however important methodological limitations to previous research which complicate causal inferences and may impede the design of effective interventions to prevent social isolation and/or its potential health effects.

Many studies lack sufficient sample sizes for reliable analyses of multidimensional measures of social isolation (Holt-Lunstad *et al.*, 2015; Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). This is particularly the case for studies examining vascular disease mortality and when stratifying cohorts according to age-group (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Berkman *et al.*, 2004; Barefoot *et al.*, 2005; Yang *et al.*, 2013). Larger sample sizes enable more robust estimation of associations and in terms of mitigating reverse causation bias, have greater capacity for excluding individuals whose health status may lead them to become more isolated (e.g. those with CHD, stroke or other chronic diseases at baseline) (Chang *et al.*, 2017; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018; Hakulinen *et al.*, 2018). Few previous studies exclude individuals on the basis of self-rated health (Figure 2.2). Previous studies suggest that poor/fair self-rated health may indicate sub-clinical disease or general illness that may cause less frequent social interaction (Floud *et al.*, 2015; Liu and Floud, 2017; Liu *et al.*, 2017). Thus, even in the largest studies to date, it is difficult to rule out reverse causation bias. One final advantage of research using large cohorts is that they are better able to estimate associations between constituent measures of multidimensional social isolation indices and outcomes. However, few large prospective studies have examined both the composite measures of social isolation and constituent measures concurrently (Chang *et al.*, 2017; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018). Doing so may clarify whether specific types of relationships or social contact are more or less relevant to health.

As discussed in Section 2.6, most previous prospective studies of general adult populations adjust for several explanatory factors. However, few have attempted to quantify the degree to which these factors explain associations between social isolation and vascular disease or mortality (Chang *et al.*, 2017; Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Analysing changes in the magnitude of associations after adjusting for these factors may clarify which, and how much of any, associations are explained by personal characteristics, health behavioural, and physiological factors.

As described in Section 1.4.2, personal characteristics such as age are believed to confound and/or modify associations between social isolation and health. From the few studies that have compared associations between social isolation and vascular disease outcomes across multiple age groups, it remains unclear whether age-differences exist (Berkman and Syme, 1979; Yang *et al.*, 2013; Hakulinen *et al.*, 2018). This is in part because previous studies did not formally test whether differences in associations by age-group were statistically significant. If indeed age represents a modifier of associations, it may be a useful indicator of high-risk individuals towards whom prevention efforts should be targeted.

The Million Women Study 12-year re-survey collected data on structural dimensions of social isolation from over 580,000 UK women. This dataset provided an unprecedented opportunity to examine social isolation in relation to vascular disease and mortality whilst addressing the limitations and gaps of previous research.

3.1.2 Objectives of Chapter

The purpose of this chapter is to understand if and how social isolation influences vascular disease incidence, vascular disease mortality, and all-cause mortality among UK women. This research will address three objectives.

1. To examine whether social isolation is associated with vascular disease incidence, vascular disease mortality, and all-cause mortality, while:
    - minimising bias due to reverse causation;
    - examining how much of any association is explained by personal characteristics, health behaviours, and physiological factors.
2. To examine constituent measures of social isolation such as, frequency of contact with family or friends, frequency of contact with social groups, and living alone, in relation to vascular disease incidence, mortality, and all-cause mortality.

3. To examine whether any associations between social isolation and vascular disease vary by age.

3.2 Methods

3.2.1 Study Design and Participants

The Million Women Study is a longitudinal cohort study initiated in 1996 primarily to examine use of hormone replacement therapy in relation to breast cancer incidence and mortality (Green *et al.*, 2018). As part of the National Health Service Breast Screening Programme, all women registered with the National Health Service (NHS) from England and Scotland, aged 50 to 64, were mailed invitations from NHS screening centres to participate in mammography every three years (Green *et al.*, 2018). Between the years 1996 and 2001, accompanying the cancer screening invitation was the Million Women Study recruitment questionnaire. This detailed questionnaire collected data related to demographics, lifestyle, socioeconomic circumstances, physical characteristics (e.g. height, weight), health status, and medical history. Ethical approval for the Million Women Study primary data collection and secondary analyses was granted by the Oxford and Anglia Multi-Centre Research Ethics Committee.

Approximately 1.32 million women consented to participate in the Million Women Study by completing and returning the questionnaire by post or when they attended the screening centre (Green *et al.*, 2018). At recruitment, the Million Women Study participants were on average 56 years of age, 13% attained tertiary education, 20% were active smokers, 21% engaged in strenuous exercise more than once per week, and their mean body mass index (BMI) was 26 kg/m^2 (Green *et al.*, 2018). Since the year 2000, these women have been invited to participate in five re-surveys at approximately three, eight, 12, 15, and 18 years from the date the recruitment questionnaire was completed. Each questionnaire and further information regarding the collected data and access policies are available online (http://www.millionwomenstudy.org).

Using a prospective cohort study design, this chapter presents analyses of the 12-year re-survey data which was completed between 2009 and 2012. Approximately 1.26 million women were invited to complete the 12-year re-survey and 586,881 (46%) completed it. The 12-year re-survey was selected as the baseline data source for these analyses because it was the first re-survey to include questions on contact with family and friends, social group participation, and household occupancy. A sample of this questionnaire is presented in Appendix B (pp.231).

3.2.2 Social Isolation

Within the 12-year re-survey questionnaire, participants were asked about frequency of contact (i.e. in person, email, telephone) with family members, friends, and groups, as well as household occupancy. These questions as they appear in the questionnaire are presented in Figure 3.1. For each category of social contact, possible responses included "rarely/never," "monthly," "weekly/fortnightly," and "most days." To optimize statistical power and align with previous research, the "rarely/never" and "monthly" categories were combined to create an "at most monthly" category for each social contact variable (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Additionally, measures for contact with family and friends were aggregated into one variable measuring frequency of contact with family or friends. Social group contact variable was also dichotomised by aggregating "most days" and "weekly/fortnightly" categories to create an "at least weekly/fortnightly" category. Living alone status was ascertained by household occupancy. Participants reporting a household occupancy of "0" or "1" were coded as living alone. Marital status is also often included in social isolation indices (Table A2.2, pp.222). Marital status was not measured in the 12-year re-survey, but marital status at the 9-year re-survey was highly correlated with living alone (Spearman correlation, ρ=0.72).

A noteworthy limitation of previous research examining associations between social isolation and health is substantial heterogeneity in the methods used for measuring social isolation (Holt-Lunstad *et al.*, 2015; Valtorta, Kanaan, Gilbody and Hanratty, 2016). To assess the combined role of social contact and living alone, a social contact index (SCI) was constructed (Figure 3.2). The design of the SCI was informed by commonly used indices (e.g. social network index and social isolation scale) in order to make the results of the current analysis more comparable with previous research (Berkman and Syme, 1979; Steptoe *et al.*, 2013; Elovainio *et al.*, 2017). Participants were given a score of one if they had social contact with family or friends "at most monthly," or if they had contact with groups "at most monthly," or if they were living alone. These individual scores were summed to calculate the overall SCI. The SCI scores thus ranged from zero (least isolated) to three (most isolated). Given the low number of participants with a SCI value of three, participants with scores of two and three were grouped into the most isolated category.

5. How often do you contact (e.g. phone, meet, email):	Rarely/ never	Monthly	Weekly/ fortnightly	Most days
Family?	☐	☐	☐	☐
Friends?	☐	☐	☐	☐
Groups (e.g. religious, WI, fitness, adult education)?	☐	☐	☐	☐

8. How many people live in your household?	☐ Number of people (incl. you)

Figure 3.1. Excerpts of the social contact and household occupancy questions from the Million Women Study 12-year re-survey questionnaire.

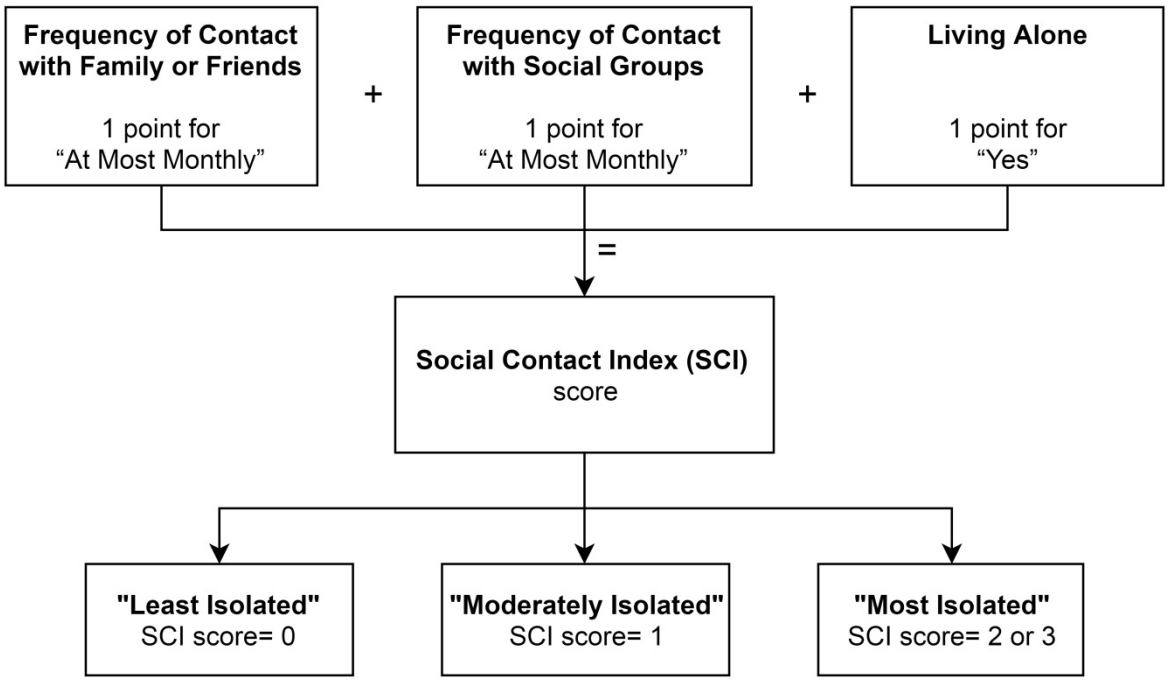


Figure 3.2. Social contact index score and social isolation category derivation diagram.

3.2.3 Outcomes

Health outcomes data for this thesis were accessed through NHS Digital and linked to the Million Women Study data using person-specific NHS numbers and dates of birth. NHS Digital is a branch of the NHS which stores and maintains hospital record data (formerly referred to as Hospital Episode Statistics) in addition to cancer registration and death certificate data from the Office for National Statistics. For each hospital episode identified with a CHD or stroke diagnosis as a primary or contributory cause of hospitalisation, the admission and discharge dates were extracted. Additional data sourced from NHS Digital include cancer registration dates, death dates, diagnosis codes for the primary cause of death or cancer, and follow-up codes identifying those who passed away or emigrated. Linkage was virtually complete with less than 1.0% of participants lost to follow-up (Green *et al.*, 2018).

The five outcomes of interest were time to first CHD event (International Classification of Diseases 10th Revision [ICD-10] codes: I20 to I25; ICD-9 codes: 410 to 414) and first cerebrovascular disease event (hereafter referred to as stroke) event (ICD-10 codes: I60 to I69; ICD-9 codes: 430 to 438), time to CHD death and stroke death, and time to death from any cause (World Health Organisation, 2010). First CHD and stroke events were defined as a participant's first hospital admission or death during the observation period due to CHD or stroke. It was hypothesized that non-vascular primary causes of morbidity may be instigated by underlying vascular disease events. Therefore, incident CHD and stroke events included hospitalisations that recorded the diagnosis as either the primary or contributory cause. Accounting for primary and contributory diagnoses of vascular disease was believed to enable more accurate estimations of vascular disease incidence. Only primary causes of death were used to ascertain mortality due to CHD or stroke. Time to death outcomes were defined as deaths occurring during the observation period and caused by CHD, stroke, or any diagnosis. Only primary causes of death were used for the incidence and mortality outcomes because of interest was the diagnosis that clinicians believed was most responsible for causing death.

3.2.4 Explanatory Factors

As discussed in Section 1.4.4, for brevity of discussion, potential confounding or mediating factors are referred to collectively in this thesis as explanatory factors because they may explain associations between social isolation and health. Each group of explanatory factors and their hypothesised relationship with social isolation and the outcomes examined are presented in Figure 3.3. This analysis-specific model conceptualises personal characteristics (i.e. age at recruitment, recruitment region, socioeconomic deprivation, educational attainment, self-reported disabilities) specifically as potential confounders because older individuals, those of lower socioeconomic position, and experiencing greater disability may face greater barriers to having frequent and meaningful social contact (Nicholson, 2012; Cotterell, Buffel and Phillipson, 2018; Holt-Lunstad, 2018b). There is also little evidence to suggest that social isolation would cause these factors to change. It should be noted that attained age was also examined as a modifier of associations. Health behaviours (i.e. physical activity, smoking, alcohol intake, body mass index [BMI]) and physiological factors (i.e. self-reported hypertension and diabetes) were conceptualised as mediators of associations because other recognised conceptual models for social relationships and health, and relevant studies tend to conceptualise them as mediators (Section 1.4.4; Berkman and Krishna, 2014; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Holt-Lunstad, 2018b). However, given the challenges with ascertaining causality in the current analysis and previous research, this thesis research acknowledges that these factors may also represent confounders (Kim and Kawachi, 2018).

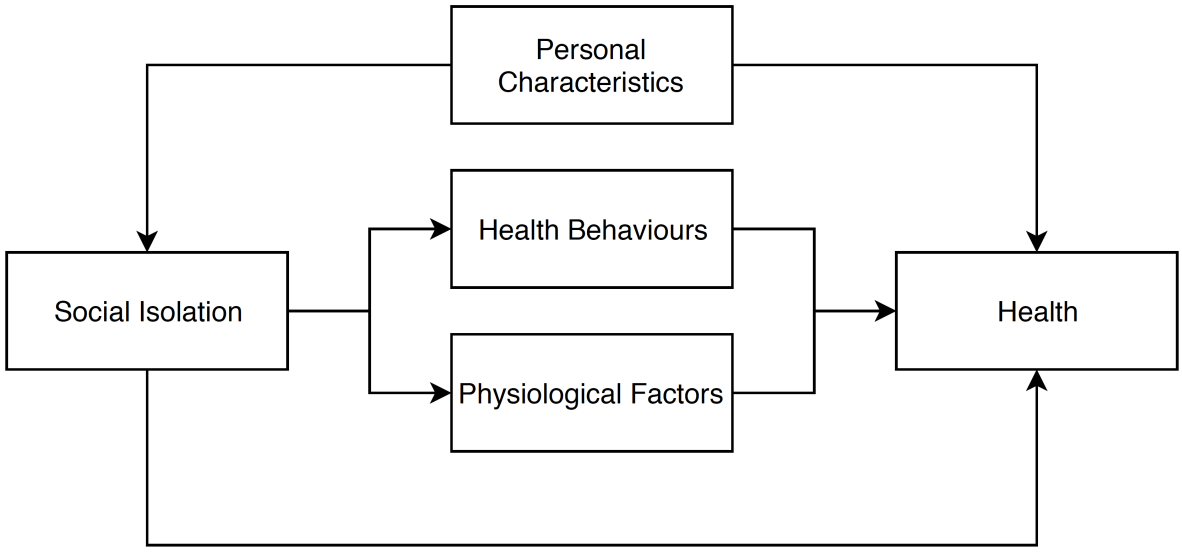


Figure 3.3. Analysis-specific conceptualisation of factors potentially modifying, confounding, and mediating associations between social isolation, vascular disease and mortality.

The categories for each explanatory factor is presented in Table 3.1. With the exception of socioeconomic deprivation, data for each variable was derived from the Million Women Study questionnaires. Birth and recruitment cohort were used to measure age at recruitment. Data on region of recruitment and educational qualifications was also sourced from the recruitment questionnaire. The 12-year re-survey questions used to measure disability were chosen according to the Washington Group on Disability Statistics' short set questionnaire which is a validated and internationally recognised tool for assessing disability (Groce and Mont, 2017). Consistent with previous Million Women Study analyses, participants that reported at least one functional limitation, sensory deficit, or receipt of disability benefits were compared to those without any of these characteristics (Floud *et al.*, 2017). To ascertain socioeconomic deprivation, participant postcode at the 12-year re-survey was linked to the English Index of Multiple Deprivation (IMD) 2010.

The IMD 2010 Income Domain was used as proxy measure of individual-level socioeconomic deprivation. Income is one of eight IMD domains which constitute the overall IMD score. An advantage of using the IMD for this thesis research is that the additional domains could be used to examine multiple neighbourhood factors as effect modifiers in Chapter 5. However, the overall score also includes domains measuring health and disability using similar morbidity and mortality data as the vascular disease outcome measures examined in the current analysis. The current analysis specifically examined the income domain to avoid underestimating any associations between social isolation and vascular disease after adjustment for deprivation. As discussed in greater detail in Section 5.2.4, IMD income domain scores represent the proportion of residents within small geographic areas called lower super output areas (LSOA) receiving income support benefits (McLennan *et al.*, 2011). An important limitation of using the English IMD 2010 is that these scores cannot be generated for those who were living in Scotland at recruitment. While a Scottish IMD exists (in addition to Welsh and Northern Irish indices), the ONS recommends that the English and Scottish IMD scores are not combined for analyses of the UK population (Smith *et al.*, 2015). This is because the rankings of scores within each domain differ across these jurisdictions.

Almost all health behavioural and physiological factors were derived from the 12-year re-survey. Due to low proportions of women reporting participation in strenuous physical activity, moderate and strenuous physical activity (days per week) was averaged across summer and winter months. Smoking status was ascertained from one question about whether participants had ever smoked tobacco. Alcohol intake was derived from questions about whether participants consumed alcohol within the past year, and if so, the total number of units

consumed per week. Body mass index (BMI) was used as a proxy for diet quality (Ford *et al.*, 2014). Height at recruitment and weight at the 12-year re-survey was used to calculate BMI. BMI values under 25.0 kg/m^2 was referred to as "desirable" due to few women having underweight BMI values (i.e. <18.5 kg/m^2). Self-reported diagnoses of hypertension and diabetes were used as proxy indicators of physiological dysregulation and were derived from single questions asking about medical history.

Table 3.1. Description of covariates adjusted for in Cox regression analyses.

Explanatory Factor Group	Explanatory Factor	Categories
Personal Characteristics	Birth cohort	≤1930 1931-1949 ≥1950
	Recruitment cohort	1996, 1997, 1998, 1999, 2000, ≥2001
	Region of Recruitment	Oxford, East Anglia, South West, Thames, West Midlands, North York, Trent, North West (Mersey), North West (Manchester/Lancaster)
	Socioeconomic deprivation (Index of Multiple Deprivation 2010)	Least deprived Moderately deprived Most deprived
	Educational qualifications	Tertiary (college/university or equivalent) Secondary (O/A levels or equivalent) Technical (teaching and nursing) None
	Self-reported disability	None At least one (i.e. difficulty performing activities of self-care, walking up a flight of stairs and having a slow walking pace or inability to walk, poor self-rated memory, poor eyesight, and/or poor hearing)
Health Behavioural Factors	Frequency of strenuous or moderate exercise	Rarely/never Sometimes (1-3 days/week) Most Days (4-6 days/week) Daily
	Smoking status	Current Never Former
	Weekly alcohol intake	0 units 1-6 units ≥7 units
	Body Mass Index	Desirable (<25 kg/m^2) Overweight (25-29.9 kg/m^2) Obese (≥30 kg/m^2)
Physiological Factors	Self-reported history of hypertension	Yes, No
	Self-reported history of diabetes	Yes, No

3.2.5 Statistical Analyses

In total, 586,881 participants were considered for analysis. Participants were first excluded if they had missing survey completion dates (*n*=2). Women recruited from Scotland (*n*=39,117) were excluded because it was not possible to ascertain socioeconomic deprivation for them using the English IMD 2010. To mitigate reverse causation bias, participants were also excluded if they had previous hospital admissions for CHD or stroke (*n*=42,509) or had self-reported history of cardiovascular disease or stroke (*n*=34,564). Participants were also excluded if they had previous cancer registrations (*n*=51,337) because like vascular disease cancer represents a major cause of death and disability which may impede a person's capacity for social interaction. As presented in Figure A3.1 (pp. 225), for any given level of SCI score, women with fair or poor self-rated health had greater risk of each outcome compared to those with good or excellent health. Since self-rated health may indicate sub-clinical illness which may impede social interaction and be associated with mortality, women reporting fair, poor or missing self-rated health (*n*=74,148) were also excluded from analysis (Floud et al., 2015; Liu et al., 2017). Finally, those with missing responses to any of the social contact or household occupancy questions, and thus having missing SCI scores, were excluded (*n*=19,035).

Participants were observed from the time of survey completion to time of event, death, loss to follow-up or 31 March 2017 as this was the latest date for which NHS Digital data was available. Cox regression was used to estimate hazard ratios (referred to hereafter as relative risks [RRs]) and 95% confidence intervals (CIs). All regression models were minimally adjusted for age at the 12-year re-survey indirectly by stratifying by birth and recruitment cohort. Stratifying analyses of Million Women Study data by these variables is advised by the Cancer Epidemiology Unit in order to account for the calendar effects of hormone replacement therapy cessation observed within this cohort in the early 2000s. Minimally adjusted models also controlled for region of recruitment to account for regional variation in breast cancer screening program recruitment. Fully adjusted models additionally controlled for further personal characteristics (i.e. socioeconomic deprivation, education, disability), health behaviours (i.e. smoking, alcohol intake, physical activity, body mass index), and physiological factors (i.e. hypertension, diabetes).

Minimally and fully adjusted models were examined for associations between social isolation and CHD and stroke incidence, CHD and stroke mortality, and all-cause mortality. Differences in RRs across levels of each exposure were tested using likelihood ratio (LR) tests of heterogeneity. Missing data for the covariates (<5.0% for all variables except frequency of physical activity, 9.9%) were assigned to a separate category. To examine the assumption of

proportional hazards, log-log plots and Schoenfeld residuals were assessed; the assumption was found to be reasonable. Spearman's correlation coefficients were used to assess correlation among the covariates. Each pairwise combination of covariates was below ρ=0.20 suggesting that multicollinearity was unlikely.

To quantify the amount that any associations between social isolation and each outcome were explained by covariates, the LR χ^2 test statistic attenuation method was used (Parish et al., 2009; Floud et al., 2016). The LR χ^2 test statistic for the differences in RRs across levels of SCI score from the minimally adjusted model was compared with those from a series of models which adjusted for each explanatory factor and for each group of explanatory factors. After each adjustment, the percentage attenuation in the minimally adjusted LR χ^2 test statistic was calculated as $\left(1 - \frac{LR\chi^2{}_{adj}}{LR\chi^2{}_{min}}\right) \cdot 100$, where $LR\chi^2{}_{min}$ is the LR χ^2 test statistic of the minimally adjusted model, and $LR\chi^2{}_{adj}$ is that of the model adjusted for additional explanatory factors.

$LR\chi^2{}_{min}$ represents a measure of the improvement of goodness of fit due to SCI score, before adjustment of additional explanatory factors. The difference in $LR\chi^2{}_{min}$and $LR\chi^2{}_{adj}$ values is a measure of how much of that improvement is due to additional explanatory factors. After adjusting for all covariates, larger reductions in $LR\chi^2{}_{min}$ (e.g. 80%) indicates that any remaining associations are more likely to be explained by residual confounding compared to smaller reductions (e.g. 30%).

To examine associations between each constituent measure of the SCI score and each outcome, minimally and fully adjusted analyses were conducted.

Sub-group analyses were performed by attained age over the follow-up period to examine age-differences in any associations between social isolation and each outcome. Attained age was used to define sub-groups because it was believed to more accurately reflect a person's baseline risk of vascular disease and mortality which may evolve over several years of observation. LR tests of interaction were used to test for interaction between social isolation and attained age (i.e. under 75 years old compared to at least 75 years old during the observation period) in relation to each outcome. Seventy-five was used as the age threshold because the 12-year re-survey cohort was primarily composed of older adults and 75 years represents the upper age threshold for premature cardiovascular disease and death (British Heart Foundation, 2018a; Office for National Statistics, 2018a). Premature morbidity and mortality is considered more

preventable because it is less likely to be influenced by comorbid conditions and the natural progression of disease (Office for National Statistics, 2018a).

To examine whether associations varied according to CHD and stroke sub-type, sensitivity analyses were conducted in relation to myocardial infarction (ICD-10 codes: I21 and I22; ICD-9 codes: 410 and 411), ischaemic stroke (ICD-10 code: I63; ICD-9 code: 434), and haemorrhagic stroke (ICD-10 codes: I60 and I61; ICD-9 codes: 430 to 432) (World Health Organisation, 2010). To further investigate reverse causation bias within the results, post-hoc sensitivity analyses examined social isolation in relation to each outcome after excluding the first two years of follow-up. Finally, to assess whether the SCI constituent measures confounded one another, each constituent measure was re-examined in relation to each outcome with mutual adjustment for each other constituent measure (e.g. analyses of living alone were additionally adjusted for frequency of contact with family or friends, and contact with groups).

All analyses were conducted using Stata 14.1 (StataCorp, College Station, TX, USA).

3.3 Results

In total, 326,169 women without previous vascular disease, cancer, or fair/poor self-rated health at baseline were included in the analysis. Cohort characteristics are presented in Table 3.2. During a follow-up period of on average 5.9 (*SD*= 1.2) years, there were 10,876 incident CHD events, 559 CHD deaths, 6,281 incident stroke events, 587 stroke deaths, and 9,667 deaths from any cause. At baseline, the mean age of participants was 67.7 years (*SD*= 4.5). Approximately 11.9% of participants were within the most isolated SCI score category. Few women (2.0%) reported at most monthly contact with family members or friends, while 48.1% reported at most monthly contact with groups, and almost a quarter (23.6%) of participants lived alone. The most isolated women tended to be more deprived, less educated, current smokers, inactive and have higher BMI than the least isolated women. They were also more likely to report experiencing disability and a history of hypertension and diabetes.

Table 3.2. Baseline characteristics of participants by level of social isolation and details of follow-up.

Characteristics	Overall N=326,169	Social Contact Index score: 0 Least Isolated n=125,712 (38.5%)	1 Moderately Isolated n=161,515 (49.5%)	2 Most Isolated n=38,942 (11.9%)
Mean Age (SD)	67.7 (4.5)	67.3 (4.2)	67.7 (4.5)	68.7 (4.9)
Most deprived tertile (%)	13.5	9.6	14.8	21.0
No educational qualifications (%)	27.9	18.4	32.5	39.2
At most monthly social contact with:				
Family or friends (%)	2.0	0.0	0.8	13.2
Groups (%)	48.1	0.0	73.3	99.2
Living alone (%)	23.6	0.0	25.9	89.9
Current smoker (%)	5.5	2.4	6.4	11.6
≥7 units alcohol per week (%)	31.7	34.4	30.8	26.7
Rarely/never, exercise (%)	7.2	5.1	8.2	10.5
BMI ≥30 kg/m^2 (%)	16.9	14.4	18.4	19.1
At least one disability (%)	13.6	10.4	14.6	19.3
History of hypertension (%)	19.0	17.4	19.8	21.3
History of diabetes (%)	3.3	2.6	3.5	4.4
Follow-up for Vascular Disease Incidence and Mortality Outcomes				
Incident CHD events (n)	10,876	3,728	5,491	1,657
Mean years of follow-up per person (SD)	5.8(1.3)	5.9(1.2)	5.8(1.3)	5.7(1.3)
Person-years (1000s)	1901	738	939	224
Incident Stroke events (n)	6,281	1,957	3,218	1,106
Mean years of follow-up per person (SD)	5.9(1.2)	5.9(1.2)	5.9(1.2)	5.8(1.3)
Person-years (1000s)	1916	744	947	226
CHD deaths (n)	559	140	280	139
Mean years of follow-up per person (SD)	5.9(1.1)	5.9(1.1)	5.9(1.2)	5.9(1.2)
Person-years (1000s)	1929	748	953	228
Stroke deaths (n)	587	163	296	128
Mean years of follow-up per person (SD)	5.9(1.1)	5.9(1.1)	5.9(1.2)	5.9(1.2)
Person-years (1000s)	1,929	748	953	228
All-cause deaths (n)	9,667	2,886	4,976	1,805
Mean years of follow-up per person (SD)	5.9(1.1)	5.9(1.1)	5.9(1.2)	5.9(1.2)
Person-years (1000s)	1,929	748	953	228

Notes: Percentages calculated based on women with complete information for each specific variable.

3.3.1 Prospective Analyses of CHD Incidence

With minimal adjustment for age and region, compared to the least isolated women, greater social isolation was associated with increased CHD incidence (Figure 3.4). These associations were strongly attenuated and marginally statistically significant after additional adjustment for personal characteristics, health behavioural, and physiological factors (Table 3.3, Figure 3.4; Moderately Isolated: *RR*=1.00, *95% CI*: 0.96-1.04; Most Isolated: *RR*=1.07, *95% CI*: 1.01-1.14; *p*=0.04). Adjustment for all explanatory factors resulted in a 92% attenuation in the minimally adjusted LR χ^2 test statistic (Table 3.3). Adjustment for health behavioural factors explained a 77% attenuation in the minimally adjusted LR χ^2 test statistic (Table 3.3). After full adjustment, living alone, and frequency of contact with family, friends, and social groups were not statistically significantly associated with incident CHD (Figure 3.5).

3.3.2 Prospective Analyses of Stroke Incidence

Before and after adjustment, greater social isolation was associated with increased stroke incidence (Figure 3.4). After adjustment, compared to the least isolated women, moderately isolated and most isolated women had 11% and 28% increased risk of incident stroke respectively (Figure 3.4, Moderately Isolated: *RR*=1.11, *95% CI*: 1.05-1.17, Most Isolated: *RR*=1.28, *95% CI*: 1.19-1.38, *p*<0.0001). Adjustment for all explanatory factors resulted in a 67% attenuation in the minimally adjusted LR χ^2 test statistic (Table 3.3). Again, adjustment for health behavioural factors resulted in the greatest degree of attenuation of minimally adjusted associations. Each constituent measure of the social contact index was associated with stroke incidence after adjustment (Figure 3.5). While at most monthly contact with family or friends had the highest magnitude of association with stroke incidence, this association had wider confidence intervals than the other constituent measures (Figure 3.5, Weekly/Fortnightly: *RR*=1.07, *95% CI*: 1.01-1.13; At Most Monthly: *RR*=1.25, *95% CI*: 1.07-1.45; *p*<0.01). Compared to living with others, living alone was associated with 16% greater stroke incidence (Figure 3.5, *RR*=1.16, *95% CI*: 1.10-1.22; *p*<0.01). Compared to at least weekly/fortnightly contact, at most monthly contact with social groups was associated with 8% greater stroke incidence (Figure 3.4, *RR*=1.08, *95% CI*: 1.03-1.14; *p*<0.01).

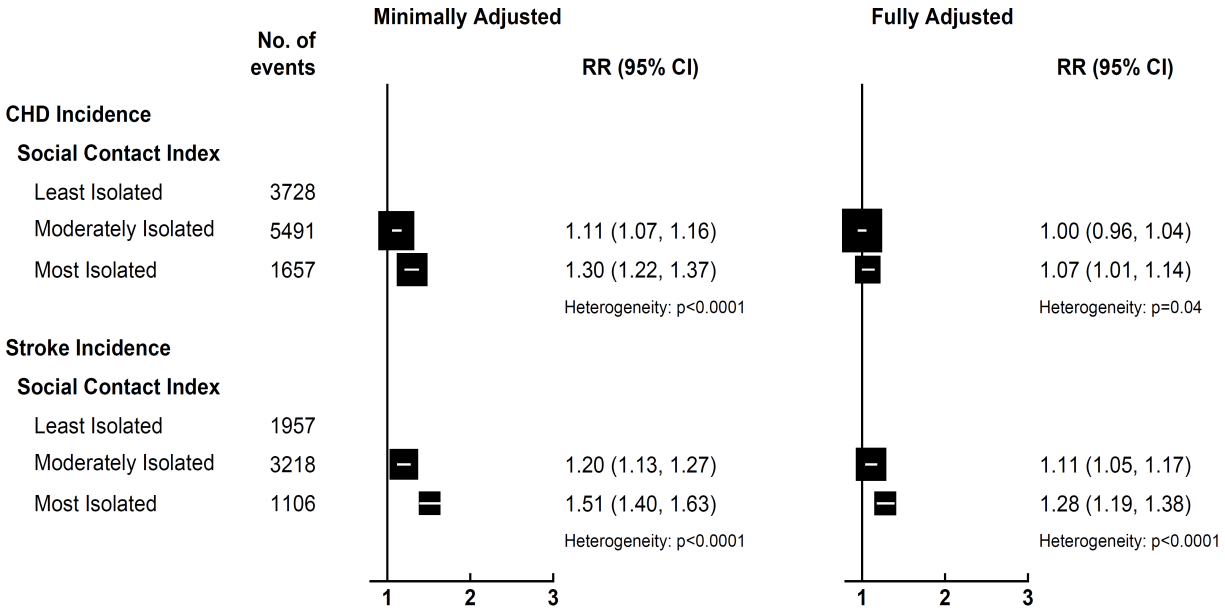


Figure 3.4. Minimally and fully adjusted RR and 95% CI for social isolation in relation to vascular disease incidence. The size of the square boxes are inversely proportional to the standard error of the relative risk estimate. Minimally adjusted models included: age and region. Fully adjusted models included: age, region, deprivation, education, disability, smoking, alcohol, physical activity, BMI, hypertension, and diabetes.

Table 3.3. RR and 95% CI for CHD and stroke incidence by level of social isolation after adjustment for each group of covariates.

	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
CHD INCIDENCE						
No. of first CHD events	3,728	5,491	1,657			
Age, region (minimally adjusted)	**1.00 (-)**	**1.11 (1.07, 1.16)**	**1.30 (1.22, 1.37)**	**<0.0001**	76	**-**
Age, region, personal characteristics	**1.00 (-)**	**1.05 (1.01, 1.10)**	**1.18 (1.11, 1.25)**	**<0.0001**	**29**	**62**
Age, region, deprivation	1.00 (-)	1.10 (1.05, 1.14)	1.26 (1.19, 1.34)	<0.0001	60	22
Age, region, education	1.00 (-)	1.08 (1.03, 1.12)	1.24 (1.17, 1.31)	<0.0001	49	36
Age, region, disability	1.00 (-)	1.09 (1.05, 1.14)	1.25 (1.17, 1.32)	<0.0001	54	29
Age, region, health behaviour factors	**1.00 (-)**	**1.03 (0.99, 1.08)**	**1.14 (1.07, 1.21)**	**<0.001**	**18**	**77**
Age, region, smoking	1.00 (-)	1.08 (1.03, 1.12)	1.21 (1.14, 1.28)	<0.0001	39	48
Age, region, alcohol	1.00 (-)	1.10 (1.06, 1.15)	1.27 (1.19, 1.34)	<0.0001	63	18
Age, region, physical activity	1.00 (-)	1.09 (1.05, 1.14)	1.26 (1.19, 1.34)	<0.0001	61	20
Age, region, body mass index	1.00 (-)	1.09 (1.05, 1.14)	1.27 (1.20, 1.35)	<0.0001	63	17
Age, region, physiological factors	**1.00 (-)**	**1.10 (1.05, 1.14)**	**1.26 (1.19, 1.34)**	**<0.0001**	**62**	**19**
Age, region, hypertension	1.00 (-)	1.10 (1.06, 1.15)	1.28 (1.21, 1.36)	<0.0001	68	10
Age, region, diabetes	1.00 (-)	1.10 (1.06, 1.15)	1.28 (1.21, 1.36)	<0.0001	69	10
Fully adjusted	**1.00 (-)**	**1.00 (0.96, 1.04)**	**1.07 (1.01, 1.14)**	**0.040**	**6**	**92**
STROKE INCIDENCE						
No. of first stroke events	1,957	3,218	1,106			
Age, region (minimally adjusted)	**1.00 (-)**	**1.20 (1.13, 1.27)**	**1.51 (1.40, 1.63)**	**<0.0001**	**117**	**-**
Age, region, personal characteristics	**1.00 (-)**	**1.16 (1.10, 1.23)**	**1.42 (1.32, 1.54)**	**<0.0001**	**82**	**30**
Age, region, deprivation	1.00 (-)	1.19 (1.12, 1.26)	1.48 (1.38, 1.60)	<0.0001	105	10
Age, region, education	1.00 (-)	1.19 (1.12, 1.26)	1.48 (1.37, 1.60)	<0.0001	103	12
Age, region, disability	1.00 (-)	1.18 (1.12, 1.25)	1.46 (1.36, 1.57)	<0.0001	99	16
Age, region, health behaviour factors	**1.00 (-)**	**1.13 (1.07, 1.19)**	**1.33 (1.23, 1.43)**	**<0.0001**	**53**	**54**
Age, region, smoking	1.00 (-)	1.15 (1.09, 1.22)	1.39 (1.28, 1.49)	<0.0001	71	39
Age, region, alcohol	1.00 (-)	1.19 (1.13, 1.26)	1.49 (1.38, 1.60)	<0.0001	108	8
Age, region, physical activity	1.00 (-)	1.18 (1.11, 1.25)	1.47 (1.36, 1.58)	<0.0001	100	14
Age, region, body mass index	1.00 (-)	1.20 (1.13, 1.27)	1.51 (1.40, 1.62)	<0.0001	116	1
Age, region, physiological factors	**1.00 (-)**	**1.19 (1.13, 1.26)**	**1.49 (1.38, 1.60)**	**<0.0001**	**109**	**7**
Age, region, hypertension	1.00 (-)	1.19 (1.13, 1.26)	1.49 (1.39, 1.61)	<0.0001	111	6
Age, region, diabetes	1.00 (-)	1.20 (1.13, 1.27)	1.51 (1.40, 1.62)	<0.0001	115	2
Fully adjusted	**1.00 (-)**	**1.11 (1.05, 1.17)**	**1.28 (1.19, 1.38)**	**<0.0001**	**39**	**67**

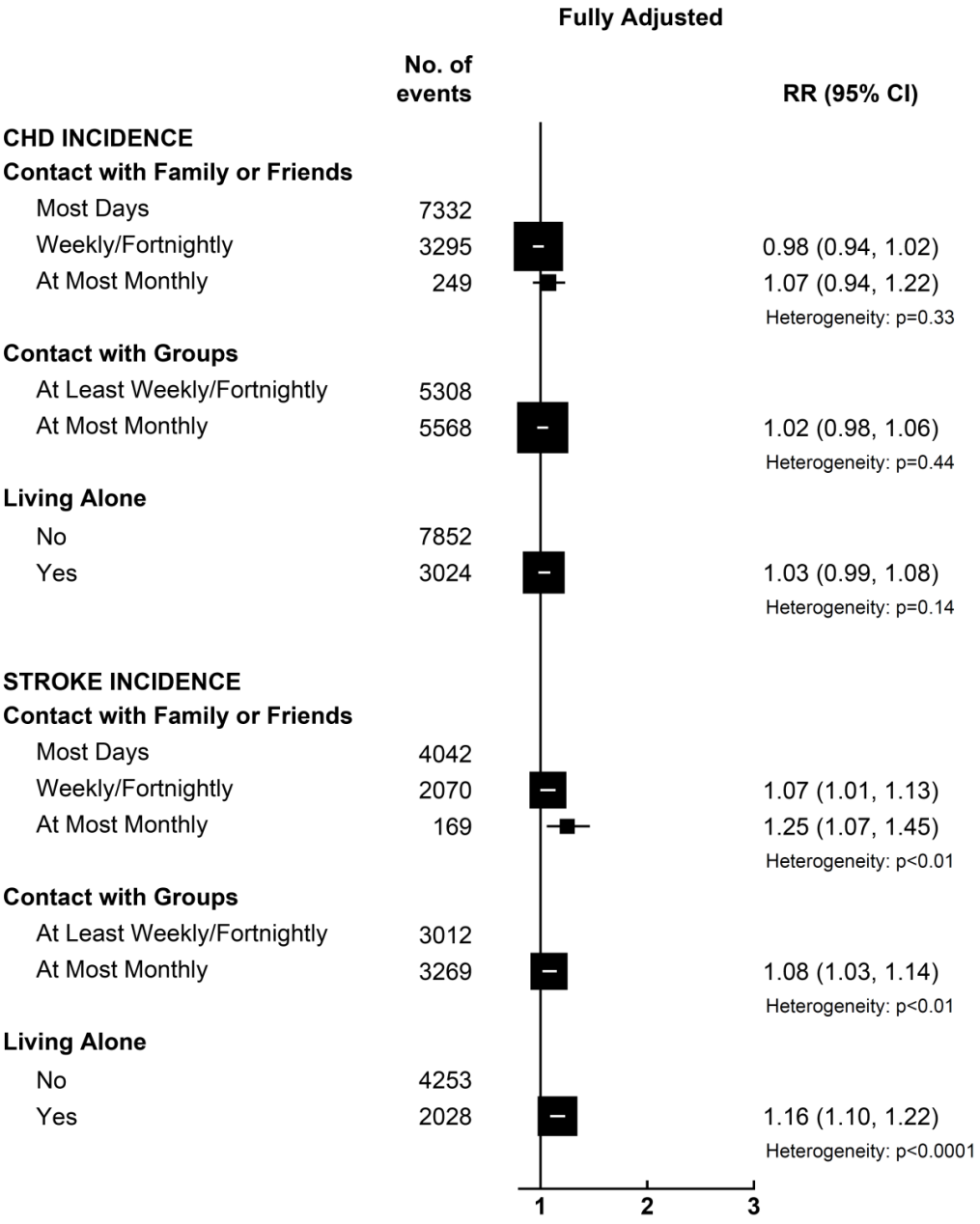


Figure 3.5. Fully adjusted RR and 95% CI for each social contact variable in relation to vascular disease incidence. The size of the square boxes are inversely proportional to the standard error of the relative risk estimate.

3.3.3 Prospective Analyses of CHD Mortality

Greater social isolation was associated with increased CHD mortality in minimally and fully adjusted analyses (Figure 3.6). After full adjustment, and compared to the least isolated, the moderately isolated and the most isolated women had 20% and 80% greater CHD mortality respectively (Figure 3.6, Moderately Isolated: *RR*=1.20, *95% CI*: 0.97-1.47, Most Isolated: *RR*=1.80, *95% CI*: 1.41-2.31, p<0.0001). The minimally adjusted LR χ^2 test statistic decreased by 64% after adjustment for all explanatory factors (Table 3.4). Health behavioural factors, particularly smoking, again accounted for the greatest proportion of minimally adjusted associations between social isolation and CHD mortality (Table 3.4). Among the measures comprising the social contact index, only living alone was statistically significantly associated with increased CHD mortality after full adjustment (Figure 3.7, Living alone: *RR*=1.48, *95% CI*: 1.25-1.77, p<0.0001).

3.3.4 Prospective Analyses of Stroke Mortality

Greater social isolation was associated with increased stroke mortality in minimally and fully adjusted analyses (Figure 3.6). Compared to the other outcomes examined, minimally adjusted associations between social isolation and stroke mortality were explained to a lesser degree by personal characteristics, health behaviours, and physiological factors (Table 3.4, LR χ^2 test statistic attenuation: 41%). After adjustment, compared to the least isolated women, the moderately isolated and the most isolated women had 21% and 70% greater stroke mortality respectively (Table 3.4, Moderately Isolated: *RR*=1.21, *95% CI*: 1.00-1.47, Most Isolated: *RR*=1.71, *95% CI*: 1.34-2.18, *p*<0.001). Among the constituent measures of the social contact index, living alone had the strongest association with stroke mortality. Compared to women who lived with others, those who lived alone had 31% greater stroke mortality (Figure 3.7, *RR*=1.31, *95% CI*: 1.10-1.56, *p*<0.01). Associations were also observed between contact with groups and stroke mortality. Compared to women with at least weekly/fortnightly contact with social groups, those with at most monthly contact had 23% greater stroke mortality (Figure 3.7, *RR*=1.23, *95% CI*: 1.04-1.46, *p*=0.02). Like CHD mortality, the associations between frequency of contact with family or friends and stroke mortality exhibited wide confidence intervals (Figure 3.7). However, for stroke mortality this association was marginally statistically significant (*p*=0.04). It should be noted that for both CHD and stroke mortality, only around 20 cases were observed in the at most monthly family or friend contact category.

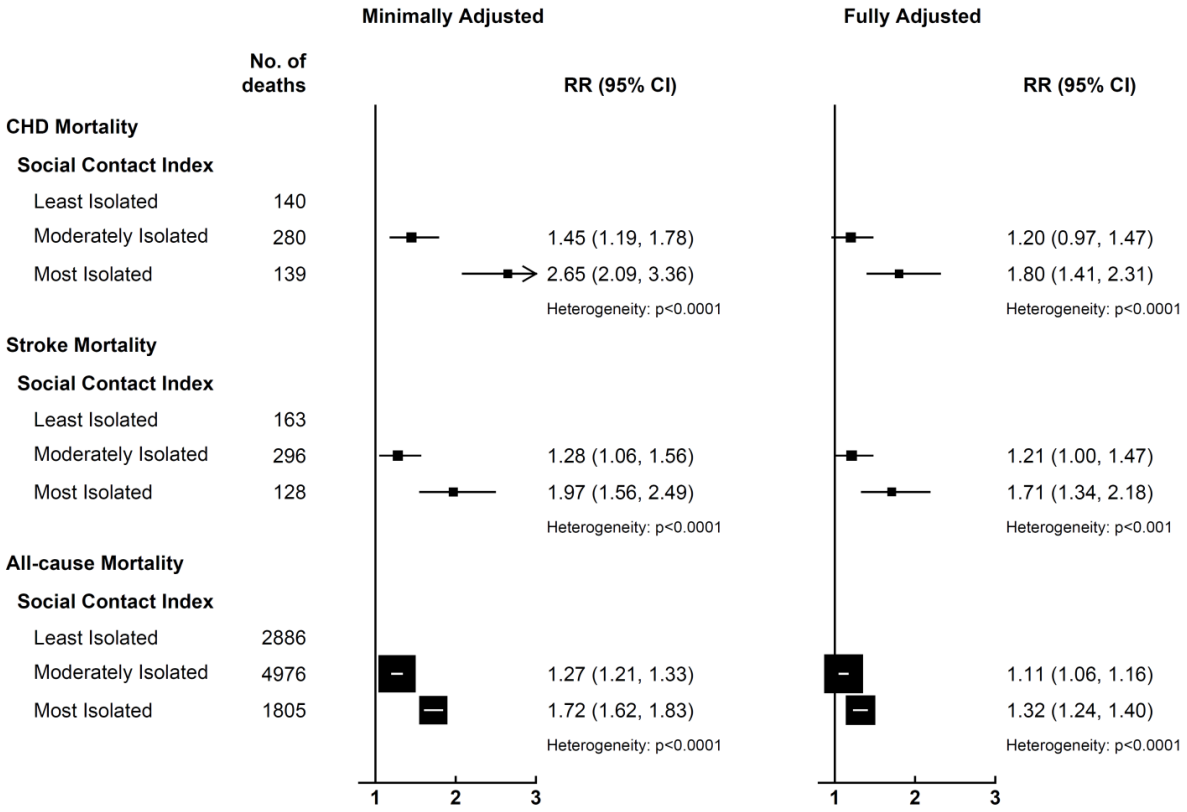


Figure 3.6. Minimally and fully adjusted RR and 95% CI for social isolation in relation to vascular disease and all-cause mortality. The size of the square boxes are inversely proportional to the standard error of the relative risk estimate. Minimally adjusted models included: age and region. Fully adjusted models included: age, region, deprivation, education, disability, smoking, alcohol, physical activity, BMI, hypertension, and diabetes.

Table 3.4. RR and 95% CI for CHD and stroke mortality by level of social isolation after adjustment for each group of covariates.

	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
CHD MORTALITY						
No. of CHD deaths	140	280	139			
Age, region (minimally adjusted)	**1.00 (-)**	**1.45 (1.19, 1.78)**	**2.65 (2.09, 3.36)**	**<0.0001**	**62**	-
Age, region, personal characteristics	**1.00 (-)**	**1.37 (1.11, 1.68)**	**2.35 (1.84, 2.99)**	**<0.0001**	**52**	**26**
Age, region, deprivation	1.00 (-)	1.42 (1.16, 1.75)	2.53 (1.99, 3.22)	<0.0001	56	10
Age, region, education	1.00 (-)	1.42 (1.16, 1.74)	2.55 (2.01, 3.25)	<0.0001	56	10
Age, region, disability	1.00 (-)	1.41 (1.15, 1.73)	2.49 (1.96, 3.16)	<0.0001	27	13
Age, region, health behaviour factors	**1.00 (-)**	**1.22 (0.99, 1.50)**	**1.89 (1.48, 2.42)**	**<0.0001**	**36**	**57**
Age, region, smoking	1.00 (-)	1.31 (1.06, 1.60)	2.11 (1.66, 2.69)	<0.0001	56	42
Age, region, alcohol	1.00 (-)	1.42 (1.16, 1.75)	2.53 (1.99, 3.21)	<0.0001	55	10
Age, region, physical activity	1.00 (-)	1.40 (1.15, 1.72)	2.50 (1.97, 3.18)	<0.0001	59	11
Age, region, body mass index	1.00 (-)	1.43 (1.17, 1.75)	2.59 (2.04, 3.28)	<0.0001	52	5
Age, region, physiological factors	**1.00 (-)**	**1.43 (1.17, 1.75)**	**2.57 (2.03, 3.26)**	**<0.0001**	**61**	**6**
Age, region, hypertension	1.00 (-)	1.45 (1.18, 1.77)	2.62 (2.07, 3.32)	<0.0001	60	2
Age, region, diabetes	1.00 (-)	1.44 (1.17, 1.76)	2.60 (2.05, 3.29)	<0.0001	54	4
Fully adjusted	**1.00 (-)**	**1.20 (0.97, 1.47)**	**1.80 (1.41, 2.31)**	**<0.0001**	**22**	**64**
STROKE MORTALITY						
No. of stroke deaths	163	296	128			
Age, region (minimally adjusted)	**1.00 (-)**	**1.28 (1.06, 1.56)**	**1.97 (1.56, 2.49)**	**<0.0001**	**31**	**-**
Age, region, personal characteristics	**1.00 (-)**	**1.27 (1.05, 1.54)**	**1.91 (1.50, 2.43)**	**<0.0001**	**27**	**12**
Age, region, deprivation	1.00 (-)	1.27 (1.05, 1.54)	1.92 (1.52, 2.43)	<0.0001	28	8
Age, region, education	1.00 (-)	1.30 (1.07, 1.58)	2.00 (1.57, 2.53)	<0.0001	31	-2
Age, region, disability	1.00 (-)	1.26 (1.04, 1.53)	1.91 (1.51, 2.42)	<0.0001	28	9
Age, region, health behaviour factors	**1.00 (-)**	**1.21 (0.99, 1.46)**	**1.72 (1.35, 2.18)**	**<0.0001**	**19**	**38**
Age, region, smoking	1.00 (-)	1.23 (1.02, 1.50)	1.81 (1.42, 2.29)	<0.0001	23	25
Age, region, alcohol	1.00 (-)	1.27 (1.05, 1.54)	1.92 (1.52, 2.43)	<0.0001	29	7
Age, region, physical activity	1.00 (-)	1.25 (1.03, 1.52)	1.90 (1.50, 2.40)	<0.0001	28	11
Age, region, body mass index	1.00 (-)	1.30 (1.07, 1.57)	1.97 (1.56, 2.50)	<0.0001	31	-1
Age, region, physiological factors	**1.00 (-)**	**1.28 (1.06, 1.55)**	**1.96 (1.55, 2.47)**	**<0.0001**	**30**	**2**
Age, region, hypertension	1.00 (-)	1.28 (1.06, 1.55)	1.95 (1.55, 2.47)	<0.0001	30	2
Age, region, diabetes	1.00 (-)	1.28 (1.06, 1.56)	1.97 (1.56, 2.49)	<0.0001	31	0
Fully adjusted	**1.00 (-)**	**1.21 (1.00, 1.47)**	**1.71 (1.34, 2.18)**	**<0.001**	**18**	**41**

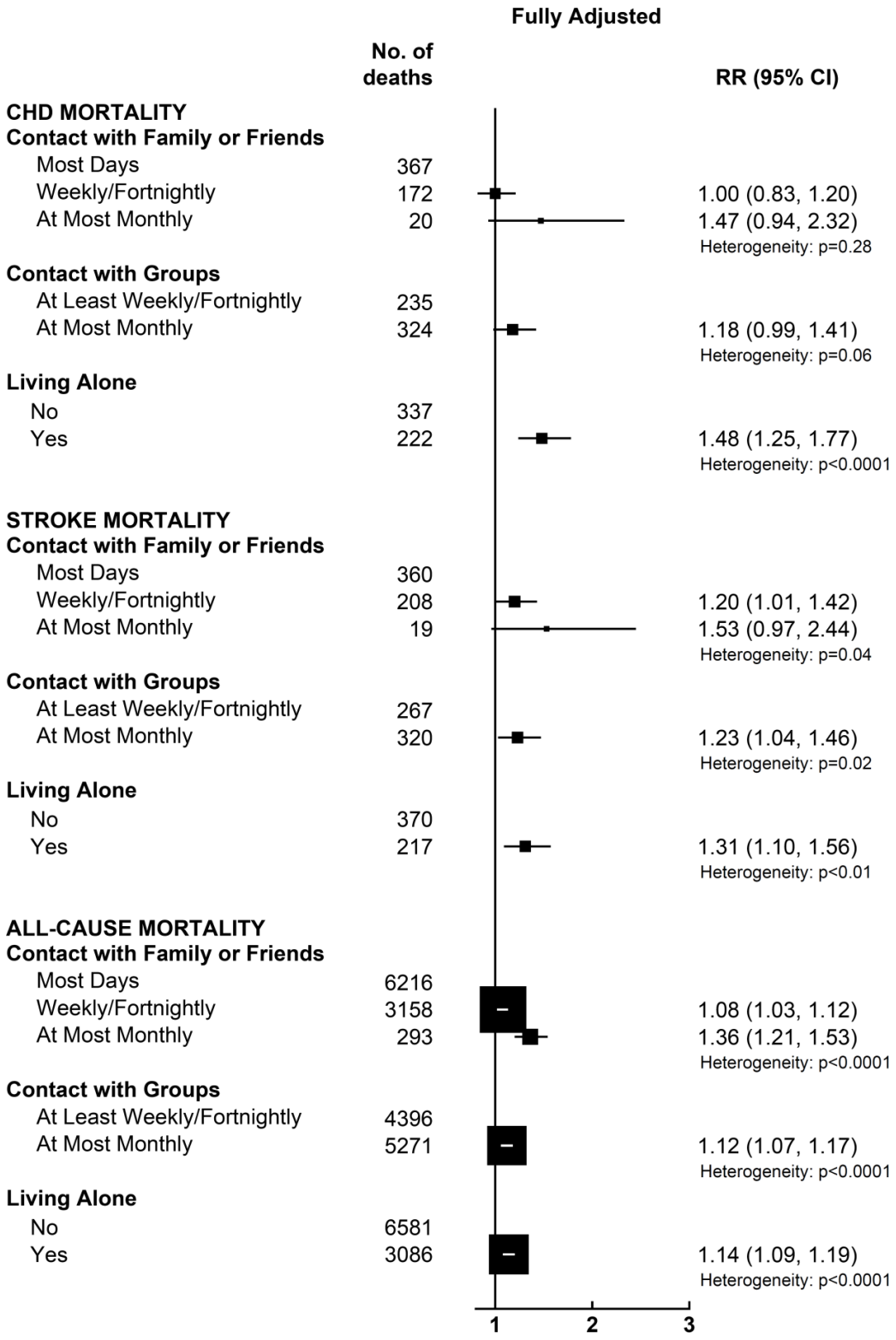


Figure 3.7. Fully adjusted RR and 95% CI for each social contact variable in relation to vascular disease and all-cause mortality. The size of the square boxes are inversely proportional to the standard error of the relative risk estimate.

3.3.5 Prospective Analyses of All-cause Mortality

Greater social isolation was associated with increased all-cause mortality in minimally and fully adjusted analyses (Figure 3.6). The minimally adjusted association was attenuated by 76% after adjustment for explanatory factors (Table 3.5). Health behaviours alone accounted for 66% of the observed attenuation in the LR χ^2 test statistic. After adjustment for explanatory factors, compared to the least isolated women, moderately isolated and the most isolated women had 11% and 32% greater all-cause mortality respectively (Table 3.5, Moderately Isolated: *RR*=1.11, *95% CI*: 1.06-1.16, Most Isolated: *RR*=1.32, *95% CI*: 1.24-1.40, $p<0.0001$). Each constituent measure of the social contact index was associated with all-cause mortality (Figure 3.7). Among them, frequency of contact with family or friends exhibited the strongest associations with at most monthly contact associated with a 36% increased risk of death (Figure 3.7, Weekly/Fortnightly contact: *RR*=1.08, *95% CI*: 1.03-1.12; At Most Monthly: *RR*=1.36, *95% CI*: 1.21-1.53, $p<0.0001$). However, like stroke mortality, lower variation was observed in estimates of association for living alone and contact with social groups in relation to all-cause mortality (Figure 3.7).

Table 3.5. RR and 95% CI for all-cause mortality by level of social isolation after adjustment for each group of covariates.

	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
ALL-CAUSE MORTALITY						
No. of deaths	2,886	4,976	1,805			
Age, region (minimally adjusted)	**1.00 (-)**	**1.27 (1.21, 1.33)**	**1.72 (1.62, 1.83)**	**<0.0001**	**314**	**-**
Age, region, personal characteristics	**1.00 (-)**	**1.20 (1.15, 1.26)**	**1.55 (1.46, 1.65)**	**<0.0001**	**198**	**37**
Age, region, deprivation	1.00 (-)	1.25 (1.19, 1.30)	1.65 (1.56, 1.76)	<0.0001	266	15
Age, region, education	1.00 (-)	1.24 (1.18, 1.30)	1.66 (1.56, 1.76)	<0.0001	263	16
Age, region, disability	1.00 (-)	1.24 (1.19, 1.30)	1.64 (1.55, 1.74)	<0.0001	261	17
Age, region, health behaviour factors	**1.00 (-)**	**1.14 (1.09, 1.19)**	**1.39 (1.30, 1.47)**	**<0.0001**	**108**	**66**
Age, region, smoking	1.00 (-)	1.19 (1.13, 1.24)	1.49 (1.40, 1.58)	<0.0001	162	48
Age, region, alcohol	1.00 (-)	1.26 (1.20, 1.31)	1.68 (1.58, 1.78)	<0.0001	284	10
Age, region, physical activity	1.00 (-)	1.24 (1.18, 1.30)	1.65 (1.56, 1.76)	<0.0001	267	15
Age, region, body mass index	1.00 (-)	1.26 (1.20, 1.32)	1.70 (1.60, 1.80)	<0.0001	298	5
Age, region, physiological factors	**1.00 (-)**	**1.26 (1.20, 1.32)**	**1.70 (1.60, 1.80)**	**<0.0001**	**299**	**5**
Age, region, hypertension	1.00 (-)	1.27 (1.21, 1.33)	1.71 (1.62, 1.82)	<0.0001	310	1
Age, region, diabetes	1.00 (-)	1.26 (1.21, 1.32)	1.70 (1.61, 1.81)	<0.0001	303	4
Fully adjusted	**1.00 (-)**	**1.11 (1.06, 1.16)**	**1.32 (1.24, 1.40)**	**<0.0001**	**75**	**76**

3.3.6 Age Differences

No statistically significant interaction was observed between social isolation and attained age in relation to each outcome (Table 3.6).

3.3.7 Sensitivity Analyses

Among the 10,876 incident CHD events, 2,738 were AMI events. Fully adjusted analyses found no statistically significant associations between social isolation and AMI incidence (Table A3.1, pp.226, Moderately Isolated: *RR*=0.99, *95% CI*: 0.91-1.08, Most Isolated: *RR*=1.10, *95% CI*: 0.97-1.23, *p*=0.20). Among the 6,281 first stroke events, 2,592 events were ischaemic strokes, and 1,033 events were haemorrhagic strokes. After full adjustment, associations between social isolation and any first stroke event were generally consistent with both stroke sub-types, however the association with haemorrhagic stroke became only marginally statistically significant (Table A3.1, Moderately Isolated: *RR*=1.00, *95% CI*: 0.87-1.15, Most Isolated: *RR*=1.25, *95% CI*: 1.04 -1.52, *p*=0.04). Among the 559 CHD deaths, 264 were due to AMI. Compared to CHD mortality, after full adjustment, weaker associations were observed between social isolation and AMI mortality (Table A3.1, Moderately Isolated: *RR*=1.06, *95% CI*: 0.78-1.42, Most Isolated: *RR*=1.61, *95% CI*: 1.12-2.30; *p*=0.02). Among the 587 stroke deaths, 45 were ischaemic strokes and 305 were haemorrhagic strokes. Few ischaemic stroke deaths were observed across levels of social isolation and while social isolation was associated with ischaemic stroke mortality there was large variation in the magnitude of associations. After full adjustment, the association between social isolation and haemorrhagic stroke mortality was consistent in magnitude with the association between social isolation and any stroke mortality (Table A3.1).

After excluding the first two years of follow-up, the association between social isolation and CHD incidence was consistent with associations from the main analysis but no longer statistically significant (Table A3.2, pp.227, Moderately Isolated: *RR*=1.00, *95% CI*: 0.95-1.06, Most Isolated: *RR*=1.06, *95% CI*: 0.99-1.14, *p*=0.22). After excluding two years of follow-up, associations between social isolation, stroke incidence, stroke mortality, and all-cause mortality were attenuated but remained statistically significant (Table A3.2). Associations between social isolation and CHD mortality increased in magnitude after excluding follow-up (Table A3.2, Moderately Isolated: *RR*=1.35, *95% CI*: 1.06-1.71, Most Isolated: *RR*=2.10, *95% CI*: 1.58-2.79, *p*<0.0001).

Estimates of association observed in analyses which mutually adjusted of each SCI constituent measure were virtually the same as the main results examining each SCI constituent measure without adjustment for the other constituent measures (Table A3.3, pp.228).

Table 3.6. RR and 95% CI of social isolation in relation to vascular disease incidence and mortality by attained age.

	< 75			≥ 75			
	No. of Cases	RR	(95% CI)	No. of Cases	RR	(95% CI)	p for interaction
CHD Incidence							
Least Isolated	2,511	1.00	(-)	1,217	1.00	(-)	0.07
Moderately Isolated	3,390	0.97	(0.92, 1.02)	2,101	1.05	(0.98, 1.13)	
Most Isolated	866	1.02	(0.94, 1.10)	791	1.16	(1.06, 1.27)	
Stroke Incidence							
Least Isolated	1,079	1.00	(-)	878	1.00	(-)	0.85
Moderately Isolated	1,653	1.10	(1.01, 1.19)	1,565	1.11	(1.02, 1.20)	
Most Isolated	473	1.25	(1.12, 1.40)	633	1.31	(1.18, 1.45)	
CHD Mortality							
Least Isolated	75	1.00	(-)	65	1.00	(-)	0.59
Moderately Isolated	135	1.07	(0.80, 1.44)	145	1.31	(0.97, 1.76)	
Most Isolated	64	1.75	(1.23, 2.49)	75	1.86	(1.31, 2.63)	
Stroke Mortality							
Least Isolated	88	1.00	(-)	75	1.00	(-)	0.79
Moderately Isolated	134	1.12	(0.85, 1.48)	162	1.29	(0.98, 1.70)	
Most Isolated	50	1.64	(1.14, 2.36)	78	1.77	(1.28, 2.47)	
All-Cause Mortality							
Least Isolated	1,666	1.00	(-)	1,220	1.00	(-)	0.07
Moderately Isolated	2,607	1.09	(1.02, 1.16)	2,369	1.13	(1.06, 1.22)	
Most Isolated	850	1.38	(1.27, 1.50)	955	1.27	(1.16, 1.38)	

3.4 Discussion

In this prospective analysis of 326,169 women without previous vascular disease, cancer, or fair/poor self-rated health at baseline, social isolation was associated with CHD and stroke incidence, CHD and stroke mortality, and all-cause mortality. After full adjustment, compared to the least isolated women, the most isolated women had approximately 7% greater CHD incidence, 28% greater stroke incidence, 80% greater CHD mortality, 71% greater stroke mortality, and 32% increased all-cause mortality. Adjustment for explanatory factors attenuated minimally adjusted associations between social isolation and vascular disease incidence and all-cause mortality to a greater degree than for associations with vascular disease mortality. Personal characteristics and health behaviours, in particular, may largely explain associations between social isolation and vascular disease incidence and all-cause mortality. The strength of associations between social isolation and vascular disease mortality represent compelling evidence of associations not fully explained by traditional explanatory factors. However, as with vascular disease incidence, measurement error in the factors adjusted for, or unmeasured explanatory factors may further account for the excess risk observed among the most isolated participants. Among the measures constituting social isolation, not one was associated with CHD incidence. Living alone tended to have the strongest associations with stroke incidence and each mortality outcome while associations with contact with family or friends and groups were generally weaker and mixed in terms of statistical significance. No statistically significant age-differences in the associations between social isolation, vascular disease, and mortality were observed.

Little Evidence of Association between Social Isolation and CHD Incidence

After applying thorough cohort exclusion criteria and fully adjusting analyses for explanatory factors, CHD and stroke incidence was 7% and 28% greater, respectively, among the most isolated women compared to the least isolated women. A recent meta-analysis of prospective studies found that people with poor social relationships (i.e. socially isolated or lonely) were approximately 30% more likely to develop CHD and stroke (Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). However, several studies included in this review did not exclude participants with underlying vascular disease or adjust for explanatory factors such as socioeconomic status and health behaviours. After studies with greater risk of bias were excluded, associations with CHD and stroke incidence were not statistically significant. Beyond those reviewed by Valtorta and colleagues (2016), several prospective studies using composite indices of social isolation have not found significant associations between social isolation and CHD incidence (Kawachi *et al.*,

1996; Barefoot *et al.*, 2005; Chang *et al.*, 2017; Hakulinen *et al.*, 2018; Valtorta, Kanaan, *et al.*, 2018).

The association between social isolation and CHD incidence observed in the current analysis may be explained by bias for a few reasons. First, adjustment for personal characteristics, health behaviours, and physiological factors almost completely attenuated the minimally association with CHD incidence. Thus, the remaining association may be due to residual confounding. Second, not one SCI constituent measure was associated with CHD incidence, making it difficult to understand exactly which aspect of social isolation could impact the development of CHD. Third, associations were not observed between social isolation and incident AMI thus challenging the hypothesis that social isolation promotes stress responses which lead to vascular inflammation and the development of AMI (Section 1.4.4). When these potential biases are considered alongside the findings of previous research, there remains little evidence of association between social isolation and the development of CHD.

Evidence of Weak Association between Social Isolation and Stroke Incidence

Few previous studies examined social isolation in relation to stroke incidence, and those that have present contrasting findings (Kawachi *et al.*, 1996; Hakulinen *et al.*, 2018) (Table 2.2). After adjusting for explanatory factors, the current analysis found that compared to the least isolated women, the moderately isolated and the most isolated women had 11% and 28% greater stroke incidence, respectively. This association was consistent for ischaemic and haemorrhagic stroke subtypes (Table A3.2, pp.227). The current analysis adds to the literature base with evidence of weak associations between social isolation and stroke incidence.

Kawachi and colleagues (1996) found that compared to the least isolated men, the most isolated men had increased risk of incident stroke (Most Isolated: *RR*=2.02, *95% CI*: 1.00-4.08, *p for trend*<0.01). A related study among American adults using the Lubben social network scale (i.e. a scale similar to the Berkman Syme social network index but includes functional dimensions of social isolation) found that compared to the least isolated adults, the most isolated had a 44% increased risk of incident stroke (*Small Social Network RR*=1.44, *95% CI*: 1.02-2.04, *p*=not reported; Nagayoshi *et al.*, 2014). Among UK Biobank participants, Hakulinen and colleagues (2018) did not find statistically significant associations between social isolation and stroke incidence after adjustment for a broader collection of covariates including depressive symptoms, blood pressure, and hand-grip strength (*RR*=1.06, *95% CI*: 0.96-1.19, *p*=0.26). However, a potentially important difference between the current analysis and Hakulinen and colleagues (2018) is the structure of the social isolation variables analysed.

While similar measures were used to ascertain social isolation in the current study, Hakulinen and colleagues (2018) grouped those with scores of zero and one as "not isolated" and those with scores of two and three as "isolated." This dichotomisation may have underestimated associations. People who were moderately isolated (i.e. score of one) may have increased the baseline hazard of the reference group thus making differences between isolated and non-isolated groups less stark.

The association between social isolation and stroke incidence observed in the current analysis could be explained by unmeasured confounding. Adjustment for explanatory factors attenuated minimally adjusted associations between social isolation and stroke incidence by 67%. While personal characteristics and health behaviours such as smoking explained much of the minimally adjusted association, it remains possible that other unmeasured confounding or mediating factors could explain the excess risk observed. Indeed, previous research offers little explanation for why social isolation would be associated with the development of stroke but not CHD. While these diseases share pathological similarities, such as atherosclerosis-related ischaemia, stroke can also be caused by blood clots and blood vessel ruptures in the brain. Factors that were under- or unaccounted for in the current analysis which may further explain the observed association may include clinically measured blood pressure and serum cholesterol levels (versus self-reported history of hypertension), and history of atrial fibrillation (Meschia *et al.*, 2014). Further research is needed to understand if and how social isolation is associated with stroke incidence.

Stronger Evidence of Associations between Social Isolation and Mortality

The current findings in relation to mortality outcomes are compelling and strengthen the evidence for associations between social isolation and vascular disease mortality. The most isolated women had 80% and 71% greater CHD and stroke mortality compared to the least isolated women, respectively. The magnitude of associations with vascular disease mortality observed in the current analysis tend to be stronger than those of previous studies. Past studies suggest that compared to less isolated adults, the most isolated have 24% to 76% greater CHD and CVD mortality (Kawachi *et al.*, 1996; Yang *et al.*, 2013; Chang *et al.*, 2017; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018). Heterogeneity in the methodological characteristics of these studies such as populations sampled, and the measurement of social isolation, explanatory factors, and outcomes may explain some of this variation in the strength of association. Compared to vascular disease incidence, the explanatory factors adjusted for in the current analysis explained lesser proportions of the minimally adjusted associations between social isolation and CHD and stroke mortality (64% and 41% attenuation of the LR χ^2 test statistic

respectively). It thus remains possible that unmeasured confounding or mediating factors, such as help-seeking behaviours, could further explain the associations observed.

Given the time-sensitive nature of CHD and stroke prognosis and that living alone can impede or delay help-seeking behaviour (e.g. calling emergency medical services), the associations between social isolation and vascular disease mortality could be in part explained by delays in seeking health care after acute vascular disease events (DeVon *et al.*, 2010; Fonarow *et al.*, 2011; Canvin *et al.*, 2018). Living with a partner or frequent contact with relatives and friends may also assist with post-hospitalization recovery, chronic disease management, or provide emotional support (Udell *et al.*, 2012; Berkman and Krishna, 2014; Floud *et al.*, 2014). The role of social support and help-seeking is indirectly supported by evidence from the current analysis which suggests that only those who are within the most isolated groups may be at increased risk of death. Moderate isolation tended to have weaker and statistically non-significant associations with vascular disease mortality compared to associations among the most isolated. Also, when considering the constituent measures of the SCI, living alone was an experience shared by approximately 90% of women in the most isolated group and tended to have the strongest associations with CHD and stroke mortality. Living alone was also highly correlated with marital status reported at the 9-year re-survey. Among the constituent measures of social isolation, previous studies more consistently find the strongest associations between being married or living with a partner and mortality outcomes (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Pantell *et al.*, 2013; Chang *et al.*, 2017; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018). Previous analyses of the Million Women Study cohort have also found that compared to unmarried or unpartnered women, those who were married or living with a partner had similar risk of developing CHD but lower risk of dying from CHD (Floud *et al.*, 2014). Further research is needed to examine the role of functional dimensions of isolation such as social support and behaviours such as timely help-seeking in explaining associations between social isolation and vascular disease mortality.

It should be noted that the vascular disease mortality outcomes examined in the current analysis were slightly different from previous studies which examined fatal incident AMI (Kawachi *et al.*, 1996; Chang *et al.*, 2017). These previous analyses censored individuals at the time of their first non-fatal vascular disease event during the observation period. As discussed in Section 1.4.5, for consistency with previous studies focused on mortality outcomes, analyses of mortality in this thesis did not censor individuals with incident non-fatal vascular disease during the observation period (Yang *et al.*, 2013; Elovainio *et al.*, 2017; Alcaraz *et al.*, 2018). As a result, during the observation period of the current analysis, some participants may have

suffered a non-fatal incident event, then have been treated, and then at another time experienced a fatal event. Some participants' baseline hazard of vascular disease mortality may thus have changed to a greater extent than others during the observation period. Given that when studying older adults it is possible for baseline hazard to evolve over several years of observation, the mortality outcomes used in the current analysis may make the results more generalizable.

For all-cause mortality, the results of the current analysis were generally consistent with previous research. After adjustment for explanatory factors, the moderately isolated and most isolated women had 11% and 32% greater all-cause mortality than the least isolated women, respectively. In their meta-analysis of 52 studies, Holt-Lunstad and colleagues (2015) estimated that compared to those who were less isolated, the most isolated had 30% greater likelihood of death from any cause (*OR*=1.30, *95% CI*:1.16-1.46). Recent prospective analyses of the English Longitudinal Study of Ageing and UK Biobank cohorts which examine indices similar to the SCI also reported 26% and 30% greater mortality among the most isolated compared to less isolated participants (Steptoe *et al.*, 2013; Elovainio *et al.*, 2017; Smith *et al.*, 2018). Previous prospective studies examining adapted Berkman Syme social network indices with four levels of social isolation tended to observe stronger but less consistent associations (Figure 2.3) (Kawachi *et al.*, 1996; Berkman *et al.*, 2004; Pantell *et al.*, 2013; Yang *et al.*, 2013; Alcaraz *et al.*, 2018). However, these studies tend to be smaller than the current analysis and previous UK Biobank analyses. Lower case frequencies distributed across four categories of isolation could lead to overestimation of the strength of association (Greenland *et al.*, 2016). All-cause mortality is a useful general indicator of population health but it measures an abundance of causes of death which may vary in their association with social isolation and potentially confounding factors. Given that in the current analysis adjustment for explanatory factors attenuated the minimally adjusted association by 76%, unmeasured confounding may at least in-part explain the excess mortality observed. However, like vascular disease mortality, delays in seeking care may be a relevant explanatory pathway for other sudden-onset conditions which all-cause mortality would measure.

Age-Differences

Personal characteristics such as age are believed to modify associations between social isolation and health. As summarised in Section 2.8, previous prospective studies which additionally examined age-differences in associations between social isolation, vascular disease, and mortality tended to crudely compare associations across subgroups defined by age at baseline. Not one of these studies formally tested whether any interaction between age and social isolation was statistically significant. In the current analysis, with the exception of

associations with all-cause mortality, higher magnitude associations tended to be observed among isolated women who were at least 75 years old compared to those who were under 75 years old. These differences were not meaningful however as no statistically significant interaction between social isolation and age was observed for each outcome. Despite evidence suggesting that older adults are at greater risk of social isolation and having more limited access to emotional support than younger adults, the current analysis suggests that these factors may have little bearing on if and how social isolation affects vascular disease and mortality (Wilson *et al.*, 2010; Marit *et al.*, 2012; Nicholson, 2012; Shor *et al.*, 2013). The current analysis suggests that age may be more appropriately conceptualised as a confounder of associations between social isolation, vascular disease, and mortality. It should be noted that the mean age of the Million Women Study 12-year re-survey cohort was 68 years old (Table 3.2). The under 75 group did not have a large number of adults of working age and those who live with dependents. Therefore, the current analysis may have underestimated age-differences across these sub-groups. Further research within younger cohorts (e.g. 40 years old and older) presents an opportunity to test the replicability of associations observed within this older cohort.

Strengths and Limitations

The key strengths and novel aspects of the current analysis are the large sample size, and the thorough approach taken to mitigate reverse causation, to account for confounding bias, and to examine the role of potential explanatory factors. This analysis improves upon similar studies among large UK cohorts as it excluded women reporting poor or fair self-rated health in addition to those diagnosed with vascular disease or cancer (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Furthermore, this analysis more closely examined and compared associations across constituent measures of social isolation and each outcome. The current analysis has limitations which merit discussion. Social isolation is a socially undesirable experience which carries a degree of stigma. The associations observed may be underestimated due to over-reporting of social contact frequency. However, measurement error of social isolation is not believed to be a concern given that the proportion of people represented in the most isolated category is consistent with previous studies among older adults in the UK (Beach and Bamford, 2014; Elovainio *et al.*, 2017). Also, given that social isolation was measured at one point in time, it was not possible to ascertain the duration of exposure to social isolation. Longitudinal measurements of exposures are useful for examining conditions such as vascular disease which develop over many years. Despite this, the current findings are believed to be robust as social isolation levels among older adults tend to remain stable over time (Valtorta, Kanaan, *et al.*,

2018). Finally, measurement error in the covariates adjusted for may also contribute some degree of under or over estimation of associations.

3.5 Conclusion and Future Directions

The current analysis was among the first and largest to examine CHD and stroke incidence and mortality within a generally healthy population of community-based women. After accounting for reverse causation and explanatory factors, the most isolated women tended to have similar risk of developing CHD as the least isolated women. However, there remained evidence that socially isolated women were at greater risk of incident stroke and death from CHD, stroke, and any cause. These fully adjusted associations did not vary across those who were under or at least 75 years old. As hypothesised in Section 2.7, the current analysis suggests that the health behaviours of more isolated women explain a considerable proportion of their increased risk of vascular disease and mortality. However, further research is needed to better understand what additional factors may, at least in-part, explain the strong associations between social isolation and vascular disease mortality and all-cause mortality. Among these factors are functional dimensions of social isolation which will be investigated further in Chapter 6. The next chapter of this thesis will examine the reproducibility of these findings within a mixed gender sample of 500,000 middle-aged and older adults from the UK.

4 Social Isolation in Relation to Vascular Disease Incidence and Mortality within the UK Biobank

4.1 Introduction

4.1.1 Background

Using data from the Million Women Study, Chapter 3 addressed many of the methodological limitations of previous research. The analysis found that within a generally healthy population of women, social isolation was more strongly associated with vascular disease mortality than with vascular disease incidence. The Million Women Study 12-year re-survey cohort was suitable for studying social isolation among older women. However, given that most participants were older than state pension age (60 years old in 2009; 65 years old as of 2010), the working and social lives (i.e. social interaction with colleagues, participation in social activities, household occupancy) of this cohort was likely to be different to that of middle-aged adults (Thurley and McInnes, 2018). While the Million Women Study analyses did not find statistically significant differences in associations between those who were younger and older than 75 years, there were too few participants to compare associations among those of working age (e.g. less than 65 years old). At approximately the same time as the Million Women Study 12-year re-survey, the UK Biobank collected data on over 500,000 women and men aged 40 to 69 years old. The UK Biobank data provided an opportunity to examine social isolation, vascular disease, and mortality within a younger, mixed-gender sample of adults living in the UK.

Two previous studies have examined social isolation in relation to vascular disease incidence and CVD mortality within the UK Biobank cohort (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). These studies used an index of social contact frequency and living alone similar to the social contact index (SCI). However, scores were dichotomised to compare the most isolated participants to those who were less isolated. Approximately 9.0% (*approximately n*=42,500) of participants within the UK Biobank were socially isolated according to this measure (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Among 479,054 UK Biobank participants (*mean follow-up*= 7.1 years), Hakulinen and colleagues (2018) found a minimally adjusted association between social isolation and incident AMI and stroke. However, these associations were no longer statistically significant after adjusting for explanatory factors (Most Isolated

compared to Less Isolated: AMI, *fully adjusted RR*=1.07, *95% CI*: 0.99-1.16, *n*=5,731; Stroke, *fully adjusted RR*=1.06, *95% CI*: 0.96-1.19, *n*=3,471) (Hakulinen *et al.*, 2018). Within a smaller sub-sample (*N*=466,901, *mean follow-up*= 6.5 years), Elovainio and colleagues (2017) found that compared to less isolated participants, those who were isolated had 24% greater risk of death from CVD (*fully adjusted RR*=1.24, *95% CI:* 1.17-1.31, *n*=2,032) and 26% increased risk of death from any cause (*fully adjusted RR*=1.26, *95% CI*: 1.20-1.33, *n*=11,593). Again the adjustment for explanatory factors, particularly personal characteristics and health behaviours explained the greatest degree of attenuation in the minimally adjusted associations (Elovainio *et al.*, 2017).

The potential for reverse causation remains an important limitation of these studies because while people with pre-existing vascular disease were excluded and the presence of chronic disease at baseline was adjusted for, participants were not excluded based on self-rated health. As discussed in Section 2.1 and 2.10, fair or poor self-rated health could indicate sub-clinical vascular disease which may cause people to become more socially isolated. In the presence of reverse causation, the direction of any associations becomes obscured, and associations can be overestimated as individuals with higher baseline risk will be overrepresented in the more isolated categories (Section 2.10). Another limitation of Elovainio and colleagues (2017) is that their CVD mortality outcome aggregated CHD deaths and stroke deaths. It thus remains unclear whether differences exist in the strength of associations between social isolation and mortality due to distinct vascular diseases like CHD and stroke.

As discussed in Section 1.4.2, social isolation is believed to affect women and men differently due in-part to differing social expectations for giving and receiving social support. To assess gender-differences, previous studies examining social isolation in relation to vascular disease and mortality tended to crudely compare estimates of association across gender sub-groups (Section 2.9). Only two studies formally assessed the statistical significance of any interaction between gender and social isolation (Steptoe *et al.*, 2013; Alcaraz *et al.*, 2018). Overall, previous studies present mixed findings in terms of the magnitude of associations within and across gender subgroups, as well as in the statistical significance of any effect modification by gender (Section 2.9). Further research among large prospective cohorts is warranted in order to accurately estimate any associations within gender subgroups and to test for statistical interaction between social isolation and gender.

4.1.2 Objectives of Chapter

The purpose of Chapter 4 is to understand if and how social isolation influences vascular disease incidence, vascular disease mortality, and all-cause mortality within the UK Biobank cohort and to compare any associations with those found in the Million Women Study analysis. This research will address three objectives.

1. To examine whether social isolation is associated with vascular disease incidence, vascular disease mortality, and all-cause mortality, while:
    - minimising bias due to reverse causation;
    - examining how much of any association is explained by personal characteristics, health behaviours, and physiological factors.
2. To examine associations between individual measures of social isolation such as, frequency of contact with family or friends, contact with social groups, and living alone, and vascular disease incidence, vascular disease mortality, and all-cause mortality.
3. To examine whether any associations between social isolation and the aforementioned outcomes vary by gender.

4.2 Methods

4.2.1 Study Design and Participants

The UK Biobank resource is a large prospective cohort study of 502,543 UK adults. Approximately 9.2 million adults aged 40 to 69 years old, who were registered with the NHS, and living within reasonable proximity (40 kilometres) to one of 22 UK Biobank assessment centres in England, Scotland, and Wales were invited via mail to participate (Fry *et al.*, 2017). Between 2006 and 2010, 503,317 women and men consented to and completed the baseline assessment representing a 5.5% response rate (Fry *et al.*, 2017). Compared to the general UK population targeted for recruitment, participants tended to be older, to live in less deprived neighbourhoods, and were less likely to be obese, to smoke, or consume alcohol on a daily basis (Fry *et al.*, 2017). Baseline assessments involved a self-administered electronic touchscreen questionnaire, nurse-led verbal interview, physical measurements, and urine and blood sampling (UK Biobank, 2007). To ascertain health outcomes the UK Biobank is linked to NHS Digital hospital records, primary care records, and cancer and death registry databases (Sudlow *et al.*, 2015). Ethics approval for primary data collection and subsequent

analysis was granted under a Human Tissue Authority (HTA) license by the Northwest Multicentre Research Ethics Committee (16/NW/0274) (UK Biobank, 2007). Further details related to the study protocol and specific data collected can be accessed online (UK Biobank, 2007, 2018). This analysis was approved by the UK Biobank Coordinating Centre (Application ID: 28946).

4.2.2 Social Isolation

The UK Biobank touchscreen questionnaire included questions related to frequency of in-person contact with family, friends, or groups, as well as household occupancy (See Box A-C, Figure 4.1 for the questions as they appear on the questionnaire). This frequency of contact with family or friends question refers to in-person contact whereas in the Million Women Study, this question also included email or telephone contact. In order to maintain consistency with the Million Women Study analysis, the categories "2-4 times a week," and "about once a week" were aggregated to derive a "weekly" category, and "about once a month," "once every few months," and "No friends/family outside household" were aggregated for the "at most monthly" category. Therefore, the analysis compared "almost daily," "weekly," and "at most monthly" categories. To derive the frequency of group contact variable, individuals who selected at least one of the listed group activities (Box B, Figure 4.1) were categorised as having "at least weekly" contact with groups, whereas those who selected "none of the above" were categorised as having "less than weekly" contact with groups. To derive the living alone variable, all participants who entered "1" for the household occupancy question were categorised as living alone (Box C, Figure 4.1).

As presented in Figure 4.2 and previously described in Section 3.2.2, these social contact and living alone variables were aggregated to create a summative social contact index (SCI) score variable which was used to ascertain levels of social isolation. Participants were given a score of one if they had social contact with family or friends "at most monthly," if they did not have weekly contact with groups, or if they were living alone. These scores were summed to calculate the overall SCI which ranged from zero (least isolated) to three (most isolated). Participants with scores of two and three were grouped into the most isolated category.

4.2.3 Outcomes

Using the procedures described in Chapter 3 (Section 3.2.3), the same five outcomes were examined in this analysis. They are the following: time to first CHD event, time to first stroke event, time to CHD death, time to stroke death, and time to death from any cause.

A. Frequency of contact with family or friends

How often do you visit friends or family or have them visit you?
☐ Almost daily ☐ 2-4 times a week ☐ About once a week ☐ About once a month ☐ Once every few months ☐ Never or almost never ☐ No friends/family outside household ☐ Do not know ☐ Prefer not to answer

B. Frequency of contact with groups

Which of the following do you attend once a week or more often? (You can select more than one)
☐ Sports club or gym ☐ Pub or social club ☐ Religious group ☐ Adult education class ☐ Other group activity ☐ None of the above ☐ Prefer not to answer

C. Living alone

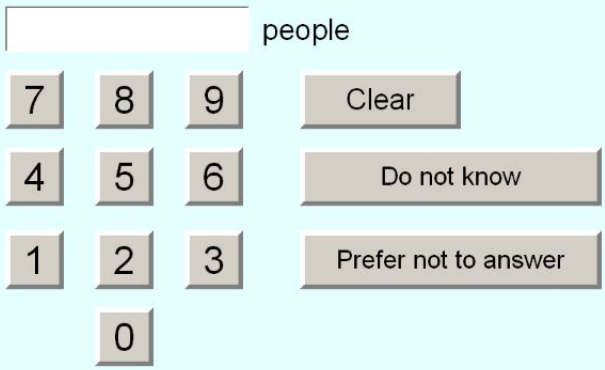
Including yourself, how many people are living together in your household? (Include those who usually live in the house such as students living away from home during term, partners in the armed forces or professions such as pilots)


Figure 4.1. Social relationships related questions (A-C) upon which social contact and living alone variables were derived.

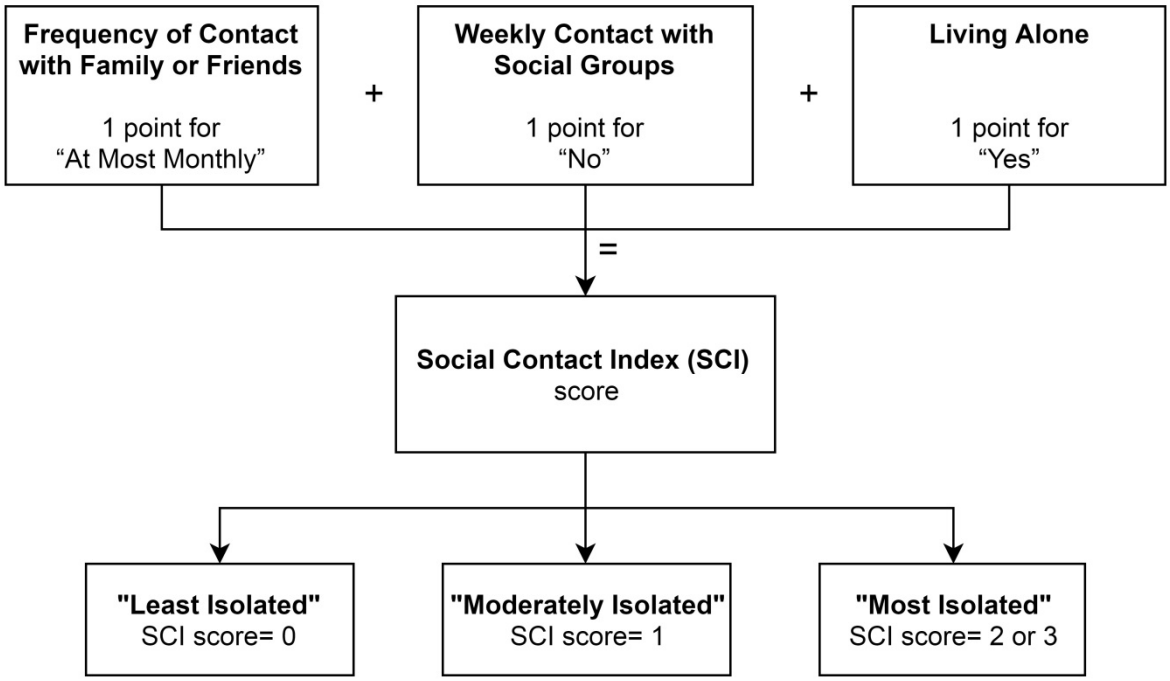


Figure 4.2. Derivation of the social contact index within the UK Biobank cohort.

4.2.4 Explanatory Factors

The UK Biobank touchscreen questionnaire was used to measure personal characteristics, health behaviours and physiological factors. These explanatory factors and their categories are shown in Table 4.1. To maintain consistency with the Million Women Study analysis, the current analysis examined similar explanatory factors as in Chapter 3 and used the same model to visualize the hypothesised relationships between social isolation, these factors, and the outcomes (Figure 4.3). Personal characteristics (age, gender, region of recruitment, socioeconomic deprivation, education, disability) were conceptualised as potential confounders. It should be noted that gender was also examined as modifier of associations. Health behavioural factors (physical activity, smoking, alcohol intake, body mass index [BMI]), and physiological factors (self-reported diagnoses of hypertension and diabetes, and prescription of cholesterol lowering medication) were conceptualised as potential mediators. Within the UK Biobank, some variables such as blood pressure were measured using multiple methods (e.g. self-reported history of hypertension and manual blood pressure measurement at baseline). The explanatory factors included in the current analysis were selected for having near complete observations, and their structure was determined to maintain consistency with the Million Women Study analysis. Several considerations about the UK Biobank variables and how they compare to the Million Women Study analysis variables are worth noting.

Table 4.1. Description of variables adjusted for in Cox regression analyses.

Explanatory Factor Group	Explanatory Factor	Values/Categories
Personal Characteristics	Age	Date of birth to date of censoring
	Gender	Female, Male
	Region of Recruitment	East Anglia, East midlands, London, North east, North west, South east, South west, Wales, West midlands, Yorkshire & Humber
	Socioeconomic deprivation (Townsend deprivation index)	Least deprived Moderately deprived Most deprived
	Educational attainment	Tertiary Secondary Less than secondary
	Receipt of disability or mobility allowance	Yes, No
Health Behavioural Factors	Frequency of strenuous or moderate exercise	Rarely/never Sometimes (1-3 days/week) Most Days (4-6 days/week) Daily
	Smoking status	Current Never Former
	Alcohol intake	0 days per week 1-4 days per week ≥5 days per week
	Body Mass Index	Desirable (<25 kg/m^2) Overweight (25-29.9 kg/m^2) Obese (≥30 kg/m^2)
Physiological Factors	Self-reported history of hypertension	Yes, No
	Self-reported history of diabetes	Yes, No
	Taking cholesterol lowering medication	Yes, No

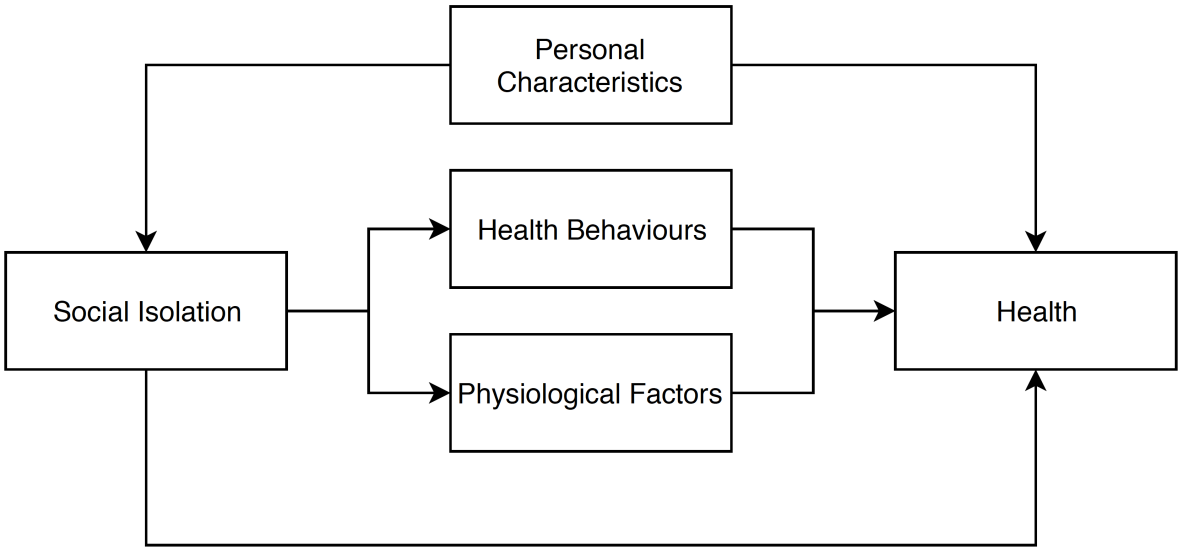


Figure 4.3. Analysis-specific conceptualisation of factors potentially modifying, confounding, and mediating associations between social isolation, vascular disease and mortality.

Biological sex recorded at baseline from NHS primary care records was used as a proxy for participant gender. Within the touchscreen questionnaire, participants are able to confirm or amend their sex when they complete the touchscreen questionnaire, but self-identified gender was not collected. Region of recruitment is the European Electoral Region that each participant's assessment centre was located. These regions align closely with the Million Women Study recruitment regions. Unlike the Million Women Study, the UK Biobank did not assess multiple dimensions of functional limitation and disability. Therefore, a disability score variable using the Washington Group criteria could not be calculated. In the current analysis, disability was ascertained based on receipt of state disability or mobility benefits (e.g. attendance or disability living allowance, or blue badge). At the time this analysis was conducted, IMD 2010 data was not available for UK Biobank participants. Therefore, the Townsend index was used as a proxy for individual-level socioeconomic deprivation.

The Townsend index is commonly used in UK health research as a proxy indicator of individual-level socioeconomic position (Adams, Ryan and White, 2005; Shavers, 2007). Townsend scores are calculated based on the proportion of households within enumeration districts (i.e. geographic areas of on average 200 households or approximately 450 people) that do not own a car, are not owner occupied, are overcrowded (i.e. greater than one person per room), and the proportion of residents that are economically active but unemployed (Townsend, Beattie and Phillimore, 1988; Office of National Statistics, 2017). The UK Biobank derived Townsend scores based on data from the 2001 census which was linked using participant postcode at the time they attended the UK Biobank assessment centre. Within the Million Women Study analysis, the Townsend index and IMD 2010 were moderately correlated (ρ=0.42), and previous research suggests that they are comparably correlated with morbidity and mortality (Jordan, Roderick and Martin, 2004; McLennan *et al.*, 2011).

Similar questions about health behaviours and physiological factors were asked in the UK Biobank touchscreen questionnaire and the Million Women Study 12-year re-survey. There are however two differences in the explanatory factors examined worth noting. First, UK Biobank participants were asked to report the number of days per week they consumed alcohol in the past year, versus, the number of units consumed per week as in the Million Women Study. The categories used for alcohol intake were chosen to compare those who drink approximately daily and less than daily with those who never or formerly consumed alcohol. Secondly, self-reported prescription of cholesterol medications was included as a physiological explanatory factor in the current analysis to adjust for exposure to high serum cholesterol levels before medication

was prescribed, and potential residual hypercholesterolemia after prescription. The Million Women Study analysis did not adjust for hypercholesterolemia because information related to self-reported diagnosis, serum cholesterol, or cholesterol medications were not available for the 12-year resurvey cohort.

4.2.5 Statistical Analyses

Similar cohort exclusion criteria as Chapter 3 (Section 3.2.5) were used to ensure the results from this analysis were comparable. In total, 502,543 adults from the UK were considered for this analysis. Participants were then excluded if they met the following criteria: were recruited from Scotland (*n*=35,845); had previous hospital admissions for CHD or stroke (*n*=21,726); had previous cancer registrations (*n*=29,647); self-reported a previous diagnosis of MI, angina, stroke, or cancer (*n*=20,159); if they reported fair or poor self-rated health (*n*=92,195); or had missing data related to social contact or living alone (*n*=6,058).

Participants were observed from the time of survey completion to time of event, death, loss to follow-up or 31 January 2016. Cox regression was used to estimate relative risks (RR) and 95% confidence intervals (CI). To adjust for age, all models used attained age (i.e. date of birth to date of event or censored) as the underlying time variable. Minimally adjusted models additionally stratified by gender and adjusted for recruitment region as a covariate. Further adjustment was made for additional personal characteristics, health behavioural factors, and physiological factors. Missing data for the covariates (<2.0% for all variables) were assigned to a separate category. To examine the assumption of proportional hazards, log-log plots and Schoenfeld residuals were assessed. The assumption was found to be reasonable.

For objectives one and two, differences in RRs across levels of each exposure were tested for all models using the likelihood ratio (LR) test of heterogeneity. To address objective one, the LR χ^2 attenuation method described in Section 3.2.5 was again used to assess the extent to which each covariate and group of covariates explained associations between social isolation and each outcome. To address objective two, fully adjusted analyses were conducted for each SCI score constituent variable in relation to each outcome. To address objective three, gender differences in associations between social isolation and each outcome were assessed using fully adjusted sub-group analyses. Differences between women and men in these associations were assessed using the LR test of interaction. To further investigate reverse causation bias within the results, sensitivity analyses examined social isolation in relation to each outcome after excluding the first two years of follow-up.

All analyses were conducted using Stata 15.1 (StataCorp College Station, TX, USA).

4.3 Results

In total, 296,913 participants without previous vascular disease, cancer, or fair/poor self-rated health at baseline were included in the analysis. Characteristics of this cohort are presented in Table 4.2. During a mean follow-up period of 6.9 years (*SD*: 0.9), there were 7,028 incident CHD events, 2,287 incident stroke events, 440 CHD deaths, 203 stroke deaths, and 4,694 deaths from any cause. Participants were on average 56 years old (*SD*: 8.1) and 55.8% identified as female. Approximately 12.6% of participants were within the most isolated SCI score category. Under a quarter of participants reported living alone (16.6%) and having at most monthly contact with relatives or friends (21.6%). Over a quarter of participants reported less than weekly contact with groups (27.8%). The most isolated participants tended to be more deprived, less educated, current smokers, have higher BMI, and be less physically active than the least isolated women. However, they tended to consume alcohol less frequently and exhibited only marginal differences according to self-reported diagnoses of hypertension and diabetes, prescription of cholesterol medications, and receipt of disability or mobility allowance.

The UK Biobank (UKB) cohort was on average 10 years younger than the Million Women Study (MWS) cohort and using the Townsend deprivation index had a greater proportion of people living in the most deprived neighbourhoods (UKB: 29.0%; MWS: 13.5%). Unlike the Million Women Study, which assessed frequency of *any* social contact (i.e. phone, email, in-person), the UK Biobank assessed frequency of in-person contact with family or friends. It is thus difficult to compare frequency of contact with family or friends across cohorts (At most monthly contact, UKB: 21.6%; MWS: 2.0%). Compared to the Million Women Study cohort, UK Biobank participants tended to have more frequent contact with groups (Less than Weekly, UKB: 27.8%; At most monthly contact, MWS: 48.1%), and fewer lived alone (UKB: 16.6%; MWS: 23.6%). As evidence of differences in the working lives and living arrangements of participants in these cohorts, post-hoc descriptive analyses found that a greater proportion of UK Biobank participants were currently working (UK Biobank: 62.7% [*n*=186,376], Million Women Study: 17.0% [*n*=55,830]), lived in multi-occupant households (Mean household occupants, UK Biobank: 2.5 [*SD*=1.3], Million Women Study: 1.9 [*SD*=0.7], and lived in urban areas (Proportion of participants living in jurisdictions with at least 10,000 residents, UK Biobank: 84.5% [*n*=248,446], Million Women Study: 69.7% [*n*=227,306]).

There were small differences in the proportion of current smokers (UKB: 8.3%; MWS: 5.5%), physically inactive individuals (UKB: 9.7%; MWS: 7.2%), and those with BMI greater or equal to 30 kg/m^2 (UKB: 18.6%; MWS: 16.9%). In both cohorts, approximately 20.0% of

participants reported previous diagnoses of hypertension and 3.0% reported previous diagnoses of diabetes. Due to differences in the response categories for educational attainment, disability, and alcohol intake, it is difficult to compare the cohorts on these characteristics. However, the proportions of participants with these characteristics changed in a consistent pattern across levels of social isolation. Compared to the least isolated participants, the most isolated tended to have lower educational attainment, greater disability, less frequent alcohol consumption (Table 3.2 and 4.2).

Table 4.2. Baseline characteristics of participants by level of social isolation and details of follow-up.

Characteristics	Overall N= 296,913	Social Contact Index score 0 Least Isolated, n=141,426 (47.6%)	1 Moderately Isolated, n=117,879 (39.7%)	2 Most Isolated, n=37,608 (12.6%)
Mean Age (SD)	56.0 (8.1)	56.2 (8.1)	55.9 (8.1)	55.5 (7.9)
Female (%)	55.8	56.9	56.0	50.9
Most deprived tertile (%)	29.0	24.4	31.2	39.4
Less than secondary education (%)	13.3	12.4	14.0	14.7
Receipt of disability/mobility allowance (%)	1.7	1.4	1.8	2.2
At most monthly social contact with family or friends (%)	21.6	0.0	30.9	74.2
Less than weekly contact with groups (%)	27.8	0.0	43.2	83.6
Living alone (%)	16.6	0.0	25.9	50.1
Current smoker (%)	8.3	6.8	8.9	12.0
Alcohol consumed ≥5 days per week (%)	21.7	22.5	21.1	20.7
Rarely/never, exercise (%)	9.7	6.7	11.2	15.9
BMI ≥30 kg/m^2 (%)	18.6	17.9	19.0	20.1
History of hypertension (%)	20.3	20.1	20.3	20.8
History of diabetes (%)	2.6	2.4	2.7	3.2
Taking cholesterol medication (%)	10.6	10.9	10.4	10.6
Follow-up for Vascular Disease Incidence and Mortality Outcomes				
Incident CHD events (n)	7,028	3,428	2,709	891
Mean years of follow-up per person (SD)	6.8(1.1)	6.8(1.1)	6.8(1.1)	6.8(1.1)
Person-years (1000s)	2020	964	802	255
Incident Stroke events (n)	2,287	1,034	908	345
Mean years of follow-up per person (SD)	6.9(1.0)	6.9(0.9)	6.9(1.0)	6.8(1.0)
Person-years (1000s)	2037	972	808	256
CHD deaths (n)	440	167	190	83
Mean years of follow-up per person (SD)	6.9(0.9)	6.9(0.9)	6.9(0.9)	6.8(0.9)
Person-years (1000s)	2044	975	811	257
Stroke deaths (n)	203	79	79	45
Mean years of follow-up per person (SD)	6.9(0.9)	6.9(0.9)	6.9(0.9)	6.8(0.9)
Person-years (1000s)	2044	975	811	257
All-cause deaths (n)	4,694	2,003	1,918	773
Mean years of follow-up per person (SD)	6.9(0.9)	6.9(0.9)	6.9(0.9)	6.8(0.9)
Person-years (1000s)	2044	975	811	257

Note: Percentages calculated based on women with complete information for each specific variable.

4.3.1 Prospective Analyses of CHD Incidence

Social isolation was not associated with CHD incidence in minimally nor fully adjusted analyses (Figure 4.4). For this reason, attenuation in the LR χ^2 test statistic was not assessed. While no associations were observed among any of the SCI score constituent measures, it should be noted that the association between frequency of contact with family or friends and CHD incidence was marginally statistically non-significant (p=0.05; Figure 4.5).

4.3.2 Prospective Analyses of Stroke Incidence

After minimal adjustment for age, gender, and region of recruitment, greater social isolation was associated with increased stroke incidence (Figure 4.4). This association was attenuated after further adjustment for all personal characteristics, health behavioural factors, and physiological factors (Figure 4.4, Table 4.3). After full adjustment, the most isolated participants had 23% greater stroke incidence than the least isolated participants (Figure 4.4, Moderately Isolated: *RR*=1.05, *95% CI*: 0.96-1.15; Most Isolated: *RR*=1.23, *95% CI*: 1.09-1.40, p<0.01). Personal characteristics and health behavioural factors, particularly deprivation and smoking, explained the greatest proportions of the minimally adjusted association (Table 4.3). The minimally adjusted association attenuated by 8% after adjusting for physiological factors. Overall, the association attenuated by 56% after full adjustment. Among the SCI score constituent measures, living alone had the strongest association with incident stroke (Figure 4.5, *RR*=1.18, *95% CI*: 1.06-1.31, p<0.01). Weekly contact with family or friends was associated with 12% decreased risk of incident stroke compared to almost daily contact, however, no association was observed for at most monthly contact (Figure 4.5, Weekly: *RR*=0.88, *95% CI*: 0.78-0.99; At Most Monthly: *RR*=1.04, *95% CI*: 0.90-1.21; p<0.01). Frequency of contact with groups was not associated with stroke incidence (Figure 4.5).

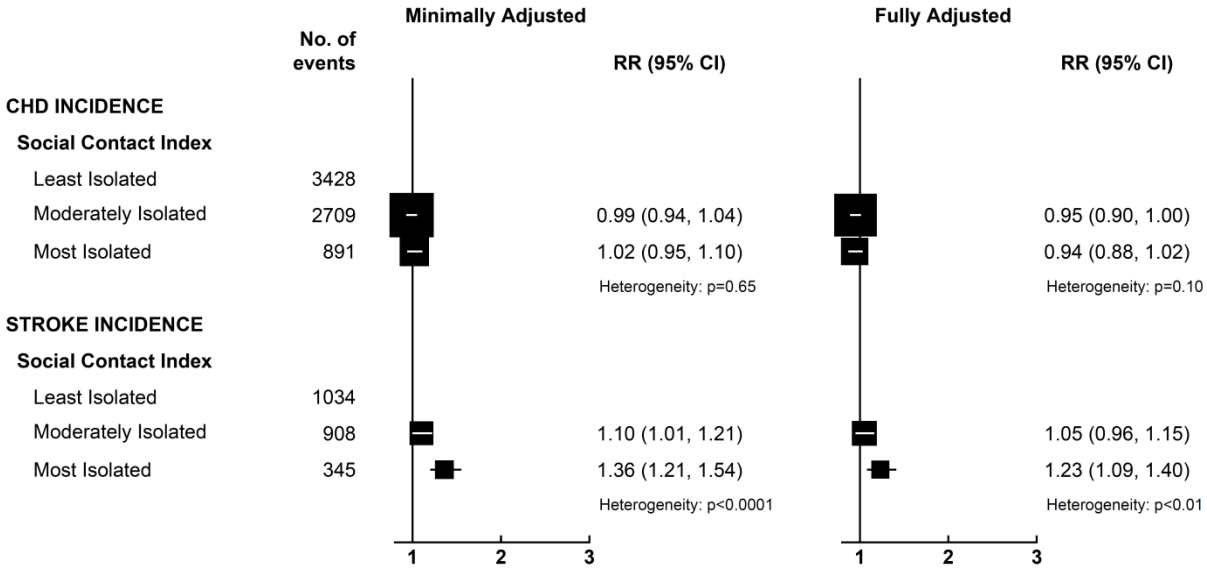


Figure 4.4. Minimally and fully adjusted RR and 95% CI for social isolation in relation to vascular disease incidence. The size of the square boxes is inversely proportional to the standard error of the relative risk estimate. Minimally adjusted models included: age, gender, region. Fully adjusted models included: age, gender, region, deprivation, education, disability, smoking, alcohol, physical activity, BMI, hypertension, diabetes, cholesterol medications.

Table 4.3. RR and 95% CI for stroke incidence by level of social isolation after adjustment for each group of covariates.

STROKE INCIDENCE	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of first stroke events	1,034	908	345			
Age, gender, region (minimally adjusted)	**1.00 (-)**	**1.10 (1.01, 1.21)**	**1.36 (1.21, 1.54)**	**<0.0001**	**23.86**	**-**
Age, gender, region, personal characteristics	**1.00 (-)**	**1.08 (0.98, 1.18)**	**1.30 (1.15, 1.47)**	**<0.001**	**16.30**	**32**
Age, gender, region, deprivation	1.00 (-)	1.08 (0.99, 1.18)	1.31 (1.16, 1.48)	<0.001	17.94	25
Age, gender, region, education	1.00 (-)	1.10 (1.00, 1.20)	1.35 (1.20, 1.53)	<0.0001	22.33	6
Age, gender, region, disability	1.00 (-)	1.10 (1.00, 1.20)	1.35 (1.19, 1.52)	<0.0001	22.06	8
Age, gender, region, health behaviour factors	**1.00 (-)**	**1.07 (0.98, 1.18)**	**1.28 (1.13, 1.45)**	**<0.001**	**15.04**	**37**
Age, gender, region, smoking	1.00 (-)	1.08 (0.99, 1.18)	1.31 (1.16, 1.48)	<0.001	17.70	26
Age, gender, region, alcohol	1.00 (-)	1.10 (1.00, 1.20)	1.34 (1.19, 1.52)	<0.0001	21.54	10
Age, gender, region, physical activity	1.00 (-)	1.10 (1.01, 1.20)	1.36 (1.20, 1.54)	<0.0001	22.84	4
Age, gender, region, body mass index	1.00 (-)	1.10 (1.01, 1.20)	1.36 (1.20, 1.54)	<0.0001	23.33	2
Age, gender, region, physiological factors	**1.00 (-)**	**1.10 (1.00, 1.20)**	**1.35 (1.19, 1.52)**	**<0.0001**	**21.93**	**8**
Age, gender, region, hypertension	1.00 (-)	1.10 (1.00, 1.20)	1.35 (1.20, 1.53)	<0.0001	22.71	5
Age, gender, region, diabetes	1.00 (-)	1.10 (1.01, 1.20)	1.35 (1.20, 1.53)	<0.0001	22.80	4
Age, gender, region, cholesterol medications	1.00 (-)	1.10 (1.01, 1.21)	1.36 (1.21, 1.54)	<0.0001	23.91	0
Fully adjusted	**1.00 (-)**	**1.05 (0.96, 1.15)**	**1.23 (1.09, 1.40)**	**<0.01**	**10.55**	**56**

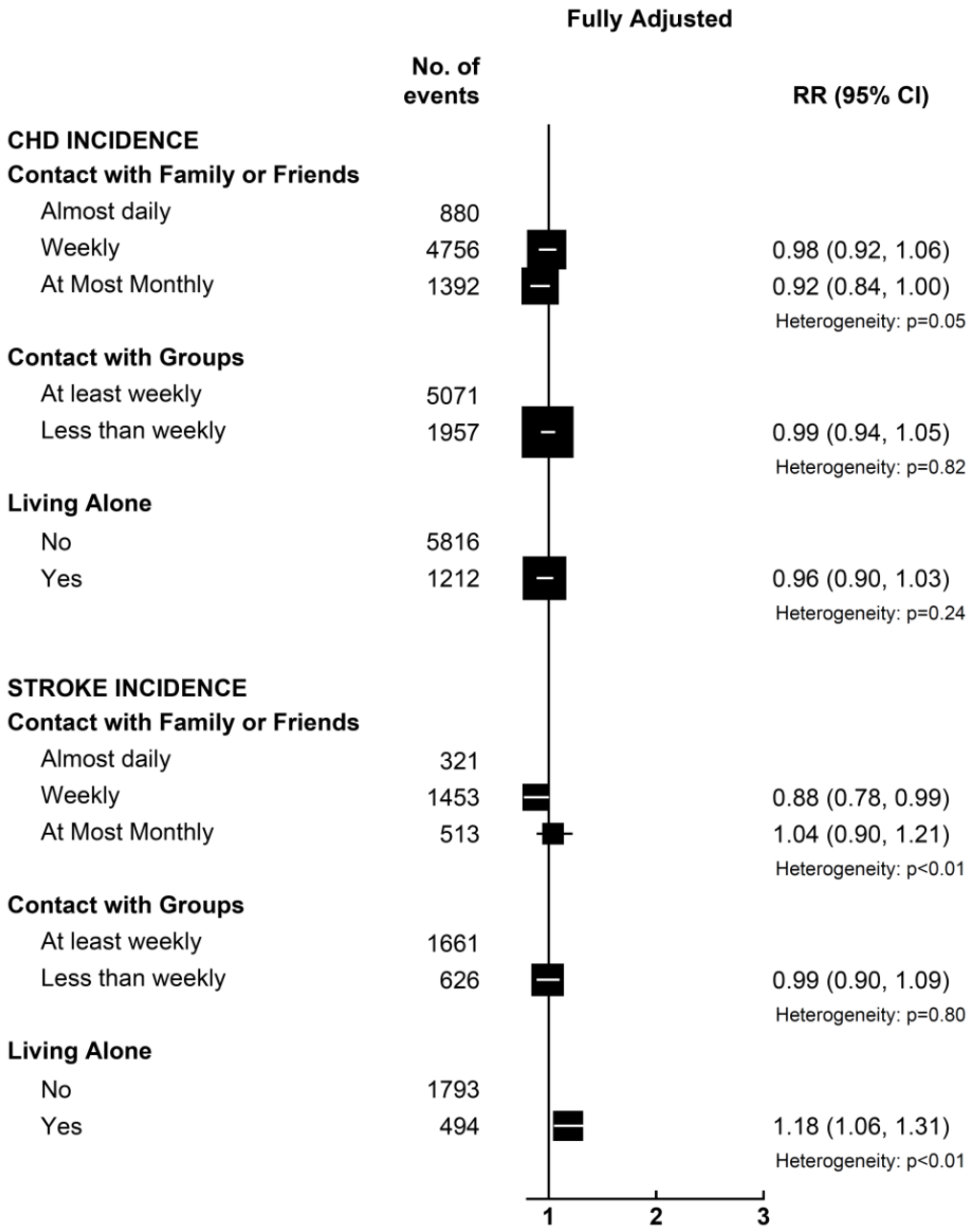


Figure 4.5. Fully adjusted RR and 95% CI for each social contact variable in relation vascular disease incidence. The size of the square boxes is inversely proportional to the standard error of the relative risk estimate.

4.3.3 Prospective Analyses of CHD Mortality

In minimally and fully adjusted analyses, social isolation was associated with CHD mortality (Figure 4.6). After full adjustment, compared to the least isolated participants, the moderately isolated and most isolated participants had 34% and 68% increased risk of death due to CHD, respectively (Figure 4.6, Moderately Isolated: *RR*=1.34, *95% CI*: 1.09-1.66; Most Isolated: *RR*=1.68, *95% CI*: 1.28-2.21, $p<0.001$). Among the covariates, personal characteristics and health behaviours again explained the greatest degree of the minimally adjusted association between social isolation and CHD mortality (Table 4.4). Deprivation and smoking each accounted for 20% and 18% of this association (Table 4.4). Overall, the association was attenuated by 38% after full adjustment (Table 4.4). The only SCI score constituent variable that was associated with CHD mortality after full adjustment was living alone (Figure 4.7, *RR*=1.70, *95% CI*: 1.37-2.12, $p<0.0001$).

4.3.4 Prospective Analyses of Stroke Mortality

Social isolation was associated with an increased risk of stroke mortality in minimally and fully adjusted analyses (Figure 4.6). After full adjustment, the most isolated participants had a two-fold increase in their risk of death from stroke (Figure 4.6, Moderately Isolated: *RR*=1.14, *95% CI*: 0.83-1.56; Most Isolated: *RR*=1.92, *95% CI*: 1.32-2.81, $p<0.01$). Like CHD mortality, personal characteristics and health behavioural factors explained the greatest degree of the minimally adjusted associations between social isolation and stroke mortality (Table 4.5, Percentage attenuation in LR χ^2, Personal characteristics: 23%, Health behaviours: 26%). Overall, the association was attenuated by 41% after full adjustment (Table 4.5). Among the SCI score constituent variables, only frequency of contact with family or friends was associated with stroke mortality (Figure 4.7, Weekly: *RR*=0.91, *95% CI*: 0.60-1.39; At Most Monthly: *RR*=1.68, *95% CI*: 1.05-2.67; $p<0.01$).

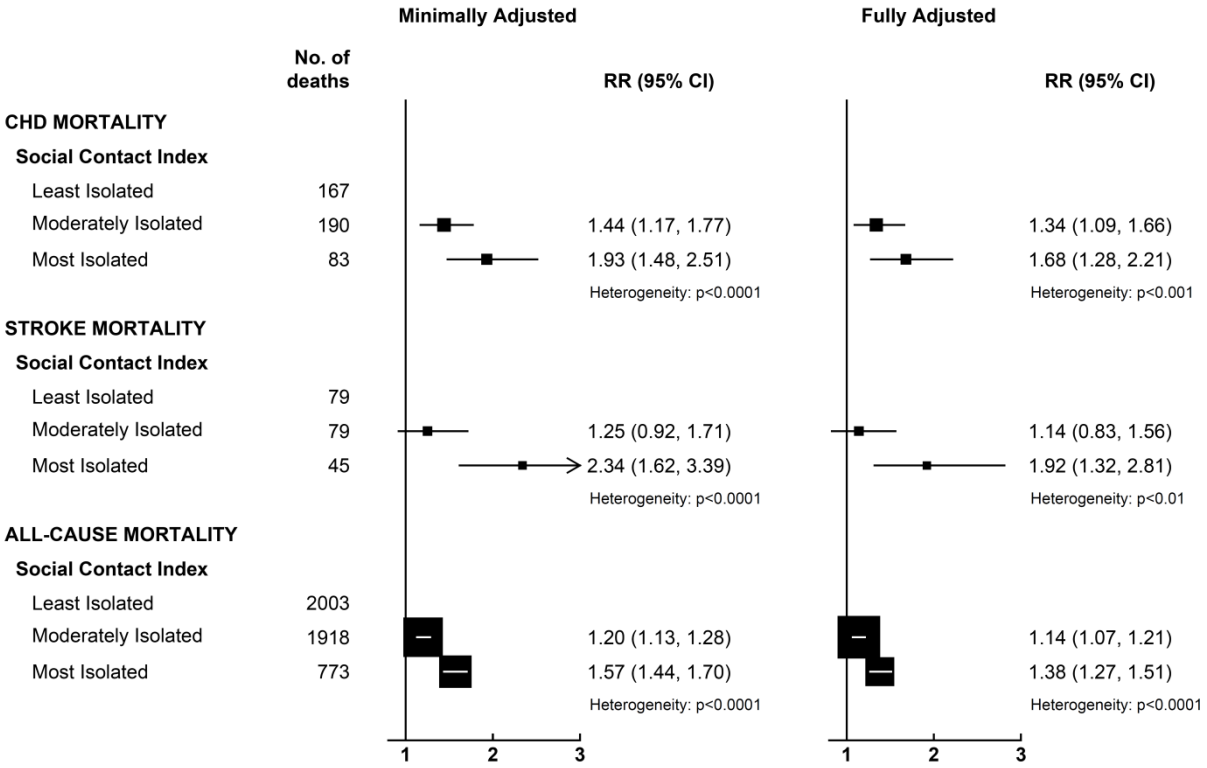


Figure 4.6. Minimally and fully adjusted RR and 95% CI for social isolation in relation to mortality outcomes. The size of the square boxes is inversely proportional to the standard error of the relative risk estimate. Minimally adjusted models included: age, gender, region. Fully adjusted models included: age, gender, region, deprivation, education, disability, smoking, alcohol, physical activity, BMI, hypertension, diabetes, cholesterol medications.

Table 4.4. RR and 95% CI for CHD mortality by level of social isolation after adjustment for each group of covariates.

CHD MORTALITY	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of CHD deaths	167	190	83			
Age, gender, region (minimally adjusted)	**1.00 (-)**	**1.44 (1.17, 1.77)**	**1.93 (1.48, 2.51)**	**<0.0001**	**25.31**	**-**
Age, gender, region, personal characteristics	**1.00 (-)**	**1.38 (1.12, 1.70)**	**1.77 (1.35, 2.31)**	**<0.0001**	**19.06**	**25**
Age, gender, region, deprivation	1.00 (-)	1.39 (1.13, 1.71)	1.80 (1.38, 2.35)	<0.0001	20.13	20
Age, gender, region, education	1.00 (-)	1.42 (1.15, 1.75)	1.90 (1.46, 2.48)	<0.0001	24.14	5
Age, gender, region, disability	1.00 (-)	1.43 (1.16, 1.76)	1.90 (1.46, 2.47)	<0.0001	24.19	4
Age, gender, region, health behaviour factors	**1.00 (-)**	**1.39 (1.13, 1.72)**	**1.82 (1.39, 2.37)**	**<0.0001**	**20.70**	**18**
Age, gender, region, smoking	1.00 (-)	1.39 (1.13, 1.72)	1.80 (1.38, 2.35)	<0.0001	20.65	18
Age, gender, region, alcohol	1.00 (-)	1.43 (1.16, 1.76)	1.91 (1.47, 2.49)	<0.0001	24.72	2
Age, gender, region, physical activity	1.00 (-)	1.44 (1.17, 1.77)	1.93 (1.48, 2.52)	<0.0001	25.33	0
Age, gender, region, body mass index	1.00 (-)	1.44 (1.17, 1.77)	1.93 (1.48, 2.51)	<0.0001	25.38	0
Age, gender, region, physiological factors	**1.00 (-)**	**1.42 (1.15, 1.75)**	**1.88 (1.44, 2.45)**	**<0.0001**	**23.51**	**7**
Age, gender, region, hypertension	1.00 (-)	1.43 (1.16, 1.76)	1.91 (1.46, 2.49)	<0.0001	24.67	3
Age, gender, region, diabetes	1.00 (-)	1.42 (1.16, 1.75)	1.90 (1.46, 2.47)	<0.0001	24.20	4
Age, gender, region, cholesterol medications	1.00 (-)	1.44 (1.17, 1.77)	1.93 (1.48, 2.51)	<0.0001	25.38	0
Fully adjusted	**1.00 (-)**	**1.34 (1.09, 1.66)**	**1.68 (1.28, 2.21)**	**<0.001**	**15.64**	**38**

Table 4.5. RR and 95% CI for stroke mortality by level of social isolation after adjustment for each group of covariates.

STROKE MORTALITY	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of stroke deaths	79	79	45			
Age, gender, region (minimally adjusted)	**1.00 (-)**	**1.25 (0.92, 1.71)**	**2.34 (1.62, 3.39)**	**<0.0001**	**18.62**	**-**
Age, gender, region, personal characteristics	**1.00 (-)**	**1.19 (0.87, 1.63)**	**2.11 (1.45, 3.06)**	**<0.001**	**14.35**	**23**
Age, gender, region, deprivation	1.00 (-)	1.21 (0.89, 1.66)	2.18 (1.50, 3.16)	<0.001	15.54	17
Age, gender, region, education	1.00 (-)	1.23 (0.90, 1.68)	2.27 (1.57, 3.28)	<0.001	17.30	7
Age, gender, region, disability	1.00 (-)	1.24 (0.91, 1.70)	2.30 (1.59, 3.33)	<0.001	17.86	4
Age, gender, region, health behaviour factors	**1.00 (-)**	**1.19 (0.87, 1.63)**	**2.09 (1.44, 3.04)**	**<0.001**	**13.85**	**26**
Age, gender, region, smoking	1.00 (-)	1.22 (0.89, 1.67)	2.19 (1.51, 3.17)	<0.001	15.83	15
Age, gender, region, alcohol	1.00 (-)	1.25 (0.92, 1.71)	2.33 (1.61, 3.36)	<0.001	18.26	2
Age, gender, region, physical activity	1.00 (-)	1.23 (0.90, 1.69)	2.26 (1.56, 3.28)	<0.001	16.99	9
Age, gender, region, body mass index	1.00 (-)	1.25 (0.91, 1.71)	2.32 (1.60, 3.35)	<0.001	18.16	2
Age, gender, region, physiological factors	**1.00 (-)**	**1.24 (0.91, 1.70)**	**2.30 (1.59, 3.33)**	**<0.001**	**17.93**	**4**
Age, gender, region, hypertension	1.00 (-)	1.25 (0.92, 1.71)	2.33 (1.61, 3.37)	<0.001	18.37	1
Age, gender, region, diabetes	1.00 (-)	1.25 (0.91, 1.71)	2.32 (1.60, 3.35)	<0.001	18.13	3
Age, gender, region, cholesterol medications	1.00 (-)	1.26 (0.92, 1.72)	2.34 (1.62, 3.39)	<0.0001	18.61	0
Fully adjusted	**1.00 (-)**	**1.14 (0.83, 1.56)**	**1.92 (1.32, 2.81)**	**<0.01**	**11.02**	**41**

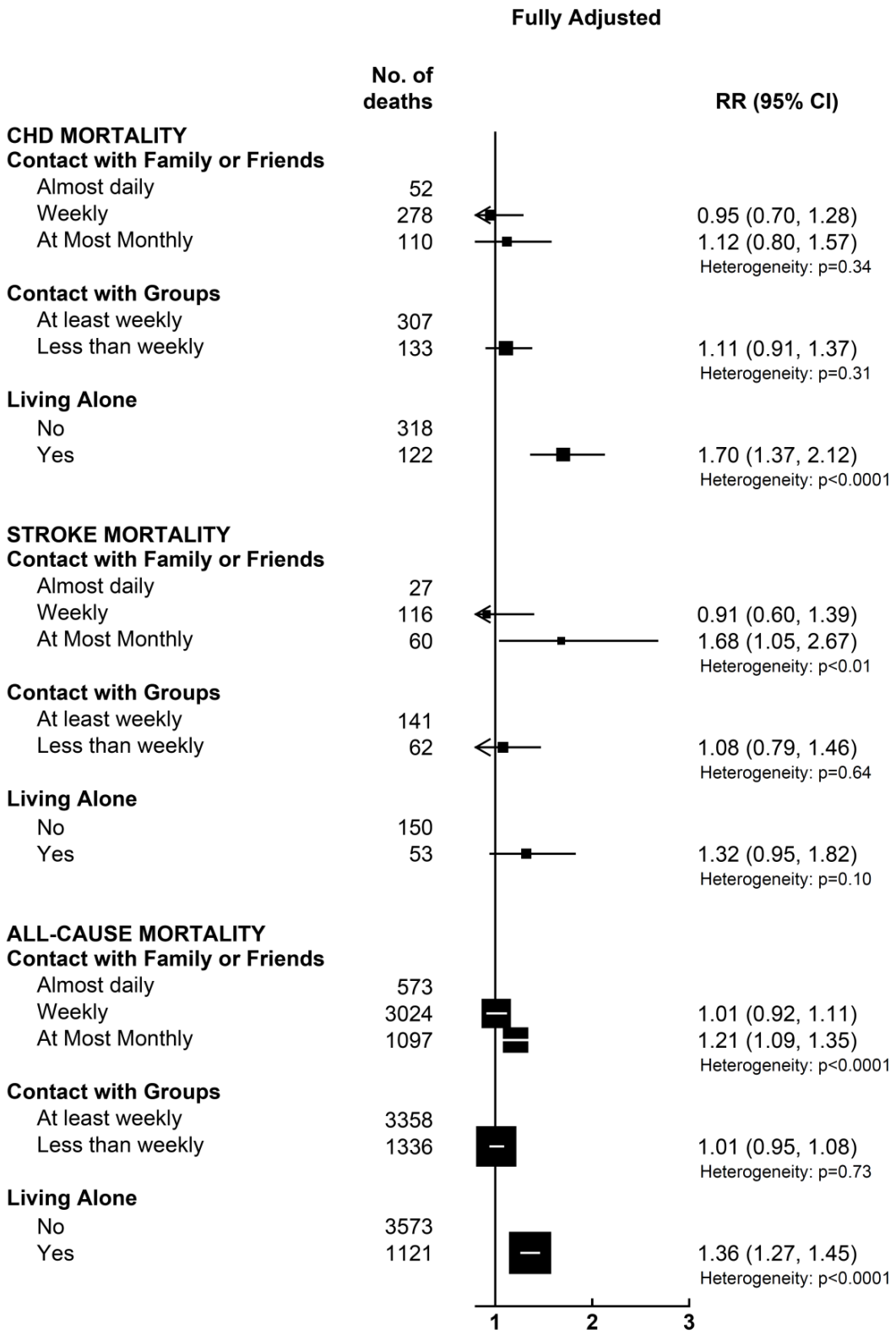


Figure 4.7. Fully adjusted RR and 95% CI for each social contact variable in relation mortality outcomes. The size of the square boxes is inversely proportional to the standard error of the relative risk estimate.

4.3.6 Prospective Analyses of All-cause Mortality

Social isolation was associated with increased all-cause mortality in minimally and fully adjusted analyses (Figure 4.6). After full adjustment, moderately isolated participants and the most isolated participants had 14% and 38% greater all-cause mortality compared to the least isolated participants (Figure 4.6, Moderately Isolated: *RR*=1.14, *95% CI*: 1.07-1.21; Most Isolated: *RR*=1.38, *95% CI*: 1.27-1.51, $p<0.0001$). Health behaviours explained the largest degree of the minimally adjusted association between social isolation and all-cause mortality, however like vascular disease mortality, personal characteristics also contributed considerably to the association (Table 4.6, percentage attenuation in LR χ^2, personal characteristics: 25%, health behaviours: 36%). Physiological factors explained 5% attenuation in the association. Overall, the explanatory factors examined accounted for 50% of the minimally adjusted association between social isolation and all-cause mortality (Table 4.6). Among the SCI score constituent measures, living alone was most strongly associated with all-cause mortality (Figure 4.7, *RR*=1.36, *95% CI*: 1.27-1.45, $p<0.0001$). Weaker associations were observed for frequency of contact with family or friends (Figure 4.7, Weekly: *RR*=1.01, *95% CI*: 0.92-1.11; At Most Monthly: *RR*=1.21, *95% CI*: 1.09-1.35; $p<0.0001$). Frequency of contact with social groups was not associated with all-cause mortality (Figure 4.7).

4.3.7 Gender Differences

There was no statistically significant interaction between social isolation and gender in fully-adjusted associations between social isolation and any of the outcomes (Table 4.7).

4.3.8 Sensitivity Analyses

After excluding the first two years of follow-up, fully adjusted associations between social isolation and stroke incidence and mortality outcomes remained consistent with the main results (Table A4.1, pp.230, Stroke Incidence, Moderately Isolated: *RR*=0.99, *95% CI*: 0.90-1.10, Most Isolated: *RR*=1.24, *95% CI*: 1.07-1.42, $p<0.01$; CHD Mortality, Moderately Isolated: *RR*=1.29, *95% CI*: 1.02-1.64, Most Isolated: *RR*=1.58, *95% CI*: 1.16-2.16, $p<0.01$; Stroke Mortality, Moderately Isolated: *RR*=1.14, *95% CI*: 0.81-1.61, Most Isolated: *RR*=1.72, *95% CI*: 1.12-2.62; $p=0.05$; All-cause Mortality, Moderately Isolated: *RR*=1.11, *95% CI*: 1.04-1.19, Most Isolated: *RR*=1.37, *95% CI*: 1.25-1.50; $p<0.0001$). The findings for social isolation and CHD incidence were consistent with the main results however, the test of heterogeneity was marginally statistically significant (Table A4.1, CHD incidence, Moderately Isolated: *RR*=0.93, *95% CI*: 0.87-0.98, Most Isolated: *RR*=0.95, *95% CI*: 0.87-1.04, $p=0.03$).

Table 4.6. RR and 95% CI for all-cause mortality by level of social isolation after adjustment for each group of covariates.

ALL-CAUSE MORTALITY	Least Isolated	Moderately Isolated	Most Isolated	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of all-cause deaths	2,003	1,918	773			
Age, gender, region (minimally adjusted)	**1.00 (-)**	**1.20 (1.13, 1.28)**	**1.57 (1.44, 1.70)**	**<0.0001**	**110.13**	**-**
Age, gender, region, personal characteristics	**1.00 (-)**	**1.17 (1.10, 1.24)**	**1.48 (1.36, 1.61)**	**<0.0001**	**82.54**	**25**
Age, gender, region, deprivation	1.00 (-)	1.18 (1.11, 1.26)	1.50 (1.38, 1.63)	<0.0001	89.53	19
Age, gender, region, education	1.00 (-)	1.19 (1.12, 1.27)	1.55 (1.42, 1.68)	<0.0001	103.62	6
Age, gender, region, disability	1.00 (-)	1.19 (1.12, 1.27)	1.55 (1.42, 1.68)	<0.0001	103.66	6
Age, gender, region, health behaviour factors	**1.00 (-)**	**1.16 (1.09, 1.23)**	**1.44 (1.32, 1.56)**	**<0.0001**	**70.88**	**36**
Age, gender, region, smoking	1.00 (-)	1.17 (1.10, 1.25)	1.48 (1.36, 1.61)	<0.0001	84.28	23
Age, gender, region, alcohol	1.00 (-)	1.20 (1.13, 1.28)	1.55 (1.42, 1.68)	<0.0001	104.86	5
Age, gender, region, physical activity	1.00 (-)	1.19 (1.12, 1.27)	1.54 (1.42, 1.68)	<0.0001	101.24	8
Age, gender, region, body mass index	1.00 (-)	1.20 (1.13, 1.28)	1.55 (1.43, 1.69)	<0.0001	106.71	3
Age, gender, region, physiological factors	**1.00 (-)**	**1.20 (1.12, 1.27)**	**1.55 (1.43, 1.68)**	**<0.0001**	**104.94**	**5**
Age, gender, region, hypertension	1.00 (-)	1.20 (1.13, 1.28)	1.56 (1.44, 1.70)	<0.0001	108.44	2
Age, gender, region, diabetes	1.00 (-)	1.20 (1.12, 1.28)	1.55 (1.43, 1.69)	<0.0001	106.39	3
Age, gender, region, cholesterol medications	1.00 (-)	1.20 (1.13, 1.28)	1.57 (1.44, 1.70)	<0.0001	110.20	0
Fully adjusted	**1.00 (-)**	**1.14 (1.07, 1.21)**	**1.38 (1.27, 1.51)**	**<0.0001**	**55.22**	**50**

Table 4.7. Fully adjusted relative risks and 95% CI of social isolation in relation to vascular disease incidence and mortality outcomes by gender.

	Female			Male			
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	p for interaction
CHD Incidence							
Least Isolated	1,137	1.00	(-)	2,294	1.00	(-)	0.87
Moderately Isolated	919	0.94	(0.86, 1.03)	1,791	0.95	(0.89, 1.01)	
Most Isolated	279	0.95	(0.84, 1.09)	612	0.93	(0.84, 1.01)	
Stroke Incidence							
Least Isolated	435	1.00	(-)	599	1.00	(-)	0.41
Moderately Isolated	401	1.07	(0.93, 1.22)	507	1.04	(0.92, 1.17)	
Most Isolated	151	1.36	(1.12, 1.64)	194	1.14	(0.97, 1.35)	
CHD Mortality							
Least Isolated	31	1.00	(-)	139	1.00	(-)	0.95
Moderately Isolated	36	1.26	(0.78, 2.05)	155	1.36	(1.08, 1.72)	
Most Isolated	15	1.72	(0.91, 3.24)	68	1.68	(1.25, 2.27)	
Stroke Mortality							
Least Isolated	38	1.00	(-)	41	1.00	(-)	0.50
Moderately Isolated	48	1.35	(0.88, 2.08)	31	0.93	(0.58, 1.49)	
Most Isolated	24	2.06	(1.22, 3.50)	21	1.85	(1.07, 3.17)	
All-Cause Mortality							
Least Isolated	855	1.00	(-)	1165	1.00	(-)	0.68
Moderately Isolated	831	1.11	(1.01, 1.22)	1103	1.16	(1.07, 1.26)	
Most Isolated	299	1.34	(1.17, 1.53)	475	1.43	(1.28, 1.60)	

4.4 Discussion

Among 296,913 women and men without previous vascular disease, cancer, or fair/poor self-rated health at baseline, there was stronger evidence of associations between social isolation and mortality than between social isolation and vascular disease incidence. After minimal adjustment for age, gender and region of recruitment, social isolation was associated with all outcomes except for CHD incidence. Before and after further adjustment for explanatory factors, greater isolation remained associated with increased stroke incidence, CHD and stroke mortality, and all-cause mortality. Adjustment for explanatory factors, particularly health behaviours such as smoking and personal characteristics such as socioeconomic deprivation, explained the largest amount of minimally adjusted associations. Among the constituent measures of social isolation, living alone had the strongest associations with stroke incidence, CHD mortality, and all-cause mortality. Frequency of contact with family or friends was the only measure associated with stroke mortality. There was little evidence for gender differences in associations between social isolation, vascular disease and mortality. As with the preceding analysis of the Million Women Study, the weaker association observed in relation to stroke incidence and associations with mortality outcomes may remain vulnerable to reverse causation bias, measurement error in the explanatory factors adjusted for, or explanation by unmeasured confounders or mediators.

Findings in Context: Million Women Study Analysis

Despite differences in demographic and social contact characteristics of the UK Biobank and Million Women Study cohorts, the current analysis findings align with those from the Million Women Study analysis (Figure 4.8). The prevalence of social isolation was consistent across both cohorts where approximately 12.0% of participants were categorized as most isolated (Most isolated: UK Biobank *n*=37,608; Million Women Study *n*=38,942). However, compared to participants of the Million Women Study, those participating in the UK Biobank tended to have less frequent contact with family or friends, more frequent contact with groups, and fewer were living alone. This could be in part explained by differences in the questions used to measure social contact. The UK Biobank asked participants about the frequency of in-person contact as opposed to any contact (i.e. including telephone or email) and asked about at least weekly participation in social groups and activities. These differences may also be reflective of UK Biobank participants being on average 10 years younger, and more likely to be working, and living with family members than Million Women Study participants.

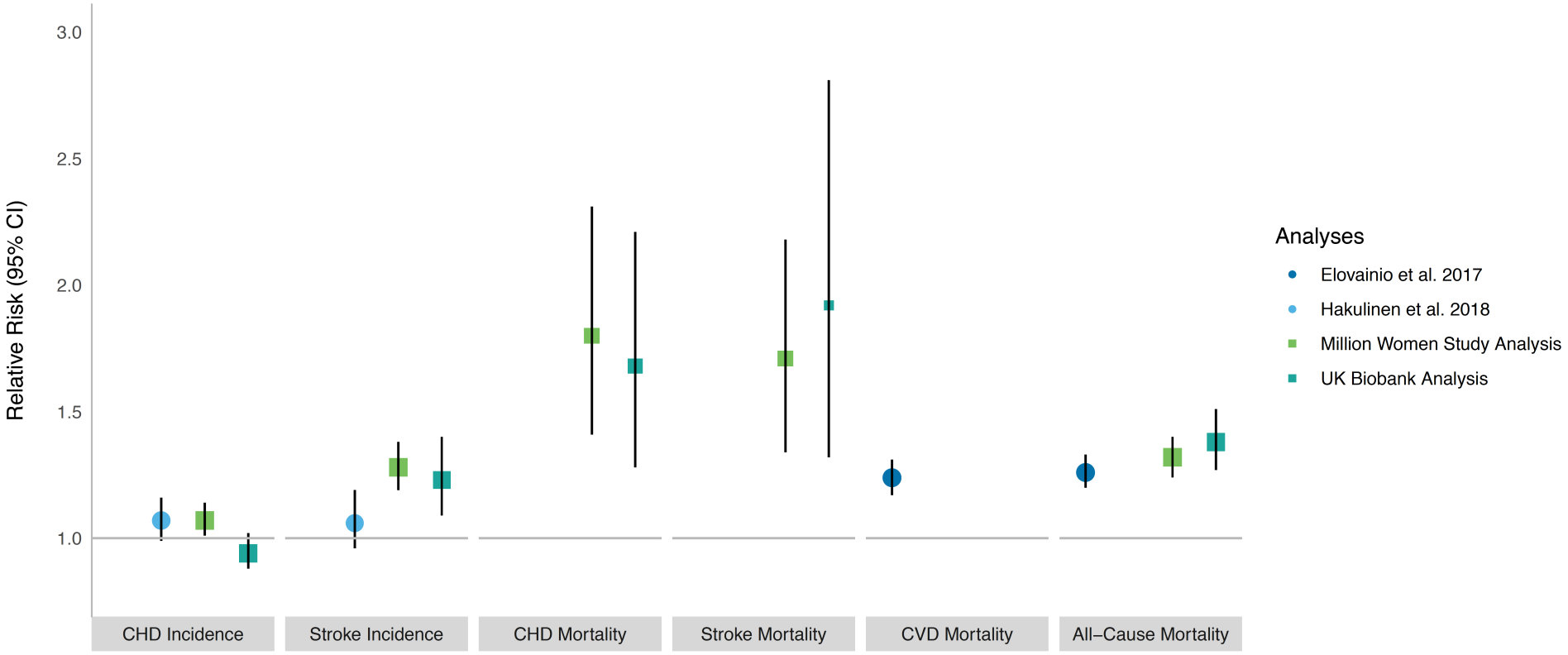


Figure 4.8. RR and 95% CI for the most isolated compared to least isolated participants in relation to each outcome examined in the Million Women Study analysis, the current analysis, and previous UK Biobank analyses. Note: Shape size is inversely proportional to standard error.

Unlike the Million Women Study analysis, the current analysis did not find a minimally adjusted association between social isolation and CHD incidence (Figure 4.4). This could be explained by the younger UK Biobank participants having lower baseline risk of CHD and thus associations may have been influenced less by unmeasured indicators of poor health compared to the Million Women Study analysis. Both analyses found weaker associations between social isolation and stroke incidence, and stronger associations with the mortality outcomes (Figure 4.8). In the current analysis, the most isolated participants had a 23% increased risk of incident stroke, 68% and 92% increased risk of death from CHD and stroke respectively, and a 38% increased risk of death from any cause. These estimates are consistent with the Million Women Study analysis considering the social contact questions were slightly different (i.e. any contact versus in-person contact) and there were fewer cases observed within the UK Biobank analysis. Due in part to the lower number of deaths, estimates of association for social isolation in relation to stroke mortality are more imprecise compared to the Million Women Study analysis (Figure 4.8).

Findings in Context: Previous UK Biobank Analyses

Two previous studies using UK Biobank data have examined social isolation in relation to vascular disease incidence and mortality (Elovainio et al., 2017; Hakulinen et al., 2018). In these studies, the proportion of participants within the most isolated category was slightly lower (9.0% [*n*=42,500]) than in the current analysis (12.6% [*n*=37,608]). The larger proportion of isolated participants in the current analysis may be due to subtle differences in the cut-off used for infrequent contact with family or friends. At most monthly as opposed to less than monthly was used in the current analysis to maintain consistency with the Million Women Study analysis. Previous UK Biobank cohorts were similar to the current analysis cohort on most other characteristics except for health status at baseline. Approximately half of the previously studied cohorts had at least one chronic disease at baseline and included participants reporting fair and poor self-rated (Elovainio et al., 2017; Hakulinen et al., 2018).

Among 479,054 UK Biobank participants, Hakulinen and colleagues (2018) found that after minimally adjusting for age, gender, and ethnicity, isolated participants (using a binary measure based on an index of social contact and living alone) had 43% and 39% increased risk of incident AMI and stroke over a seven-year follow-up period (Figure 4.8). After adjustment for personal characteristics, health behaviours, physiological factors, psychological factors, and baseline health status, these associations were attenuated to 7% and 6% increased risk for AMI

and stroke respectively, and were not statistically significant (Hakulinen et al., 2018). In contrast to Hakulinen and colleagues (2018), the current analysis did not find a minimally adjusted association with CHD incidence, and after adjustment, social isolation remained associated with stroke incidence.

These contrasting findings may be explained by differences in cohort exclusion criteria, the social isolation measures used, and the explanatory factors adjusted for. Given that Hakulinen and colleagues (2018) did not exclude participants of fair or poor self-rated health, the minimally adjusted association with AMI incidence may be explained by their cohort having poorer baseline health than the current analysis cohort. The absence of association between social isolation and stroke incidence could be in part explained by the binary structure of the social isolation variable used. If those whom in the current analysis were categorised as moderately isolated were grouped together with the least isolated participants, as was done in Hakulinen and colleagues (2018), one might expect the baseline risk of stroke to increase within the least isolated group and thus reduce the magnitude of difference in baseline risk between the most and less isolated groups. As a result, fully adjusted analyses may have underestimated associations between social isolation and stroke incidence. Lastly, the previous UK Biobank analysis adjusted for a broader set of explanatory factors including depressive symptoms (i.e. frequency of depressed mood, unenthusiasm/disinterest, tiredness/lethargy, and tenseness/restlessness within past two weeks), hand-grip strength, and clinically assessed blood pressure. This may to some degree contribute to greater attenuation of the association with stroke incidence.

Compared to another previous UK Biobank analysis (Elovainio et al., 2017), the current analysis found stronger albeit generally consistent associations between social isolation and vascular disease mortality and all-cause mortality (Figure 4.8). Among 466,901 UK Biobank participants, Elovainio and colleagues (2017) found that compared to non-isolated participants, those who were isolated had 30% and 24% increased risk of CVD and all-cause mortality, respectively. The higher magnitude associations found in the current analysis may be explained by differences in the measurement of vascular disease mortality, social isolation, and explanatory factors. First, the broad CVD mortality (ICD-10 codes I05-I89) measure used by Elovainio and colleagues (2017) may include causes of death which have little evidence of associations with social isolation (e.g. disease of the myocardium or cardiac valves, rheumatic and pulmonary heart disease, or hypertensive diseases). The inclusion of such causes of death may have attenuated the association. The lower frequency of cause-specific deaths in the current analysis likely contributes to the wider confidence intervals for CHD and stroke

mortality associations. While more strongly associated, the magnitude of association may be less precise than in Elovainio and colleagues (2017). Second, as in Hakulinen and colleagues (2018), the binary social isolation variable used by Elovainio and colleagues (2017) may also contribute to lower magnitude associations. Finally, the associations found in Elovainio and colleagues (2017) may also have been attenuated to a greater degree than in the current analysis by the broader set of explanatory factors examined including those from Hakulinen et al. (2018) and additionally cognitive performance.

Findings in Context: Previous Prospective Studies Overall

Similar to this analysis among a healthy adult population, several other studies among general adult populations have not observed statistically significant associations between social isolation and the onset of CHD or AMI (Table 2.1) (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Barefoot *et al.*, 2005; Chang *et al.*, 2017). In light of these previous and the current findings, the marginally statistically significant association found in the Million Women Study analysis is not strongly supported. While a meta-analysis by Valtorta and colleagues (2016) found social isolation to be associated with increased risk of incident CHD (*pooled RR*=1.29, *95% CI*: 1.04-1.59, *n*=11), this finding may be biased by heterogeneity in the exposure variables and adjustment for explanatory variables. Indeed, after studies at greater risk of bias were excluded from their analysis, associations with CHD incidence increased in magnitude and imprecision (*pooled RR*=1.42, *95% CI*: 1.00-2.01, *n*=7) (Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). Furthermore, in the current analysis there were no statistically significant gender differences in this association, or any associations between the SCI score constituent variables and CHD incidence. These findings in combination with previous research suggest that any association between social isolation and CHD incidence is likely the result of confounding by factors such as socioeconomic deprivation, or explained by deleterious health behaviours such as smoking (Section 3.4; Chang *et al.*, 2017; Hakulinen *et al.*, 2018).

Valtorta and colleagues (2016) found social isolation associated with 32% increased risk of incident stroke events. However, after studies at greater risk of bias were excluded from their analysis, associations with stroke incidence were marginally statistically non-significant (*pooled RR*=1.30, 95% CI: 0.98-1.71, n=4) (Valtorta, Kanaan, Gilbody, Ronzi, *et al.*, 2016). Within the current analysis the most isolated UK Biobank participants had a 26% increased risk of incident stroke compared to the least isolated participants. This could suggest that social contact and living with others may reduce one's risk of developing a stroke. Consistent with the Million Women Study analysis, living alone was likely the driver of this association. Increased stroke incidence among more isolated people could at least in part be explained by

spending less time around others who may detect symptoms of sub-clinical cerebrovascular disease (e.g. transient ischaemic attacks) and initiate healthcare seeking before the onset of a full stroke. While this hypothesis has yet to be investigated directly, research suggests that people who do not live alone are more likely to seek care earlier upon stroke and transient ischemic attack symptom onset (Faiz *et al.*, 2014). More frequent social contact may also encourage people to utilise preventative health services which may reduce stroke risk (Stafford *et al.*, 2018). However, residual and unmeasured confounding bias cannot be ruled out. In the current analysis, the Million Women Study analysis, and Hakulinen and colleagues' (2018) analysis, personal characteristics, health behaviours, and physiological factors explained over 55% of the minimally adjusted association between social isolation and stroke incidence. It remains possible that unmeasured confounding factors may further explain the observed association.

Particularly after excluding the first two years of follow-up, the current findings in relation to CHD, stroke, and all-cause mortality, were consistent with other prospective studies (Kawachi *et al.*, 1996; Yang *et al.*, 2013; Chang *et al.*, 2017; Alcaraz *et al.*, 2018) beyond the previous UK Biobank analyses (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Previous research suggests that those who are more isolated have a 29% to 76% increased risk of CHD or CVD mortality (Kawachi *et al.*, 1996; Yang *et al.*, 2013; Chang *et al.*, 2017; Alcaraz *et al.*, 2018). The current analysis results were within this range. A stronger association was observed between social isolation and stroke mortality. This association with stroke mortality may however be overestimated given the low ratio of deaths in the most isolated category to the number of explanatory factors (i.e. less than 4 deaths per covariate) (Greenland *et al.*, 2016). According to Greenland and colleagues (2016), in the presence of sparse data, estimates of association can be biased away from the null. However, adjustment for explanatory factors would also be expected to be inflate associations further away from the null. In the current analysis, attenuation was observed after adjustment for explanatory factors. While the relatively low number of stroke deaths may still contribute to imprecision in the estimates of association, sparse data bias is thus not believed to affect the interpretation of results. Beyond Hakulinen and colleagues (2018), only one other study examined stroke mortality, however, too few cases of stroke were observed to reliably estimate associations with social isolation (Kawachi et al., 1996). The magnitude of associations observed in recent studies examining social isolation and all-cause mortality range from 26% to 80% increased mortality among the most isolated compared to least isolated participants (Pantell *et al.*, 2013; Steptoe *et al.*, 2013; Yang *et al.*, 2013; Kim *et al.*, 2016; Alcaraz *et al.*, 2018; Laugesen *et al.*, 2018; Smith *et al.*, 2018). The 38% increased mortality observed among the most isolated participants in the

current analysis is within range and also consistent with Holt-Lunstad and colleagues' (2015) meta-analysis.

In the current and Million Women Study analyses as well as in other previous studies, personal characteristics and health behaviours most strongly attenuated associations between social isolation, vascular disease, and mortality (Chang *et al.*, 2017; Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). Compared to the Million Women Study analysis, personal characteristics, health behavioural factors and physiological factors tended to explain a lower degree of the unadjusted associations between social isolation and stroke incidence (MWS: 67%; UKB: 56%), CHD mortality (MWS: 64%; UKB: 43%), stroke mortality (MWS: 41%; UKB: 42%), and all-cause mortality (MWS: 76%; UKB: 51%). These differences may be due to differences in the covariate measurement and sample demographics. Particularly in the UK Biobank cohort, socioeconomic factors and health behaviours explained similar proportions of minimally adjusted associations (Tables 4.3-4.6) (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). While socioeconomic deprivation may itself confound these associations, previous research from the Million Women Study suggests that much of the attenuation attributed to adjustment for deprivation may be explained by health behaviours (Floud *et al.*, 2016). Therefore, health behaviours likely are key factors explaining how social isolation could affect vascular disease and mortality.

This was the first analysis of UK Biobank data to examine the constituent measures of social isolation in relation to vascular disease and mortality outcomes. Within the Million Women Study and the current analyses, living alone tended to have the strongest associations with mortality outcomes. A recent meta-analysis suggested that those who live alone have a 32% increased risk of all-cause mortality (Holt-Lunstad *et al.*, 2015). This estimate is consistent with the 16% to 40% range observed in the current and Million Women Study analyses, and previous studies examining related variables such as marital status (Kawachi *et al.*, 1996; Eng *et al.*, 2002; Pantell *et al.*, 2013). As discussed in Section 3.4, further research is needed to understand how much assistance in seeking timely medical care could explain associations between social isolation and mortality.

Frequency of contact with family or friends, whether in-person (UK Biobank analysis) or additionally via telephone or email (Million Women Study analysis), exhibited statistically significant associations with stroke incidence and mortality, and all-cause mortality, but not CHD incidence or mortality. However, it should be noted that the wide confidence intervals for stroke mortality suggest that there were too few deaths to reliably measure this association. Like co-habitation, more regular contact with family or friends is believed to promote timely

help-seeking (Berkman and Krishna, 2014; Holt-Lunstad, 2018b). The availability of emotional support enabled by having these closer relationships is also believed to buffer stress arising from perceived isolation (Hawkley and Cacioppo, 2010; Berkman and Krishna, 2014; Holt-Lunstad, 2018b). The associations between contact with family or friends and stroke incidence and all-cause mortality suggest that explanatory factors such as assistance in help-seeking and emotional support may more relevant to stroke pathophysiology than CHD pathophysiology. However, these associations tended to be weak and it remains possible that they are at least in-part explained by unmeasured confounding factors.

Gender Differences

The associations observed between social isolation vascular disease incidence, vascular disease mortality, and all-cause mortality were consistent across women and men. Previous studies examining gender differences in associations between social isolation and mortality tend to crudely compare the magnitude of associations across women and men (House *et al.*, 1982; Kaplan *et al.*, 1988; Yang *et al.*, 2013; Elovainio *et al.*, 2017). Alcaraz and colleagues (2018) did however find statistically significant evidence of gender differences. In their study, compared to the most isolated men, the most isolated women had increased risk of death from CVD and any cause (Alcaraz *et al.*, 2018). In contrast, Steptoe and colleagues (2013) found no statistically significant differences in associations between social isolation and all-cause mortality by gender. As highlighted in Sections 1.4.2 and 2.7, previous research offers few explanations for how associations between social isolation and vascular disease outcomes may vary by gender. The current analysis when considered alongside previous research presents little evidence that explanatory pathways linking social isolation and mortality are influenced gender.

Strengths and Limitations

The primary strength of the current analysis is its size. The large sample size enabled for robust estimation of associations between social isolation, vascular disease, and mortality, whilst applying thorough exclusion criteria to minimise reverse causation bias. The current analysis is also among the first and largest to formally examine gender differences and the role of constituent measures of social isolation in the aforementioned associations. In addition to the methodological limitations of measuring social isolation discussed in Section 3.4, a few other limitations merit consideration. As discussed, bias due to reverse causation and confounding by unmeasured explanatory factors cannot be ruled out. However, the current analysis thoroughly sought to mitigate bias from reverse causation by excluding participants with

previous vascular disease, cancer, or if they reported their health as poor or fair. Additionally, sensitivity analysis excluding the first two years of follow-up generated consistent findings with the main analysis. The current analysis additionally assessed several known vascular disease risk factors, and potential mediators or confounders of associations between social isolation, vascular disease, and mortality. However potentially relevant psychological and physiological factors were not examined. As discussed in Section 1.4.4, previous research suggests that psychological factors such as depression may be more relevant in explaining associations between functional or perceived dimensions of social isolation as opposed to structural dimensions. This hypothesis was supported by previous UK Biobank analyses (Elovainio *et al.*, 2017; Hakulinen *et al.*, 2018). For this reason, and to maintain consistency with the Million Women Study analysis, the role of psychological factors were not examined in the current analysis. Chapter 6 of this thesis will examine the role psychological factors as explanatory pathways linking structural, functional, and perceived dimensions of social isolation and mortality. Due to data availability limitations, broader physiological factors such as inflammatory biomarkers of vascular inflammation were not examined. While vascular inflammation may further explain the associations observed, previous research examining associations between social isolation and inflammatory biomarkers is inconclusive (Ford, Loucks and Berkman, 2006; Loucks, Berkman, *et al.*, 2006; Loucks, Sullivan, *et al.*, 2006; Shankar *et al.*, 2011; Yang *et al.*, 2013). Gender effect modification analyses may have been underpowered to detect differences given the low number of CHD and stroke deaths observed within female and male sub-groups. Since this was the first study identified to examine gender differences in associations between social isolation and vascular disease mortality, further research among large cohorts would clarify the degree to which this is a limitation. Finally, the response rate for UK Biobank participation was 5.5% (Fry *et al.*, 2017). The UK Biobank acknowledges the following:

> *"while…participants are not representative of the general population (and hence cannot be used to provide representative disease prevalence and incidence rates), valid assessment of exposure-disease relationships are nonetheless widely generalizable and do not require participants to be representative of the population at large."* (2017)

Given the consistency between the Million Women Study (46.0% response rate, Section 3.2.1) and UK Biobank analyses, the associations observed are likely generalisable to healthy adults within the UK.

4.5 Conclusion and Future Directions

Within a large prospective cohort of generally healthy women and men, there was stronger evidence for associations between social isolation and increased vascular disease mortality and all-cause mortality than vascular disease incidence. These associations were similar across women and men. As hypothesised in Section 2.5 and confirmed in the current and Million Women Study analyses, the adoption or maintenance of poor health behaviours (e.g. smoking) is likely an important explanation for how social isolation may affect these outcomes. Among the SCI score constituent variables, living alone was most consistently associated with mortality. These findings highlight the need for further research into functional dimensions of isolation and help-seeking behaviours also potentially modifying or mediating associations with mortality.

Among the aims of Chapters 3 and 4 was to generate robust estimates of association for social isolation in relation to vascular disease and mortality. These chapters additionally assessed the validity of beliefs related to the nature of these associations such as there being age and gender differences. Additional factors related to the social and physical environments within which people live, work, and play are also believed to shape one's risk of becoming socially isolated and the degree to which this experience affects health. However little research has examined whether these factors represent modifiers of associations between social isolation and health (Marcus *et al.*, 2016). Examining the potential effect modifying role of neighbourhood factors is the focus of the following chapter.

5 Neighbourhood Environments, Social Isolation, and Vascular Disease Incidence and Mortality

5.1 Introduction

5.1.1 Background

The social and physical characteristics of the environments where people live, work, and play are believed to influence their capacity to build and maintain social relationships as they age (Berkman and Krishna, 2014; World Health Organization, 2015). Previous reviews suggest social and physical characteristics of neighbourhoods (here forward referred to as neighbourhood factors) can influence people's social relationships by fostering or impeding opportunities for social interaction and by affecting the quality of social interaction (literature review search terms and results presented in Table A5.1, pp.231) (Matsuoka and Kaplan, 2008; Chaix, 2009; Nicholson, 2009; Abraham, Sommerhalder and Abel, 2010; Talen and Koschinsky, 2014; Hassen and Kaufman, 2016; Cotterell *et al.*, 2018; Holt-Lunstad, 2018b; Thurber, Bohmann and Heflinger, 2018). The first hypothesis examined in this chapter is that social isolation is more prevalent within neighbourhoods that are more deprived, have higher crime, are further from services, and have less greenspace.

Previous reviews suggest that a wide range of neighbourhood factors may facilitate or impede interaction among residents. Commonly examined social characteristics include the socioeconomic status of residents and the nature of relationships and behaviours shared among residents (e.g. crime, violence, cohesion) (Diez Roux and Mair, 2010). Stigma and distrust between members of different socioeconomic positions or racial/ethnic backgrounds is believed to affect the quality of social interaction (Chaix, 2009; Nicholson, 2009; Talen and Koschinsky, 2014; Cotterell *et al.*, 2018; Thurber *et al.*, 2018). Neighbourhood crime rates and the condition of public spaces (e.g. vandalism) may influence the appeal and perceived safety of leaving one's home for social interaction (Abraham *et al.*, 2010; Nicholson, 2012; Hassen and Kaufman, 2016). While not directly assessed in this thesis, the social characteristics of the broader society within which people engage also merit consideration. The size and sociodemographic composition of an electorate is believed to influence policy decisions affecting the design of neighbourhoods, investments in public space, and transportation infrastructure (Chaix, 2009; Cotterell *et al.*, 2018; Holt-Lunstad, 2018b). Cultural norms (e.g. the Western "individualistic" lifestyle) or widely-held implicit biases (i.e. discrimination) may

also influence which neighbourhoods people migrate to and the degree to which people interact within their neighbourhoods (Chaix, 2009; Talen and Koschinsky, 2014; Cotterell *et al.*, 2018; Thurber *et al.*, 2018).

Physical characteristics of neighbourhoods commonly examined in previous research relate to the availability of venues for social interaction outside one's home, geographic factors affecting the distance to and from these venues, and characteristics of infrastructure which facilitates transport to and from these venues. In areas with greater geographic distances between people and venues for social interaction (e.g. houses, shops, cafes, parks), it can be more difficult for people to travel between where they live and where they socialise (Abraham *et al.*, 2010; Hassen and Kaufman, 2016). Factors impeding ease of transport, particularly for older adults, include distance to services and amenities, physical terrain (e.g. steepness of the route), the availability and quality of pedestrian infrastructure (e.g. sidewalks), and availability of public transport (Diez Roux and Mair, 2010; Hassen and Kaufman, 2016). Also, characteristics of how land is used in an area (e.g. residential, industrial, or commercial land development) and availability of public space, may influence the location and types of venues available for people to congregate (Diez Roux and Mair, 2010; Hassen and Kaufman, 2016). Greenspace and publicly accessible spaces such as libraries, community centres, recreational facilities are believed to facilitate social engagement (Matsuoka and Kaplan, 2008; Chaix, 2009; Abraham *et al.*, 2010; Talen and Koschinsky, 2014; Hassen and Kaufman, 2016; Cotterell *et al.*, 2018; Holt-Lunstad, 2018b).

Despite this body of research suggesting that neighbourhood factors affect the prevalence of social isolation, most social isolation interventions do not address these factors (Cattan *et al.*, 2005; Health Quality Ontario, 2008; Valtorta and Hanratty, 2016). This may be due to the lack of research examining neighbourhood factors as modifiers of associations between social relationships and health (Chaix, 2009; Marcus *et al.*, 2015; Holt-Lunstad, 2018b). The second hypothesis examined in this chapter is that social isolation is more detrimental to health in neighbourhoods that are more deprived, have higher crime, are further from services, and have less access to greenspace.

Only two identified studies examined whether neighbourhood factors modified associations between social isolation and mortality (Marcus *et al.*, 2016, 2017). Both studies hypothesised that mortality risk would be greater among isolated people living in more compared to less impoverished neighbourhoods. Among over 16,000 American adults participating in the Third National Health and Nutrition Examination Survey, Marcus and colleagues (2016) observed

subtle differences in associations between social isolation and all-cause mortality according to neighbourhood poverty (Most Isolated compared to Less Isolated, High Poverty: *RR*=1.41, *95% CI*: 1.27-1.58, *p*<0.0001; Low Poverty: *RR*=1.45, *95% CI*: 1.18-1.78, *p*<0.0001) (Marcus *et al.*, 2016). However, the statistical significance of effect modification across neighbourhood poverty strata was not formally assessed. When all-cause mortality among those who were doubly exposed to isolation and poverty, and singly exposed to isolation or poverty was compared to participants who were doubly unexposed to isolation and poverty, the strongest associations between social isolation and mortality were observed among the doubly exposed (Less Isolated—Low Poverty compared to, Less Isolated—High Poverty: *RR*=1.10, *95% CI*: 0.95-1.28, *p*=0.19; Most Isolated—Low Poverty: *RR*=1.42, *95% CI*: 1.28-1.59, *p*<0.0001; Most Isolated—High Poverty: *RR*=1.63, *95% CI*: 1.35-1.96, *p*<0.0001) (Marcus *et al.*, 2016). Using these estimates of association, measures of effect modification on an additive scale (e.g. relative excess risk due to interaction, synergy index, attributable proportion due to interaction) were calculated, however no statistically significant modification was observed.

In a subsequent study, no effect modification by neighbourhood poverty was observed in relation to cancer mortality (Marcus *et al.*, 2017). Marcus and colleagues' (2016, 2017) hypotheses were informed by the Berkman and Krishna model for social relationships and health. However, the potential mechanisms through which social isolation could be modified by poverty were not clearly described. Each of these studies emphasise the need for further research to understand if and how neighbourhood factors, including and beyond those related to poverty, influence associations between social isolation and health.

5.1.2 Objectives of Chapter

The purpose of the current chapter was to understand the degree to which neighbourhood factors influence associations between social isolation, vascular disease, and mortality. The analyses had two primary objectives:

1. To quantify and compare the prevalence of social isolation across four neighbourhood factors (i.e. socioeconomic deprivation, crime, distance to services, greenspace).

2. To examine whether these neighbourhood factors modify the association between social isolation and vascular disease incidence, vascular disease mortality, and all-cause mortality.

5.2 Methods

5.2.1 Study Design and Participants

This Chapter involved parallel analyses of the Million Women Study 12-year re-survey and UK Biobank cohorts.

5.2.2 Social Isolation

The social contact index (SCI) scores described in Sections 3.2.2 and 4.2.2 were the primary exposure variables used to measure social isolation within the Million Women Study and UK Biobank. To maximise case frequencies across sub-categories of social isolation and neighbourhood factors, moderately isolated and least isolated participants were grouped together and compared to the most isolated participants. Dichotomising SCI score was deemed reasonable given that the strongest associations were observed in Chapters 3 and 4 when comparing the most isolated and least isolated participants versus the moderately isolated and least isolated participants.

5.2.3 Outcomes

Participants were observed from the time of baseline survey completion to time of event, death, loss to follow-up, or end of follow-up (Million Women Study: 31 March 2017; UK Biobank: 31 January 2016). The vascular disease incidence, vascular disease mortality, and all-cause mortality outcomes examined in Chapters 3 and 4 were examined in the current analysis. They are the following: time to first CHD event, (ICD-10 codes: I20 to I25; ICD-9 codes: 410 to 414) and time to first stroke event (ICD-10 codes: I60 to I69; ICD-9 codes: 430 to 438), time to CHD death, time to stroke death, and time to all-cause death (World Health Organisation, 2010). First CHD and stroke events were defined as a participant's first hospital admission or death due to CHD or stroke as the primary or secondary diagnosis. CHD, stroke, and all-cause deaths were defined as participant deaths with CHD, stroke, or any-cause recorded as the primary cause of death.

5.2.4 Neighbourhood Factors

Four neighbourhood factors were examined in this analysis. They were socioeconomic deprivation, crime rates, distance to services, and greenspace availability. Each neighbourhood factor except for greenspace availability was derived from the English Index of Multiple Deprivation (IMD) 2010. Greenspace availability data was derived from the Generalised Land Use Database for England (GLUD) 2005. Distance to services data was only available for

Million Women Study participants, and greenspace availability was only available for UK Biobank participants.

As discussed in Chapter 3 (Section 3.2.1), the IMD 2010 is a measurement tool which estimates levels of deprivation experienced by individuals residing within small geographic areas of approximately 1,500 people known as lower super output areas (LSOA) (McLennan *et al.*, 2011). The overall IMD 2010 measures deprivation in the following eight domains: income; employment; education, skills and training; living environment; barriers to housing and social services; crime; health and disability (McLennan *et al.*, 2011). The Office of National Statistics constructs neighbourhood socioeconomic deprivation, crime rate, and distance to services measures using data from the following organisations: Department of Work and Pensions, Her Majesty's Revenue and Customs, the Home Office, the Department of Education, police forces, the National Health Service, Post Office Limited, and MapInfo (McLennan *et al.*, 2011). These data were current to the year 2008 (McLennan *et al.*, 2011). To ascertain IMD domain scores within specific geographic boundaries (e.g. postcode), these data are superimposed onto a geographic grid using geographic information system (GIS) applications (McLennan *et al.*, 2011). For this analysis, 2001 LSOA codes were ascertained using the Office of National Statistics' Postcode Directory according to Million Women Study participant postcode at the time of the 12-year re-survey (Office of National Statistics, 2016). IMD scores for each domain were then ascertained for participants according to their LSOA code using the Department of Communities and Local Government's IMD directory (Ministry of Housing Communities and Local Government, 2011). Further detail regarding the IMD 2010 and each domain's score calculation can be found in the IMD 2010 technical report (McLennan *et al.*, 2011).

The UK Biobank ascertained overall and domain-specific IMD 2010 scores for each participant in their database. However, the distance to services scores were not available in the dataset because the composite domain within which distance to services scores were nested (i.e. geographic barriers) was not disaggregated before data linkage. Wheeler (2016) ascertained measures of greenspace availability for each UK Biobank participant using map grid coordinates of each participant home's location and data from the GLUD 2005. The GLUD 2005 contains data on the proportion of land within the 2001 census output areas that are categorized into the following nine general classifications: greenspace, domestic buildings, non-domestic buildings, roads, paths, rail, gardens (domestic), other, and unclassified (Department for Communities and Local Government, 2007).

In the current analysis, each neighbourhood factor was categorised into tertiles. National tertile thresholds were used in the analysis of each IMD-derived neighbourhood factor in order to improve the generalisability of results. However, national tertile thresholds were not available for the GLUD 2005. Participant neighbourhood was defined as the LSOA of residence for analyses of socioeconomic deprivation, crime rates, and distance to services. For the analysis of greenspace availability, the census output area was used to define participant neighbourhood.

Socioeconomic Deprivation

Socioeconomic deprivation was derived from the IMD 2010 income deprivation domain. Using municipal administrative data, income deprivation scores are calculated according to the number of resident adults and children within low-income and/or unemployed families receiving the following benefits: Income Support, Income-based Jobseeker's Allowance, Pension Credit, the Child Tax Credit, and subsistence and/or accommodation support (McLennan *et al.*, 2011). To calculate an income deprivation score, the Office of National Statistics adds the number of individuals receiving any of these benefits and divides the sum by the total population of the LSOA (McLennan *et al.*, 2011). In the current analysis and Chapter 4, socioeconomic deprivation was analysed as a proxy for individual-level socioeconomic position and was thus conceptualised as a confounder. In this analysis, socioeconomic deprivation is conceptualised as a potential neighbourhood-level effect modifier. Socioeconomic deprivation tertiles were referred to as least, moderately, and most deprived.

Crime Rates

Crime was measured using the crime and disorder domain score which reflects the risk of personal or material victimisation within each LSOA. Local police forces are required by law to report notifiable offences related to violence, burglary, theft and criminal damage to the Home Office with details such as geographic location of each reported offence (McLennan *et al.*, 2011). The Office of National Statistics uses GIS applications to overlay the location of each offence with LSOA boundaries (McLennan *et al.*, 2011). The IMD crime domain is then calculated based on the rate of violence, burglary, theft, and criminal damage per 1000 people at risk (McLennan *et al.*, 2011). Crime rate tertiles were referred to as low, moderate, and high crime.

Distance to Services

Distance to services was measured using the geographic barriers sub-domain of the "barriers to housing and social services domain." Geographic barriers sub-domain scores are derived from the mean road distance from the geographic centre of each LSOA to the closest general practitioner surgery, supermarket or convenience store, primary school, and post office. The distance to services variable was analysed as a proxy measure for the walkability of participants' neighbourhoods. Tertiles were referred to as closer, moderate, and further distance.

Greenspace Availability

Greenspace availability was measured using the GLUD 2005 greenspace percentage 300m buffer measure. This measures the proportion of land within a 300m diameter of a person's residence that is classified as greenspace. More specifically, greenspace percentage is the weighted mean percentage of greenspace within each census output area that a participant's 300m residential buffer zone intersects (Wheeler, 2016). In the UK Biobank, greenspace percentage measures were available for 300m and 1km buffer zones (Wheeler, 2016). The current analysis used the 300m buffer zone measure in order to examine greenspace that was in closer proximity to participants' homes and which could in theory be more easily accessed by participants than greenspace within a 1km buffer zone. GLUD 2005 land use classifications are based on more specific classifications generated by Ordnance Survey from topographical and registered land use function data for urban areas greater than six squared kilometres in England and Wales (Department for Communities and Local Government, 2007; Ordnance Survey, 2017b). Technical details regarding the derivation of Ordnance Survey's MasterMap Greenspace product classifications can be found elsewhere (Ordnance Survey, 2017a). Greenspace is characterised by Ordnance Survey as woodlands, semi-natural, beach, man-made or multi-service space that is publicly or privately accessible. These spaces include parks, community gardens, school grounds, golf courses, playing fields, sports facilities, religious grounds, and commercial/business amenity greenspace. Greenspace tertiles were referred to as least, moderate, and most greenspace.

5.2.5 Explanatory Factors

The same explanatory factors described in Sections 3.2.4 and 4.2.4 were included in the current analyses with one exception. Unlike Chapters 3 and 4, socioeconomic deprivation was conceptualised as a neighbourhood factor (i.e. modifier of associations) instead of a proxy indicator of individual-level socioeconomic position. To adjust for potential confounding by individual-level socioeconomic position, the current analyses used self-reported educational attainment. As in Chapters 3 and 4, all other explanatory factors were conceptualised as potential confounders or mediators of associations between social isolation and each outcome.

5.2.6 Statistical Analyses

The Million Women Study database was updated between the Chapter 3 analysis and the current analysis. As a result, 586,885 women, versus 586,881, were considered for inclusion. As in Chapter 4, 502,543 UK Biobank participants were considered for inclusion. Consistent with Chapters 3 and 4, participants were excluded from the analysis if they were observed with the following characteristics: missing survey completion dates (Million Women Study: *n*=2; UK Biobank: *n*=0), recruited from Scotland and Wales (Million Women Study: *n*=39,118; UK Biobank: *n*=56,653), previous hospital admissions for or self-reported diagnoses of vascular disease (Million Women Study: *n*=77,074; UK Biobank: *n*=30,325), self-reported or registered prior cancer diagnoses (Million Women Study: *n*=51,338; UK Biobank: *n*=38,050), reported fair or poor or missing self-rated health (Million Women Study: *n*=74,148; UK Biobank: *n*=88,103), or missing responses to any of the social contact or household occupancy questions (Million Women Study: *n*=19,035; UK Biobank: *n*=5,934). For the current analyses, participants were also excluded if they had missing data for IMD income deprivation, crime, or distance to services measures (Million Women Study: *n*=3,582; UK Biobank: *n*=8,382) and or GLUD greenspace availability (UK Biobank: *n*=2,500).

To address objective one, social isolation was cross-tabulated against each neighbourhood factor. Chi-square tests were used to test for associations between social isolation and neighbourhood factors.

To address objective two, for each neighbourhood factor, analyses of effect modification were conducted as follows. Cox regression was used to estimate relative risks (RR) and 95% confidence intervals (CI) for SCI score in relation to each outcome by level of each neighbourhood factor. Time in study was the underlying time variable for the Million Women Study analysis and attained age was the underlying time variable for the UK Biobank analysis. The Million Women Study analysis stratified for birth and recruitment cohort (i.e. age) and

adjusted for additional personal characteristics (i.e. recruitment region, education, disability), health behaviours (i.e. smoking, alcohol intake, physical activity, body mass index), and physiological factors (i.e. hypertension, diabetes). The UK Biobank analyses were stratified by gender and adjusted for additional personal characteristics (i.e. recruitment region, education, disability), health behaviours (i.e. smoking, alcohol intake, physical activity, body mass index), and physiological factors (i.e. hypertension, diabetes, cholesterol medications). To assess effect modification, an interaction term between the neighbourhood factor and SCI score was fitted. Models with and without the interaction term were then compared using a likelihood ratio (LR) test to determine statistical significance.

Pair-wise spearman correlation tests did not indicate multicollinearity among explanatory factors ($\rho < 0.20$). Weak to moderate correlation was observed amongst the neighbourhood factors ($\rho = 0.17$ to 0.49). Covariates in the Million Women Study and UK Biobank cohorts had minimal missing data (<5.0% missing observations) except for physical activity in the Million Women Study (10.0% missing observations). Missing observations were assigned to a separate category for each variable for analysis. Schoenfeld residuals and log-log plots indicated that the assumption of proportional hazards was reasonable.

The neighbourhood factors examined were derived from neighbourhood-level data and social isolation from individual-level social relationships data. Vascular disease incidence and mortality may be patterned not only by social isolation level, but also by neighbourhood. It was thus deemed appropriate to assess whether clustering of outcomes within neighbourhoods (i.e. intra-class correlation) could affect the standard error of the associations between social isolation and the focal outcomes. Fully-adjusted sensitivity analyses of social isolation and all-cause mortality by level of socioeconomic deprivation were conducted. To account for intra-class correlation, robust standard errors were calculated using a clustered sandwich estimator (Williams, 1995, 2000; Floud *et al.*, 2016). All-cause mortality was specifically chosen for this sensitivity analysis as it was associated with social isolation in Chapters 3 and 4 and measured a larger number of deaths which if clustered, would be more likely to affect associations compared to vascular disease-specific deaths. Socioeconomic deprivation was chosen because it was the only neighbourhood factor that had previous research with which to compare results.

All analyses were conducted using Stata 15.1 (StataCorp College Station, TX, USA).

5.3 Results

In total, 322,588 Million Women Study participants and 272,596 UK Biobank participants without pre-existing vascular disease or cancer or fair/poor self-rated health were included in this analysis. The current analysis cohorts were smaller than those examined in Chapters 3 and 4 due to the exclusion of people with missing data for IMD 2010 and GLUD measures. Despite this, the characteristics of both cohorts were similar to those from Chapter 3 and 4 (Tables: A5.2, A5.3, pp.232-233; 3.3; 4.2). The mean age was 67.7 (*SD*=4.5) years and 56 years (*SD*=8.1) for the Million Women Study and UK Biobank respectively, and in both cohorts approximately 12.0% were within the most isolated SCI score category (Million Women Study: *n*=38,514; UK Biobank: *n*=34,483). Compared to the least isolated participants, the most isolated participants tended to be less educated, have greater disability, to be current smokers, less physically active, have higher BMI and have pre-existing hypertension and diabetes. Million Women Study participants were followed for on average 5.9 years (*SD*= 1.1), and there were 10,819 incident CHD events, 6,234 incident stroke events, 555 CHD deaths, 584 stroke deaths, and 9,561 deaths from any cause (Table A5.3, pp.233). UK Biobank participants were followed for on average 6.8 years (*SD*=0.9), and there were 6,439 incident CHD events, 2,068 incident stroke events, 405 CHD deaths, 180 stroke deaths, and 4,253 deaths from any cause (Table A5.3).

Social isolation tended to increase in prevalence in neighbourhoods with greater socioeconomic deprivation, higher crime rates, and less greenspace (Table 5.1). In contrast to the original hypothesis, social isolation tended to be more prevalent within neighbourhoods that were closer to rather than further from services (Table 5.1). The proportion of participants within the most isolated category varied by approximately five percentage points across levels of each neighbourhood factor (e.g. Million Women Study, Percentage Most Isolated, Low Crime: 10.3%, Moderate Crime: 12.7%, High Crime: 15.7%; UK Biobank, Percentage Most Isolated, Low Crime: 10.9%, Moderate Crime: 12.6%, High Crime: 15.0%). More modest variation was observed according to greenspace availability (UK Biobank, Percentage Most Isolated, Least Greenspace: 13.9%, Moderate Greenspace: 12.7%, Most Greenspace: 11.4%) and greater variation was observed according to socioeconomic deprivation in the Million Women Study (Percentage Most Isolated: Least Deprived: 9.6%, Moderately Deprived: 12.9%, Most Deprived: 18.5%). Variation in the proportion of participants across levels of isolation and each neighbourhood factor was statistically significant (*unadjusted p*<0.0001, Table 5.1).

Table 5.1. Participants' neighbourhood characteristics by level of social isolation.

Neighbourhood Factors	n	Most Isolated (%)	p-value
A. Million Women Study	N=322,588		
Socioeconomic Deprivation Tertile			
Least Deprived	165,907	9.6	<0.0001
Moderately Deprived	113,059	12.9	
Most Deprived	43,622	18.5	
Crime Rate Tertile			
Low Crime	171,017	10.3	<0.0001
Moderate Crime	99,144	12.7	
High Crime	52,427	15.7	
Distance to Services Tertile			
Closer Distance	64,991	14.9	<0.0001
Moderate Distance	104,860	12.4	
Further Distance	152,737	10.3	
B. UK Biobank	N=272,596		
Socioeconomic Deprivation Tertile			
Least Deprived	140,317	11.0	<0.0001
Moderately Deprived	85,884	13.0	
Most Deprived	46,395	16.9	
Crime Rate Tertile			
Least Crime	98,194	10.9	<0.0001
Moderate Crime	101,629	12.6	
Most Crime	72,773	15.0	
Greenspace Availability Tertile			
Least Greenspace	89,439	13.9	<0.0001
Moderate Greenspace	88,225	12.7	
Most Greenspace	94,932	11.4	

Note: p-value from chi-square test of heterogeneity

5.3.1 Socioeconomic Deprivation

Vascular Disease Incidence

Within the Million Women Study, no statistically significant differences in associations between social isolation, CHD incidence, and stroke incidence were observed according to neighbourhood socioeconomic deprivation. However, the test of interaction for associations with stroke incidence was marginally statistically non-significant (Table 5.2; *p for interaction*=0.05). Within the UK Biobank, no statistically significant differences in associations between social isolation, CHD incidence, and stroke incidence were observed according to neighbourhood socioeconomic deprivation. However, the test of interaction for associations with CHD incidence was marginally statistically non-significant (Table 5.2; *p for interaction*=0.05).

Vascular Disease Mortality

Within both cohorts, no statistically significant differences in associations between social isolation and CHD mortality were observed according to neighbourhood socioeconomic deprivation (*p for interaction*≥0.31). Within both cohorts, there were statistically significant differences in the associations between social isolation and stroke mortality according to neighbourhood deprivation (Table 5.2). From least deprived to most deprived, the most isolated Million Women Study participants had 81%, 6%, and 92% greater stroke mortality than less isolated participants respectively (*p for interaction*=0.04; Table 5.2). The most isolated UK Biobank participants in the least deprived neighbourhoods had 14% lower stroke mortality than less isolated participants, and the most isolated participants from moderately and the most deprived neighbourhoods had 128% and 194% greater stroke mortality than less isolated participants respectively (*p for interaction*=0.02; Table 5.2). It should be noted that in the UK Biobank cohort, few stroke deaths were observed across sub-categories of social isolation and socioeconomic deprivation tertiles.

All-Cause Mortality

Within the Million Women Study, there were statistically significant differences in the associations between social isolation and all-cause mortality according to neighbourhood deprivation (*p for interaction*<0.01; Table 5.2). From least deprived to most deprived, the most isolated women had 30%, 9%, and 36% greater all-cause mortality than less isolated women respectively (Table 5.2). Within the UK Biobank, no statistically significant differences in

associations between social isolation and all-cause mortality were observed according to neighbourhood socioeconomic deprivation.

5.3.2 Crime Rates

Vascular Disease Incidence

In both the Million Women Study and UK Biobank cohorts, there were no statistically significant differences in associations between social isolation, CHD incidence, and stroke incidence according to neighbourhood crime rates (*p for interaction*≥0.10).

Vascular Disease Mortality

In both the Million Women Study and UK Biobank cohorts, there were no statistically significant differences in associations between social isolation and CHD mortality according to neighbourhood crime tertile (*p for interaction*≥0.66). Within the Million Women Study, no statistically significant differences in associations between social isolation and stroke mortality were observed according to neighbourhood crime rates (*p for interaction*=0.95). Within the UK Biobank, there were statistically significant differences in associations between social isolation and stroke mortality (*p for interaction*=0.03; Table 5.3). The most isolated UK Biobank participants from low crime neighbourhoods had 33% lower stroke mortality than less isolated participants, and the most isolated participants from moderate and high crime neighbourhoods had 101% and 183% greater stroke mortality than less isolated participants respectively (Table 5.3). It should be noted that few stroke deaths were observed across sub-categories of social isolation and neighbourhood crime tertiles.

All-Cause Mortality

Within the Million Women Study, there were statistically significant differences in associations between social isolation and all-cause mortality according to neighbourhood crime rates (*p for interaction*=0.02; Table 5.3). From low crime to high crime, the most isolated women had 15%, 26%, and 39% greater all-cause mortality than less isolated women respectively (Table 5.3). Within the UK Biobank, no statistically significant differences in associations between social isolation and all-cause mortality were observed according to neighbourhood crime rates (*p for interaction*=0.87).

Table 5.2. Fully adjusted RR and 95% CI for social isolation in relation to all outcomes by neighbourhood socioeconomic deprivation tertile.

	Least Deprived		Moderately Deprived		Most Deprived		
	n	RR 95% CI	n	RR 95% CI	n	RR 95% CI	p for interact-ion
A. Million Women Study							
CHD Incidence							
Less Isolated	4,598	1.00 (-)	3,279	1.00 (-)	1,294	1.00 (-)	0.35
Most Isolated	640	1.08 (0.99, 1.17)	607	1.03 (0.94, 1.12)	401	1.15 (1.02, 1.28)	
Stroke Incidence							
Less Isolated	2,605	1.00 (-)	1,866	1.00 (-)	669	1.00 (-)	0.05
Most Isolated	435	1.21 (1.09, 1.34)	393	1.10 (0.99, 1.23)	266	1.38 (1.19, 1.59)	
CHD Mortality							
Less Isolated	197	1.00 (-)	155	1.00 (-)	65	1.00 (-)	0.31
Most Isolated	57	1.83 (1.36, 2.47)	44	1.31 (0.93, 1.83)	37	1.72 (1.15, 2.59)	
Stroke Mortality							
Less Isolated	218	1.00 (-)	178	1.00 (-)	60	1.00 (-)	0.04
Most Isolated	57	1.81 (1.35, 2.43)	37	1.06 (0.74, 1.52)	34	1.92 (1.26, 2.93)	
All-Cause Mortality							
Less Isolated	3,795	1.00 (-)	2,828	1.00 (-)	1,151	1.00 (-)	<0.01
Most Isolated	706	1.30 (1.20, 1.41)	610	1.09 (1.00, 1.19)	471	1.36 (1.22, 1.51)	
B. UK Biobank							
CHD Incidence							
Less Isolated	2,910	1.00 (-)	1,735	1.00 (-)	983	1.00 (-)	0.05
Most Isolated	315	0.87 (0.77, 0.97)	284	1.08 (0.95, 1.22)	212	0.96 (0.83, 1.12)	
Stroke Incidence							
Less Isolated	885	1.00 (-)	562	1.00 (-)	313	1.00 (-)	0.26
Most Isolated	118	1.12 (0.92, 1.35)	93	1.11 (0.89, 1.38)	97	1.40 (1.11, 1.76)	
CHD Mortality							
Less Isolated	163	1.00 (-)	101	1.00 (-)	63	1.00 (-)	0.63
Most Isolated	30	1.45 (0.98, 2.15)	21	1.35 (0.84, 2.16)	27	1.82 (1.16, 2.86)	
Stroke Mortality							
Less Isolated	76	1.00 (-)	36	1.00 (-)	28	1.00 (-)	0.02
Most Isolated	8	0.86 (0.41, 1.78)	13	2.28 (1.21, 4.32)	19	2.94 (1.63, 5.28)	
All-Cause Mortality							
Less Isolated	1,735	1.00 (-)	1,172	1.00 (-)	653	1.00 (-)	0.84
Most Isolated	274	1.29 (1.14, 1.47)	223	1.25 (1.08, 1.44)	196	1.33 (1.13, 1.56)	

Table 5.3. Fully adjusted RR and 95% CI for social isolation in relation to all outcomes by neighbourhood crime rate tertile.

	Low Crime		Moderately Crime		High Crime		p for interact-ion
	n	RR 95% CI	n	RR 95% CI	n	RR 95% CI	
A. Million Women Study							
CHD Incidence							
Less Isolated	4,785	1.00 (-)	2,876	1.00 (-)	1,510	1.00 (-)	0.72
Most Isolated	750	1.10 (1.02, 1.19)	542	1.06 (0.97, 1.16)	356	1.05 (0.93, 1.18)	
Stroke Incidence							
Less Isolated	2,730	1.00 (-)	1,595	1.00 (-)	815	1.00 (-)	0.10
Most Isolated	461	1.11 (1.01, 1.23)	390	1.30 (1.16, 1.45)	243	1.25 (1.08, 1.44)	
CHD Mortality							
Less Isolated	210	1.00 (-)	138	1.00 (-)	69	1.00 (-)	0.62
Most Isolated	63	1.71 (1.29, 2.28)	42	1.40 (0.99, 1.98)	33	1.74 (1.15, 2.65)	
Stroke Mortality							
Less Isolated	236	1.00 (-)	146	1.00 (-)	74	1.00 (-)	0.95
Most Isolated	55	1.48 (1.10, 2.00)	45	1.59 (1.14, 2.23)	28	1.54 (0.99, 2.39)	
All-Cause Mortality							
Less Isolated	4,020	1.00 (-)	2,416	1.00 (-)	1,338	1.00 (-)	0.02
Most Isolated	727	1.15 (1.06, 1.25)	600	1.26 (1.15, 1.38)	460	1.39 (1.25, 1.54)	
B. UK Biobank							
CHD Incidence							
Less Isolated	2,101	1.00 (-)	2,074	1.00 (-)	1,453	1.00 (-)	0.87
Most Isolated	260	0.99 (0.87, 1.12)	288	0.95 (0.84, 1.07)	263	0.95 (0.83, 1.08)	
Stroke Incidence							
Less Isolated	633	1.00 (-)	638	1.00 (-)	489	1.00 (-)	0.66
Most Isolated	84	1.10 (0.88, 1.38)	108	1.18 (0.96, 1.45)	116	1.27 (1.04, 1.56)	
CHD Mortality							
Less Isolated	115	1.00 (-)	122	1.00 (-)	90	1.00 (-)	0.95
Most Isolated	22	1.49 (0.94, 2.35)	27	1.48 (0.97, 2.25)	29	1.61 (1.06, 2.46)	
Stroke Mortality							
Less Isolated	48	1.00 (-)	58	1.00 (-)	34	1.00 (-)	0.03
Most Isolated	4	0.67 (0.24, 1.87)	17	2.01 (1.16, 3.47)	19	2.83 (1.61, 4.99)	
All-Cause Mortality							
Less Isolated	1,293	1.00 (-)	1,253	1.00 (-)	1,014	1.00 (-)	0.87
Most Isolated	212	1.34 (1.16, 1.55)	232	1.27 (1.10, 1.46)	249	1.29 (1.12, 1.48)	

5.3.3 Distance to Services

In the Million Women Study, there were no statistically significant differences in associations between social isolation and each outcome according to neighbourhood distance to services (all associations: *p for interaction*≥0.12; Table 5.4).

5.3.4 Greenspace Availability

Vascular Disease Mortality

Within the UK Biobank, there were statistically significant differences in associations between social isolation and stroke mortality according to greenspace availability (*p for interaction*=0.02; Table 5.5). The most isolated participants from neighbourhoods with the least and moderate greenspace had 114% and 189% greater stroke mortality than less isolated participants, and the most isolated participants from neighbourhoods with the most greenspace had 21% lower stroke mortality than less isolated participants respectively (Table 5.5). It should be noted that few stroke deaths were observed across sub-categories of social isolation and neighbourhood greenspace availability tertile.

There was no statistically significant evidence for associations between social isolation and any other outcomes varying according to neighbourhood greenspace availability (all other associations: *p for interaction*≥0.74; Table 5.5).

5.3.5 Sensitivity Analyses

After accounting for intra-class correlation, there were negligible changes in the confidence intervals for associations between social isolation and all-cause mortality by level of socioeconomic deprivation (Table A5.4, pp.233).

Table 5.4. Fully adjusted RR and 95% CI for social isolation in relation to all outcomes by neighbourhood distance to services tertile.

	Closer Distance		Moderate Distance		Further Distance		
	n	RR 95% CI	n	RR 95% CI	n	RR 95% CI	p for interact-ion
Million Women Study							
CHD Incidence							
Less Isolated	1,979	1.00 (-)	3,007	1.00 (-)	4,185	1.00 (-)	0.83
Most Isolated	442	1.05 (0.95, 1.16)	558	1.08 (0.98, 1.18)	648	1.09 (1.01, 1.19)	
Stroke Incidence							
Less Isolated	1,089	1.00 (-)	1,685	1.00 (-)	2,366	1.00 (-)	0.24
Most Isolated	322	1.31 (1.16, 1.49)	357	1.15 (1.03, 1.29)	415	1.16 (1.04, 1.29)	
CHD Mortality							
Less Isolated	87	1.00 (-)	151	1.00 (-)	179	1.00 (-)	0.12
Most Isolated	39	1.72 (1.17, 2.51)	39	1.21 (0.85, 1.73)	60	1.93 (1.44, 2.60)	
Stroke Mortality							
Less Isolated	96	1.00 (-)	154	1.00 (-)	206	1.00 (-)	0.44
Most Isolated	41	1.84 (1.27, 2.66)	39	1.33 (0.93, 1.90)	48	1.50 (1.09, 2.06)	
All-Cause Mortality							
Less Isolated	1,579	1.00 (-)	2,572	1.00 (-)	3,623	1.00 (-)	0.77
Most Isolated	454	1.22 (1.10, 1.36)	633	1.28 (1.17, 1.39)	700	1.23 (1.13, 1.34)	

Table 5.5. Fully adjusted RR and 95% CI for social isolation in relation to all outcomes by neighbourhood greenspace availability tertile.

	Least Greenspace		Moderate Greenspace		Most Greenspace		
	n	RR 95% CI	n	RR 95% CI	n	RR 95% CI	p for interact-ion
UK Biobank							
CHD Incidence							
Less Isolated	1,670	1.00 (-)	1,896	1.00 (-)	2,062	1.00 (-)	0.77
Most Isolated	276	1.00 (0.88, 1.13)	274	0.94 (0.83, 1.07)	261	0.94 (0.83, 1.08)	
Stroke Incidence							
Less Isolated	567	1.00 (-)	546	1.00 (-)	647	1.00 (-)	0.84
Most Isolated	108	1.18 (0.96, 1.45)	95	1.16 (0.94, 1.45)	105	1.26 (1.03, 1.55)	
CHD Mortality							
Less Isolated	113	1.00 (-)	99	1.00 (-)	115	1.00 (-)	0.99
Most Isolated	29	1.53 (1.01, 2.30)	24	1.50 (0.96, 2.36)	25	1.58 (1.02, 2.43)	
Stroke Mortality							
Less Isolated	43	1.00 (-)	39	1.00 (-)	58	1.00 (-)	0.02
Most Isolated	16	2.14 (1.20, 3.82)	18	2.89 (1.65, 5.08)	6	0.79 (0.34, 1.82)	
All-Cause Mortality							
Less Isolated	1,103	1.00 (-)	1,144	1.00 (-)	1,313	1.00 (-)	0.74
Most Isolated	234	1.29 (1.12, 1.49)	241	1.36 (1.19, 1.57)	218	1.26 (1.09, 1.46)	

5.4 Discussion

Within two large cohorts of adults in England without vascular disease, cancer, and poor or fair self-rated health, social isolation was more prevalent in neighbourhoods with greater deprivation, higher crime, closer proximity to services, and less greenspace. The Million Women Study and UK Biobank analyses present inconsistent evidence that social isolation was more detrimental to health in more deprived and higher crime neighbourhoods. In fully adjusted Million Women Study analyses, the most isolated participants living in the least and most deprived neighbourhoods tended to have the greatest all-cause mortality compared to moderately deprived neighbourhoods. This finding did not align with the hypothesis that the strength of association between social isolation and mortality would increase as socioeconomic deprivation increased. No differences in associations were observed among UK Biobank participants according to socioeconomic deprivation. As hypothesised, in the Million Women Study, greater all-cause mortality was observed among the most isolated participants living in moderate and high crime neighbourhoods compared to those living in low crime neighbourhoods. Within the UK Biobank, no such differences were observed across neighbourhood crime tertiles. Statistically significant effect modification was observed for associations between social isolation and stroke mortality across neighbourhood deprivation tertiles in the Million Women Study and UK Biobank. Statistically significant effect modification on social isolation and stroke mortality was also observed across crime rate tertiles and greenspace availability in the UK Biobank. However, few stroke deaths were observed across deprivation, crime, and greenspace tertiles, and the strength of associations across these tertiles did not vary in the hypothesised directions. Statistically significant effect modification was not observed according to neighbourhood deprivation, crime rates, or greenspace availability for any other outcomes. Finally, there was no evidence that social isolation was more detrimental to health in neighbourhoods that were further from services.

Prevalence of Social Isolation across Neighbourhood Factors

As hypothesised, social isolation tended to be more prevalent in neighbourhoods with greater deprivation, higher crime, and with lesser greenspace availability. These findings were supported by previous research (Abraham *et al.*, 2010; Diez Roux and Mair, 2010; Nicholson, 2012; Hassen and Kaufman, 2016). It was also hypothesised that social isolation would be more prevalent in neighbourhoods that were further from services. However, the bivariate analyses found lower prevalence of social isolation in these neighbourhoods. An explanation for this finding could be that individuals living in areas with greater distances between people

and amenities may place greater value in seeking regular interaction, have stronger cultural norms around social connection, and thus be less social isolated as observed in previous qualitative research (Winterton and Warburton, 2011; Menec *et al.*, 2015, 2019). It should be noted, that variation in the prevalence of social isolation across tertiles of neighbourhood factors was generally subtle and these bivariate analyses did not adjust for other factors which may explain the observed heterogeneity (e.g. age demographics of specific neighbourhoods, cultural factors affecting social interaction).

Effect Modification by Neighbourhood Deprivation and Crime

The general hypothesis explored in the current analysis was the following: certain neighbourhood environments may influence how social isolation is interpreted and experienced psychologically, responded to behaviourally, and embodied physiologically, and this may lead to stronger or weaker associations with health (Krieger, 2001; Berkman and Krishna, 2014; Kubzansky *et al.*, 2014). The current analyses found some, albeit largely weak and inconsistent, evidence of effect modification between socioeconomic deprivation, crime rates, and social isolation. In line with previous research, it was hypothesised that the strength of association between social isolation and all-cause mortality would increase with greater deprivation and crime (Marcus *et al.*, 2016). Within the current analysis of the Million Women Study participants, associations between social isolation and all-cause mortality were strongest among the least and most deprived neighbourhoods. This represents a novel finding within the literature as the only other study examining the effect modification of neighbourhood deprivation on social isolation and mortality observed modestly stronger associations between social isolation and all-cause mortality in high poverty compared to low poverty neighbourhoods (*High poverty RR*=1.41, *95% CI*: 1.27-1.58, $p<0.0001$; *Low poverty RR*=1.45, *95% CI*: 1.18-1.78, $p<0.0001$). However, in this study the statistical significance of effect modification on the multiplicative scale was not assessed. If indeed causal associations exist between social isolation and mortality, the current analysis suggests that living conditions within the most affluent and most deprived neighbourhoods may share or have unique characteristics which make social isolation more detrimental to health compared to moderately deprived neighbourhoods. As hypothesised, within the Million Women Study, associations between social isolation and all-cause mortality strengthened as neighbourhood crime rates increased. The current analysis is the first to assess neighbourhood crime as an effect modifier of these associations, and this finding complements hypotheses originating from previous qualitative research.

Given that the effect modification observed for social isolation and all-cause mortality by socioeconomic deprivation and crime was not replicated within the UK Biobank, and the lack of strong supporting evidence from previous empirical studies, caution should be exercised when interpreting these findings. Qualitative research suggests that isolated people in more deprived and higher crime neighbourhoods may have less access to health and social services and experience fear or insecurity which is believed to dissuade older adults from engaging within their communities (Nicholson, 2012; Finlay and Kobayashi, 2018; Portacolone *et al.*, 2018). People living in more deprived communities may also be predisposed to forming different types of relationships which may confer different health promoting or deleterious effects on mortality (Marcus *et al.*, 2015). However, research has yet to offer explanation for why the magnitude of association between social isolation and mortality would be greater in the least deprived neighbourhoods and most deprived neighbourhoods than in moderately deprived neighbourhoods.

The statistically significant effect modification observed may be at least in-part explained by chance and unmeasured confounding. If Bonferroni correction for multiple testing was applied, effect modification for associations between social isolation and all-cause mortality by neighbourhood socioeconomic deprivation would remain statistically significant at *p for interaction*=0.03 (*Bonferroni corrected p-value* = $p \cdot \kappa$; where p is the observed p-value [0.0017] and κ is the number of significance tests performed [15]) (Bland and Altman, 1995). However, the Bonferroni corrected p for interaction for all other outcomes and neighbourhood factors would exceed *p for interaction*=0.27. While the Bonferroni method is a conservative approach to accounting for multiple testing, similar results would be found if α=0.01 was used as the threshold for statistical significance. In summary, the problem of multiple comparisons further weakens the evidence for effect modification of associations between social isolation and mortality by neighbourhood deprivation and crime.

Weak Evidence of Modification of Associations between Social Isolation and Stroke Mortality

Statistically significant variation in associations between social isolation and stroke mortality were observed across tertiles of socioeconomic deprivation, crime rates (UK Biobank only), and greenspace availability. Caution should be exercised when interpreting these findings. In the current analysis, low case frequencies may limit the accuracy and reliability of associations and statistically significant effect modification observed. For the UK Biobank analyses in particular, at most 20 stroke deaths were observed among the most isolated participants within the aforementioned tertiles (Tables 5.2, 5.3 and 5.5). The overestimation of associations

between social isolation within specific tertiles of a neighbourhood factor with few deaths, may have biased the RR estimates away from the null. The problem of multiple comparisons should again be considered given that there was only weak evidence of effect modification (*p for interaction* range: 0.02 to 0.04). While generally it remains unclear whether associations between social isolation and stroke mortality are influenced by neighbourhood deprivation, crime rates, and greenspace, considering the probability of bias in these findings, it is unlikely that the effect modification observed was meaningful.

Effect Modification by Neighbourhood Distance to Services and Greenspace

Within both the Million Women Study and the UK Biobank, no statistically significant effect modification was observed according to neighbourhood distance to services and by and large, greenspace availability. This finding is noteworthy because no previous studies have examined physical characteristics of neighbourhoods as modifiers of associations between social isolation and health. It was hypothesised that greater proximity and exposure to greenspace and venues for social interaction may buffer any deleterious effects of stress induced by social isolation (Pun, Manjourides and Suh, 2018). The current analyses suggest that factors like distance to and the availability of venues for social interaction like shops and parks, may not influence any explanatory pathways linking social isolation, vascular disease, and mortality. Alternatively, any effect modification could have been too weak to detect because these neighbourhood factors may be indirectly implicated along potential causal pathways and be contingent on a several other mediating and confounding factors. However, given the size of the cohorts examined and the number of incident cases and all-cause deaths observed, insufficient statistical power was not perceived as a concern for these analyses.

Implications for Intervention

Despite weak evidence of effect modification by neighbourhood factors on associations between social isolation, vascular disease, and mortality, neighbourhood factors may still be suitable targets for preventing social isolation and promoting population health. It remains possible that the baseline risk of mortality may vary across neighbourhood factor tertiles and thus indicate higher-risk communities who may particularly benefit from targeted interventions. Due in part to this, some advocate for examining effect modification on multiplicative and additive scales (VanderWeele and Knol, 2014). Marcus and colleagues (2016) did not find statistically significant evidence of effect modification on an additive scale. However, the relative excess risk due to interaction and attributable proportion due to interaction measures of additive interaction and—to a lesser degree—the synergy index used

by Marcus and colleagues (2016) may be biased measures of interaction in the presence of confounding (Skrondal, 2003). Additive hazards regression may be a useful method for assessing effect modification on an additive scale (Rod *et al.*, 2012). Additive hazards regression was not implemented in the current analysis because the Million Women Study and UK Biobank data accommodated the proportional hazards assumption. Therefore, to maintain consistency throughout this thesis, Cox regression was deemed most appropriate method of analysis. Future research should examine whether methods for studying additive interaction such as additive hazards modelling produce similar findings as the current analysis.

Strengths and Limitations

The large size and novel use of data from the IMD 2010 and GLUD 2005 are key strengths of the current analysis. However, there are limitations which merit discussion. First, there may be a few sources of measurement error in the neighbourhood factors examined. The Million Women Study 12-year re-survey and UK Biobank data was predominantly collected between 2010 and 2012, the data used to calculate IMD 2010 scores were collected in 2008, and the GLUD 2005 uses census output area boundaries used in the 2001 census. There may thus be misclassification bias from participants moving address, and changes in these neighbourhood factors or neighbourhood boundaries over time. However, few are believed to have moved during the observation period and it is unlikely that neighbourhood scores on these IMD domains nor percentage greenspace would change considerably over this timeframe. Also, the spatial scale used to define neighbourhoods (i.e. LSOA) may not accurately represent what participants perceive as their neighbourhood. A person's perceived neighbourhood, or where they spend most of their time may not be within the LSOA boundaries. Therefore, it may be unreasonable to assume that all people within the LSOA have uniform level of exposure. The distance to services measure does not account for people's distance to neighbours or access to other important sources of, or facilitators to social interaction (e.g. public transportation, places of worship, cafes and restaurants, community centres). Therefore, the distance to services measure may have misclassified neighbourhoods which in reality are more or less proximal to sources and facilitators of social interaction and thus attenuated any differences in associations across distance tertiles. Finally, the neighbourhood factor and social isolation data was collected at one point in time. It is unclear whether neighbourhood factors preceded the onset of social isolation, and how long participants were exposed to these factors. While the current analysis assumes a direction of associations from neighbourhood factors to social isolation to health outcomes (Figure A5.1), causal associations between social isolation and the examined health outcomes have not been established nor can be inferred from these analyses.

In terms of generalisability, the nature and magnitude of socioeconomic deprivation and prevalence of crime may differ across unrepresented regions of the UK (e.g. Scotland and Wales), and other high, middle, and low-income countries. Given the size of both cohorts and the response rate of the Million Women Study, the generalisability of these findings among generally healthy adults in the UK is believed to be strong. Despite these limitations, the findings of the current analysis are robust given the sample size, the thorough approach to mitigating reverse causation bias, and adjustment for potentially explanatory factors.

5.5 Conclusion and Future Directions

The current analyses were the largest to examine neighbourhood deprivation and first to examine neighbourhood factors such as crime rates, distance to services, and greenspace availability as modifiers of associations between social isolation and vascular disease incidence and mortality. While neighbourhood deprivation, crime rates, distance to services, and greenspace availability were related to the prevalence of social isolation, there was only weak and inconsistent evidence that deprivation and crime modified associations between social isolation and mortality outcomes. There is little evidence to suggest that social isolation interventions which modify the neighbourhood factors examined, may influence vascular disease incidence or mortality outcomes within a population.

In order to advance current theories explaining associations between social isolation and health, it will be essential that future research explicitly defines the hypothesised relationships between neighbourhood factors, social isolation, and the health outcomes being examined. Such hypotheses are largely missing from previous research (Marcus *et al.*, 2016, 2017). Given the focus of this chapter was to examine neighbourhood factors as effect modifiers, it was beyond scope to conduct adjusted analyses of neighbourhood factors in relation to social isolation. Longitudinal research examining neighbourhood environments and the incidence of social isolation while adjusting for various potential explanatory factors is warranted. Data sources such as Understanding Society (i.e. UK Household Longitudinal Study) may represent a key opportunity for this research. To assess the utility of examining effect modification on multiplicative and additive scales, future research examining neighbourhood factor effect modification on social isolation and mortality should consider comparing results from Cox regression and additive hazards models (Rod *et al.*, 2012). Further research examining the neighbourhood factors included in the current analyses and other neighbourhood factors may further clarify if and to what the degree any associations between social isolation and health outcomes are modifiable by neighbourhood factors. Future research into these and other

neighbourhood factors will be important for municipal planners, policy makers, and service providers as they design strategies to address social isolation and promote population health.

Until this point, all analyses of social isolation, vascular disease, and mortality examined structural dimensions of social isolation. Functional and perceived dimensions of social isolation are another group of factors also believed to influence associations between social isolation and health. The following chapter is focused on examining if and to what degree this this is true.

6 Functional and Perceived Dimensions of Social Isolation in Relation to Mortality within the UK Biobank

The results presented in Chapters 3 and 4 showed stronger evidence for associations between social isolation and mortality than between social isolation and vascular disease incidence within the Million Women Study and UK Biobank cohorts. Compared to the least isolated participants, those who were most isolated had 68% to 92% increased risk of death from vascular disease and 30% to 38% increased risk of death from any cause. These analyses examined structural characteristics of people's relationships, that is, more objective measures of social contact frequency, social group participation, and living alone. A potential limitation of the social contact index (SCI) score is that it is more reflective of the quantity as opposed to the quality of social relationships. Within health and social science research communities, some believe that the concept of social isolation should be expanded to include broader dimensions of social relationships including functional characteristics of relationships (e.g. social support), and more subjective feelings which accompany perceived isolation (e.g. loneliness and relationship satisfaction) (Zavaleta *et al.*, 2017; Holt-Lunstad, 2018b; Wister *et al.*, 2019). Multi-dimensional social isolation measures are believed to provide a more comprehensive and accurate assessment of the experience of social isolation and potential effects on health (Holt-Lunstad *et al.*, 2010; Zavaleta *et al.*, 2017; Holt-Lunstad, 2018b; Wister *et al.*, 2019). However, research has yet to compare the independent associations of structural, functional, and perceived isolation in relation to mortality while also examining associations between combinations of more than one dimension (Holt-Lunstad *et al.*, 2015). For example, it is hypothesised that people who are exposed to either structural or perceived isolation and people who are exposed to both have greater risk of death than those who are not exposed to either structural or perceived isolation (Holt-Lunstad *et al.*, 2015). For brevity, here forward, analyses examining associations between specific combinations of social isolation dimensions and mortality will be referred to as "joint associations" or "joint association analyses."

When examining associations between perceived isolation and health it is important to assess how much of any associations can be explained by depression. Psychological pathways such as depression were not examined in Chapter 3 and 4 as it was hypothesised that psychological factors such as depression would be more relevant in explaining associations between

perceived isolation and health (Uchino *et al.*, 1999; Courtin and Knapp, 2017; Wang *et al.*, 2018). Evidence from one prospective cohort study of social isolation and mortality found depressive symptoms to explain a lower proportion of minimally adjusted associations between structural isolation and mortality compared to perceived isolation and mortality (Elovainio *et al.*, 2017). However, this analysis of UK Biobank examined perceived isolation using an index of loneliness which was constituted by a measure of social support and a measure of frequency of loneliness. Therefore, further analyses are needed to examine the role of depression in any independent and joint associations between structural, functional (i.e. social support), and perceived isolation (i.e. loneliness and relationship satisfaction) and mortality.

Associations between structural and perceived dimensions of social isolation have been compared to established risk factors such as cigarette smoking (House *et al.*, 1988; Kawachi *et al.*, 1996; Holt-Lunstad *et al.*, 2010; Pantell *et al.*, 2013). Smoking represents a major global risk factor for disease and premature mortality. Worldwide, approximately 146.8 million disability adjusted life years (DALYs) and 6.4 million deaths were attributable to smoking in 2015 (Reitsma *et al.*, 2017). The claim that associations between social isolation and health are comparable to smoking and health has thus gained international attention (Brody, 2013; National Health Service, 2015; AgeUK, 2017; CBC News, 2017; Tate, 2018; Coughlan, 2019; Mahder-Bashi and Savage, 2019) and is cited in scientific literature (Patterson, 2016; Tanskanen and Anttila, 2016; Yang *et al.*, 2016; Courtin and Knapp, 2017). However, research has yet to rigorously examine whether associations between measures of social isolation and mortality are indeed equal to that of smoking.

The current chapter will be presented in two parts. Part 1 will examine multiple dimensions of social isolation in relation to all-cause mortality within the UK Biobank while assessing the role of depression as an explanatory factor. Part 2 will examine whether independent associations between structural, functional, or perceived dimensions of social isolation and mortality are comparable to that of smoking.

6.1 Part 1 – Functional and Perceived Isolation and Mortality

6.1.1 Background

Functional Isolation

Social support is generally described as a perceived resource available or function carried out by someone in order to assist another person (Umberson *et al.*, 2010). For this reason, the near or complete absence of social support can be referred to as functional isolation (Zavaleta *et al.*, 2017; Holt-Lunstad, 2018b). Social support is often categorised as emotional, informational, and instrumental. Emotional support relates to demonstrations of empathy and compassion, informational support relates to sharing helpful information, appraisal, or advice, and instrumental support relates to sharing material goods and assisting with activities (Shor *et al.*, 2013; Berkman and Krishna, 2014). Greater detail and discussion of these concepts is presented in Section 1.4.3.

Associations between social support and mortality have been studied widely (Holt-Lunstad *et al.*, 2010; Umberson *et al.*, 2010; Shor *et al.*, 2013). In their meta-analysis of 73 studies, Holt-Lunstad and colleagues (2010) estimated people with lower levels of informational, instrumental, or emotional support had 35% greater mortality compared to those with high higher levels of support (*weighted mean OR*=1.35, *95% CI*: 1.22-1.49). This estimate may however be inflated by the inclusion of results from unadjusted analyses. Most recently, Shor and colleagues (2013) conducted a meta-analysis of 50 studies examining self-reported informational, instrumental, and emotional support in relation to mortality. Most studies included in this meta-analysis examined emotional support. After adjusting for covariates, study participants with lower levels of support had 11% increased mortality compared to those with higher levels of emotional support (*mean HR*=1.11, *95% CI*: 1.05-1.17, $n_{\text{estimates}}$=121). However, these studies exhibited substantial heterogeneity (I^2=83.4, p<0.05). In sub-group analyses, compared to participants with high social support, there was stronger evidence for increased risk among those with no support (*mean HR*: 1.15, *95% CI*: 1.09-1.27, $n_{studies}$=74), as opposed to those with some support (*mean HR*: 1.08, *95% CI*: 0.99-1.17, $n_{studies}$=47). While lacking social support (i.e. functional isolation) is associated with increased mortality, it remains unclear to what degree associations are explained by structural dimensions of social isolation, and whether the combination of structural and functional isolation amplifies any associations (Holt-Lunstad *et al.*, 2010, 2015).

Perceived Isolation

Perceived isolation is often referred to as loneliness (Section 1.4.3; Berkman and Krishna, 2014; Zavaleta, Samuel and Mills, 2017). Loneliness is defined as "a distressing feeling that accompanies the perception that one's social needs are not being met by the quantity or especially the quality of one's social relationships" (Hawkley and Cacioppo, 2010). Among studies which did and did not adjust for explanatory factors, Holt-Lunstad and colleagues (2010) estimated that lonely participants had 45% greater mortality compared to those who were not lonely (*weighted mean OR*=1.45, *95% CI*: 1.08-1.94, *n*=8). A subsequent meta-analysis which included analyses focusing on studies adjusting for multiple covariates, found loneliness to be associated with 26% higher mortality compared to participants who were not lonely (*weighted mean OR*=1.26, *95% CI*: 1.04-1.53, *n*=13; Holt-Lunstad *et al.*, 2015). Among the prospective studies of structural isolation reviewed in Chapter 2, three additionally examined associations between loneliness and all-cause mortality (Steptoe *et al.*, 2013; Tanskanen and Anttila, 2016; Elovainio *et al.*, 2017). Note, Steptoe and colleagues (2013) was previously reviewed by Holt-Lunstad and colleagues (2015). Not one study observed associations between loneliness and mortality after adjustment for explanatory factors such as age, gender, socioeconomic factors, health behaviours, baseline physical health status and depressive symptoms. Furthermore, two studies did not observe statistically significant interaction between structural measures of social isolation and loneliness (Steptoe *et al.*, 2013; Tanskanen and Anttila, 2016). However, both studies were relatively small (less than 1,500 deaths) and may be underpowered to detect interaction between structural and perceived isolation. Larger studies which account for reverse causation and confounding are warranted to examine joint associations between structural and perceived isolation, and mortality.

Satisfaction with relationships is another approach to measuring perceived dimensions of isolation (Zavaleta *et al.*, 2017). Few studies have examined general measures of family relationship and friendship satisfaction in relation to mortality. A larger body of work has however examined marital satisfaction and health (Robles *et al.*, 2014). Robles and colleagues' (2014) meta-analysis examining marital satisfaction and mortality found that compared to those with higher quality relationships with their spouse, those with lower quality relationships had approximately 50% higher mortality (pooled estimate of association converted to OR in Holt-Lunstad *et al.* 2017: *OR*=1.49, *95% CI*: 1.16-1.94). These estimates may however be limited by reverse causation bias as some of the studies included patients with poor health (e.g. end-stage renal disease, and cardiovascular disease) at baseline. Particularly in older adulthood, relationships with family members beyond one's spouse (e.g. children) and friends may play

an important role in one's life. Further research is needed to understand whether satisfaction with family relationships and friendships more generally is associated with mortality.

6.1.1.1 Objectives

The primary objective of this Section is to examine whether functional and perceived dimensions of social isolation are associated with all-cause mortality, while:

- minimising bias due to reverse causation;
- examining how much of any association is explained by personal characteristics, health behaviours, physiological factors, and depressive symptoms;
- examining whether any associations are independent of structural dimensions, and;
- examining whether experiencing functional or perceived isolation in addition to structural isolation affects mortality over and above each dimension individually.

6.1.2 Methods

6.1.2.1 Study Design and Participants

Data from UK Biobank was examined for this analysis because participants were asked questions about frequency of loneliness, availability of confiding support, and relationship satisfaction. The UK Biobank cohort is described in detail within Section 4.2.1. The Million Women Study 15-year resurvey also asked participants about loneliness; however, data was only available for a subsample of participants with a shorter follow-up period (approximately four years). Due to low death frequencies across levels of the social contact index (SCI) and loneliness and incomplete data for key covariates like smoking, the Million Women Study data was not analysed.

6.1.2.2 Exposures

The main exposures examined were functional isolation (i.e. confiding support), and perceived isolation (i.e. loneliness and relationship satisfaction). In addition to questions regarding frequency of social contact and living alone, the UK Biobank touchscreen questionnaire asked participants if they often feel lonely, how often they are able to confide in someone close to them, and their level of satisfaction with family relationships and friendships. These questions as they appear in the questionnaire are presented in Figure 6.1. To ascertain those who had at least some access to confiding support, the following categories were combined: "almost

daily," "2-4 times a week," "about once a week," "about once a month," "once every few months." Participants who were "never/almost never" able to confide were considered as having "no support" while those who were able to confide at least every few months were considered as having "support." Participants who responded "Yes" to often feeling lonely were considered "lonely" and those who did not were considered "not lonely." Relationship satisfaction questions were added to the touchscreen questionnaire in 2012. As a result, only a sub-sample of participants completed these questions. Participants were asked, "In general how satisfied are you with your family relationships?" and "In general how satisfied are you with your friendships?" Response options included "extremely happy," "very happy," "moderately happy," "moderately unhappy," "very unhappy," "extremely unhappy," "do not know," and "prefer not to answer." It was unclear from previous literature whether there were meaningful differences in the experience of satisfaction with family relationships versus friendships. Therefore, these variables were combined in order to assess satisfaction with relationships generally (i.e. family or friendships). If participants responded extremely, very, or moderately happy for both family and friendship satisfaction questions, they were considered "satisfied." Due to the low frequency of participants who reported being extremely, very, or moderately unhappy with family relationships and friendships, participants were considered "not fully satisfied" if they were unhappy with either family relationships or friendships. "Do not know" and "prefer not to answer" responses were grouped with missing responses for relationship satisfaction, loneliness, and confiding support variables.

The SCI score described in section 4.1.3 was again used to measure structural social isolation. Due to low case frequencies within some sub-categories of structural, functional, and perceived isolation when examining joint associations and participants within "least isolated" and "moderately isolated" categories were grouped together as in Section 5.2.2.

6.1.2.3 Outcomes

Time to all-cause death was chosen as the outcome of interest because there were insufficient vascular disease deaths observed across levels of the combined social isolation variables.

6.1.2.4 Explanatory Factors

The current analysis examined the same set of explanatory factors as in Chapter 4 in addition to depressive symptoms (Table A6.1, pp.234). It was hypothesised that depression may be a psychological explanatory factor either confounding or mediating associations between loneliness, confiding support and mortality (Shor *et al.*, 2013; Holt-Lunstad *et al.*, 2015; Elovainio *et al.*, 2017). Therefore, self-reported frequency of depressed mood was used as a

proxy measure for depression. UK Biobank participants were asked “Over the past two weeks, how often have you felt down, depressed or hopeless?” Those responding, “Several days,” “More than half the days” or “Nearly every day,” were grouped as having depressive symptoms. Those responding “Not at all” were grouped as not having depressive symptoms. Those responding, “Do not know” and “Prefer not to answer” were grouped as missing.

A. Frequency of Loneliness

Do you often feel lonely?
☐ Yes ☐ No ☐ Do not know ☐ Prefer not to answer

B. Ability to Confide

How often are you able to confide in someone close to you?
☐ Almost daily ☐ 2-4 times a week ☐ About once a week ☐ About once a month ☐ Once every few months ☐ Never or almost never ☐ Do not know ☐ Prefer not to answer

C. Relationship Satisfaction - Family

In general how satisfied are you with your FAMILY RELATIONSHIPS?
☐ Extremely happy ☐ Very happy ☐ Moderately happy ☐ Moderately unhappy ☐ Very unhappy ☐ Extremely unhappy ☐ Do not know ☐ Prefer not to answer

D. Relationship Satisfaction - Friends

In general how satisfied are you with your FRIENDSHIPS?
☐ Extremely happy ☐ Very happy ☐ Moderately happy ☐ Moderately unhappy ☐ Very unhappy ☐ Extremely unhappy ☐ Do not know ☐ Prefer not to answer

Figure 6.1. Confiding support, loneliness and relationship satisfaction questions as they appear on the UK Biobank touchscreen questionnaire.

6.1.2.5 Statistical Analyses

Similar cohort exclusion criteria as described in Section 4.1.5 were used for the current analysis. In total, 502,543 adults from the UK were considered for this analysis. Participants were excluded if they met the following criteria: were recruited from Scotland (*n*=35,845); had previous hospital admissions for CHD or stroke (*n*=21,726); had previous cancer registrations (*n*=29,647); self-reported a previous diagnosis of MI, angina, stroke, or cancer (*n*=20,159); if they reported fair or poor self-rated health (n=92,195); or had missing data for social contact or living alone variables (*n*=6,058), or loneliness (*n*=3,850), or confiding support (*n*=8,484). Analyses of relationship satisfaction additionally excluded persons who were not asked or did not respond to this question (*n*=183,356).

Participants were observed from the time of survey completion to time of death, loss to follow-up, or 31 January 2016. Cox regression was used to estimate relative risks (RR) and 95% confidence intervals (CI). To adjust for age, all models used attained age as the underlying time variable. Minimally adjusted models were also stratified by gender and adjusted for recruitment region. Fully adjusted models further controlled for additional personal characteristics (i.e. socioeconomic deprivation, education, disability), health behaviours (i.e. smoking, alcohol intake, physical activity, BMI), physiological factors (i.e. history of hypertension, history of diabetes, prescription of lipid medications), and psychological factors (i.e. depressed mood). Missing responses for the covariates (less than 3.5% for all variables) were assigned to a separate category.

For the Cox regression analyses, first, minimally and fully adjusted models examined independent associations between confiding support, loneliness, relationship satisfaction, and SCI score and all-cause mortality. In order to assess the degree to which each covariate and group of covariates, particularly depressed mood, explained any associations, the same sequential adjustment approach and LR χ^2 attenuation method described in Section 3.2.5 was conducted. The fully adjusted model for each dimension of isolation was referred to as Model 1. Likelihood ratio χ^2 attenuation analyses of SCI score were previously conducted in Chapter 4. Structural isolation was included in the current analysis in order to compare associations across each dimension of isolation using the same sample of people and to examine the degree to which depressed mood explained minimally adjusted associations between structural isolation and mortality.

Next, to assess whether any associations between measures of functional or perceived isolation were explained by structural isolation, each Model 1 was additionally adjusted for SCI score. These mutually adjusted models were referred to as Model 2. The LR test of heterogeneity was used to assess the statistical significance of the associations in both Models 1 and 2. Finally, an interaction term between structural isolation and each measure of functional and perceived isolation was added to each respective Model 2. These models were referred to as Model 3. To test the statistical significance of any interaction, the LR test of interaction was conducted comparing Model 2 and Model 3. Linear combinations of regression coefficients from Model 3 were used to estimate associations between structural isolation and mortality within strata of functional and perceived isolation.

To examine the assumption of proportional hazards, log-log plots and Schoenfeld residuals were assessed. The assumption was found to be reasonable. To assess multicollinearity, pair-wise spearman correlation coefficients (ρ) were used. Multicollinearity was not believed to bias the analyses as only weak correlation (i.e. $\rho<0.20$) was observed for all covariates except for loneliness and depressed mood which had slightly greater correlation ($\rho=0.33$). All analyses were conducted using Stata 15.1 (StataCorp College Station, TX, USA).

6.1.3 Results

In total, 284,579 participants without previous vascular disease, cancer, or fair/poor self-rated health at baseline were included in analyses involving loneliness and confiding support. Characteristics of this cohort are presented in Table 6.1. During a mean follow-up period of approximately seven years (*SD*: 0.9), there were 4,469 deaths in total. Approximately 12.5% (*n*=35,665) reported never or almost never being able to confide in someone close to them and 14.5% (*n*=41,129) of participants often or always felt lonely. Approximately 21.1% and 20.1% of those who did not have confiding support or who felt lonely, respectively, were within the most isolated SCI score group, compared to 11.3% of those who had support or were not lonely.

Participants reporting no support were more likely to be older and male. Whereas participants reporting loneliness tended to be slightly younger and female. Compared to participants with at least some confiding support, participants who lacked confiding support were more likely to have less education, recently experienced depressed mood, and to be among the most isolated. Compared to participants who did not often or always feel lonely, those who did tended to be more deprived, to have recently experienced depressed mood, and to be among the most isolated. Differences in the proportion of people reporting recent depressed mood across levels of loneliness were marked (Percent reporting depressed mood, Not Lonely: 12.9%; Lonely: 51.8%; Table 6.1).

Within the sub-sample of 101,223 participants who had complete information for relationship satisfaction, 1,235 deaths were observed over a mean follow-up time of six years (*SD*: 0.5) (Table 6.1). Approximately 6.3% (*n*=6,423) of participants were somewhat or very dissatisfied with either their family relationships or friendships. Approximately 23.2% of those who were not fully satisfied with their relationships, were within the most isolated SCI score group, compared to 12.0% of those who had support or were not lonely.

Participants who were not fully satisfied with their relationships were slightly younger and more likely to be male than those who were fully satisfied with their relationships. Compared to those who were fully satisfied with their relationships, those who were not tended to be more deprived, to have recently experienced depressed mood, and to be among the most isolated. Again, the differences in the proportion of people reporting depressed mood across relationship satisfaction were particularly marked (Percent reporting depressed mood, Satisfied: 16.2%; Not Fully Satisfied: 50.5%; Table 6.1).

Table 6.1. Characteristics of UK Biobank cohort by each measure of functional and perceived social isolation.

	Functional Isolation		Perceived Isolation			
	Confiding Support		Loneliness		Satisfaction with Relationships	
Characteristics	Support n=248,914 (87.5%)	No Support n=35,665 (12.5%)	Not Lonely n=243,450 (85.5%)	Lonely n=41,129 (14.5%)	Satisfied n=94,800 (93.7%)	Not Fully Satisfied n=6,423 (6.3%)
Mean age (SD)	55.9 (8.1)	57.0 (7.9)	56.2 (8.1)	55.1 (8.1)	56.4 (8.1)	53.7 (8.0)
Female (%)	57.9	42.1	54.2	65.8	56.5	51.5
Less than secondary education (%)	12.3	18.6	12.7	15.3	11.9	7.9
Most Deprived (%)	28.4	30.9	27.5	35.8	31.5	39.0
Receipt of disability allowance (%)	1.6	2.2	1.5	2.6	1.5	2.2
Current smoker (%)	8.0	9.8	7.8	11.0	7.8	10.7
Alcohol consumed ≥ 5 days/week (%)	21.9	21.6	22.3	19.1	21.8	21.5
Rarely/never exercise (%)	9.2	12.4	9.3	11.0	8.4	9.6
BMI ≥ 30 kg/m^2 (%)	18.3	20.6	18.2	20.8	18.2	17.7
History of hypertension (%)	19.9	22.1	20.3	19.6	20.2	17.3
History of diabetes (%)	2.5	3.1	2.6	2.7	2.8	2.4
Taking cholesterol medications (%)	10.4	11.8	10.8	9.3	11.6	8.3
Depressed mood, past 2 weeks (%)	17.4	25.0	12.9	51.8	16.2	50.5
Structural Isolation						
Most Isolated (%)	11.3	21.1	11.3	20.1	12.0	23.2
Follow-up Information						
Deaths, n	3,688	781	3,808	661	1,164	71
Mean Follow-up (SD)	6.9(0.9)	6.9(0.9)	6.9(0.9)	6.9(0.9)	6.0(0.5)	6.0(0.5)
Person-years (1000s)	1,712	247	1,676	283	572	39

Notes: *N*= 284,579 for analyses of confiding support and loneliness. *N*=101,223 for analyses of relationship satisfaction; Proportions calculated from total of participants with complete information for the respective variable; Participants with missing relationship satisfaction data were included in proportions for loneliness and confiding support, but not relationship satisfaction.

6.1.3.1 Prospective Analyses of Functional Isolation and Mortality

After minimal adjustment for age, gender, and region of recruitment, participants lacking confiding support had 24% increased mortality compared to those with confiding support (Table 6.2, *RR*=1.24, *95% CI*: 1.15-1.34, $p<0.0001$). After full adjustment for personal characteristics, health behaviours, physiological factors, and depressed mood, participants lacking confiding support had 18% greater mortality compared to those with confiding support (Table 6.2, *RR*=1.18, *95% CI*: 1.09-1.27, $p<0.0001$). These covariates explained 42% of the minimally adjusted association (Table 6.2). Personal characteristics and health behaviours accounted for 27% and 26% attenuation in the minimally adjusted associations, respectively. Depressed mood explained 8% of the association. After Model 1 for confiding support was additionally adjusted for SCI score, the association was slightly attenuated but remained statistically significant (Table 6.3, No Support: *RR*=1.15, *95% CI*: 1.06-1.24, $p<0.001$).

As explained in Section 6.1.2.5, one reason SCI score was included in the current analysis was to facilitate comparison of associations across each dimension of social isolation (Tables 6.3 and 6.5). After full adjustment, the most isolated participants had 29% higher mortality than less isolated participants (Table 6.3 and 6.5, Most Isolated: *RR*=1.29, *95% CI*: 1.19-1.40, $p<0.0001$). After Model 1 for SCI score was additionally adjusted for confiding support, the association was slightly attenuated but remained statistically significant (Table 6.3, Most Isolated: *RR*=1.27, *95% CI*: 1.17-1.38, $p<0.0001$).

Interaction between SCI score and confiding support was not statistically significant (Table 6.3, *p for interaction*=0.11). Given the absence of interaction, linear combinations of regression coefficients from Model 2 for each category of SCI score and confiding support were used to examine the magnitude of any joint association (Figure 6.2). After full adjustment, participants who were less isolated and lacked support had 15% greater mortality than those who were less isolated and had confiding support (Figure 6.2, Less Isolated and No Support: *RR*=1.15, *95% CI*: 1.06-1.24). Among the most isolated participants, those with support had 27% greater mortality, and those who lacked support had 46% greater mortality than participants who were less isolated and had support (Figure 6.2, Most Isolated and Support: *RR*=1.27, *95% CI*: 1.17-1.38; Most Isolated and No Support: *RR*=1.46, *95% CI*: 1.31-1.62).

Table 6.2. RR and 95% CI for confiding support in relation to all-cause mortality after adjustment for each group of covariates.

ALL-CAUSE MORTALITY	Support	No Support	p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of deaths	3,688	781			
Age, gender, region (minimally adjusted)	**1.00 (-)**	**1.24 (1.15, 1.34)**	**<0.0001**	**27.9**	**-**
Age, gender, region, personal characteristics	**1.00 (-)**	**1.20 (1.11, 1.30)**	**<0.0001**	**20.4**	**27**
Age, gender, region, deprivation	1.00 (-)	1.22 (1.13, 1.32)	<0.0001	24.5	12
Age, gender, region, education	1.00 (-)	1.22 (1.12, 1.31)	<0.0001	23.2	17
Age, gender, region, disability	1.00 (-)	1.23 (1.14, 1.33)	<0.0001	26.6	5
Age, gender, region, health behaviour factors	**1.00 (-)**	**1.20 (1.11, 1.30)**	**<0.0001**	**20.6**	**26**
Age, gender, region, smoking	1.00 (-)	1.22 (1.13, 1.32)	<0.0001	23.8	15
Age, gender, region, alcohol	1.00 (-)	1.23 (1.14, 1.33)	<0.0001	27.0	3
Age, gender, region, physical activity	1.00 (-)	1.23 (1.14, 1.33)	<0.0001	25.8	7
Age, gender, region, body mass index	1.00 (-)	1.23 (1.14, 1.33)	<0.0001	26.7	4
Age, gender, region, physiological factors	**1.00 (-)**	**1.24 (1.14, 1.34)**	**<0.0001**	**27.3**	**2**
Age, gender, region, hypertension	1.00 (-)	1.24 (1.15, 1.34)	<0.0001	27.6	1
Age, gender, region, diabetes	1.00 (-)	1.24 (1.14, 1.34)	<0.0001	27.6	1
Age, gender, region, cholesterol medications	1.00 (-)	1.24 (1.15, 1.34)	<0.0001	28.1	-1
Age, gender, region, depressed mood	**1.00 (-)**	**1.23 (1.14, 1.33)**	**<0.0001**	**25.6**	**8**
Fully adjusted	**1.00 (-)**	**1.18 (1.09, 1.27)**	**<0.0001**	**16.1**	**42**

Table 6.3. Fully adjusted RR and 95% CI for confiding support in relation to all-cause mortality before and after adjustment for SCI score and in combination with SCI score.

	Model 1			Model 2			Model 3				
							Support		No Support		
	RR	95% CI	p for hetero-geneity	RR	95% CI	p for hetero-geneity	RR	95% CI	RR	95% CI	p for interaction
SCI Score											
Less Isolated, n=3,745	1.00	(-)	<0.0001	1.00	(-)	<0.0001	1.00	(-)	1.00	(-)	0.11
Most Isolated, n=724	1.29	(1.19, 1.40)		1.27	(1.17, 1.38)		1.22	(1.11, 1.34)	1.42	(1.21, 1.66)	
Confiding Support											
Support, n=3,688	1.00	(-)	<0.0001	1.00	(-)	<0.001	-	-	-	-	-
No Support, n=781	1.18	(1.09, 1.27)		1.15	(1.06, 1.24)		-	-	-	-	

Notes: Model 1: Confiding support in relation to all-cause mortality adjusted for personal characteristics, health behaviours, physiological factors, and psychological factors; Model 2: Model 1 additionally adjusted for SCI score; Model 3: Sub-group analysis of SCI score in relation to all-cause mortality within strata of confiding support and adjusted for personal characteristics, health behaviours, physiological factors, and depressed mood.

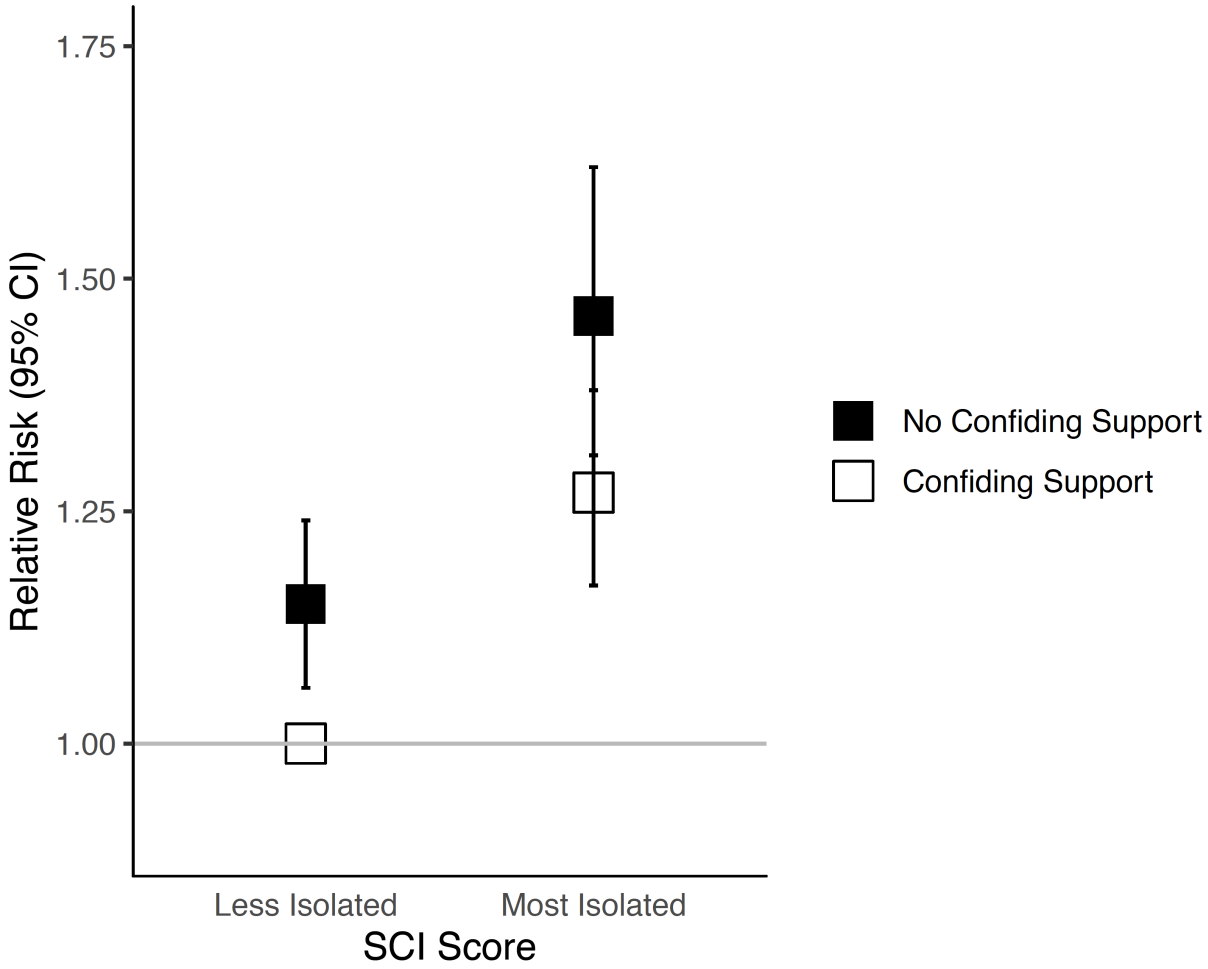


Figure 6.2. Fully adjusted RR and 95% CI for linear combination of regression coefficients from Model 2 for each level of SCI score and confiding support in relation to all-cause mortality.

6.1.3.2 Prospective Analyses of Perceived Isolation and Mortality

After minimal adjustment, lonely participants had 23% increased mortality compared to those who were not lonely (Table 6.4, *RR*=1.23, *95% CI*: 1.13-1.33, *p*<0.0001). Adjustment for explanatory factors attenuated this association by 77%. After full adjustment, lonely participants had 11% greater mortality than those who were not lonely (Table 6.4, Lonely: *RR*=1.11, *95% CI*: 1.01-1.21, *p*=0.02). Personal characteristics and health behaviours accounted for 48% and 40% attenuation in the minimally adjusted associations, respectively. Depressed mood explained 30% of the minimally adjusted association. After Model 1 for loneliness was additionally adjusted for SCI score, the association was attenuated and no longer statistically significant (Table 6.5, Lonely: *RR*=1.08, *95% CI*: 0.99-1.18, *p*=0.10). However, after Model 1 for SCI score was additionally adjusted for loneliness, the association was only slightly attenuated (Table 6.5, Most Isolated: *RR*=1.28, *95% CI*: 1.18-1.39, *p*<0.0001).

Interaction between SCI score and loneliness was not statistically significant (*p* for interaction=0.83). Again, linear combinations of regression coefficients from Model 2 for each category of SCI score and loneliness were used to examine the magnitude of any joint association (Figure 6.3). After full adjustment, participants who were less isolated and lonely had 9% greater mortality than those who were less isolated and not lonely (Figure 6.3, Less Isolated - Lonely: *RR*=1.09, *95% CI*: 0.98-1.20). Among the most isolated participants, those who were grouped as not lonely had 29% greater risk of death and those who were grouped as lonely had 37% increased risk of death compared to participants who were less isolated and not lonely (Figure 6.3, Most Isolated and Not Lonely: *RR*=1.29, *95% CI*: 1.17-1.41; Most Isolated and Lonely: *RR*=1.37, *95% CI*: 1.17-1.59).

In both minimally and fully adjusted models, satisfaction with relationships was not associated with all-cause mortality (Table 6.6). For this reason, Model 1 was not additionally adjusted for SCI score, and interaction between SCI score and relationship satisfaction was not examined.

Table 6.4. RR and 95% CI for loneliness in relation to all-cause mortality after adjustment for each group of covariates.

ALL-CAUSE MORTALITY	Not Lonely		Lonely		p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of deaths	3,688		781				
Age, gender, region (minimally adjusted)	**1.00**	**(-)**	**1.23**	**(1.13, 1.33)**	**<0.0001**	**22.4**	**-**
Age, gender, region, personal characteristics	**1.00**	**(-)**	**1.17**	**(1.08, 1.27)**	**<0.001**	**13.4**	**40**
Age, gender, region, deprivation	1.00	(-)	1.20	(1.10, 1.30)	<0.0001	17.1	24
Age, gender, region, education	1.00	(-)	1.21	(1.12, 1.32)	<0.0001	19.9	11
Age, gender, region, disability	1.00	(-)	1.21	(1.11, 1.31)	<0.0001	19.3	14
Age, gender, region, health behaviour factors	**1.00**	**(-)**	**1.16**	**(1.07, 1.26)**	**<0.001**	**11.6**	**48**
Age, gender, region, smoking	1.00	(-)	1.18	(1.08, 1.28)	<0.001	13.9	38
Age, gender, region, alcohol	1.00	(-)	1.22	(1.13, 1.33)	<0.0001	21.8	3
Age, gender, region, physical activity	1.00	(-)	1.22	(1.13, 1.33)	<0.0001	21.5	4
Age, gender, region, body mass index	1.00	(-)	1.22	(1.12, 1.32)	<0.0001	20.6	8
Age, gender, region, physiological factors	**1.00**	**(-)**	**1.22**	**(1.12, 1.33)**	**<0.0001**	**21.1**	**6**
Age, gender, region, hypertension	1.00	(-)	1.23	(1.13, 1.33)	<0.0001	22.1	2
Age, gender, region, diabetes	1.00	(-)	1.22	(1.12, 1.33)	<0.0001	21.3	5
Age, gender, region, cholesterol medications	1.00	(-)	1.23	(1.13, 1.33)	<0.0001	22.4	0
Age, gender, region, depressed mood	**1.00**	**(-)**	**1.20**	**(1.10, 1.31)**	**<0.0001**	**15.7**	**30**
Fully adjusted	**1.00**	**(-)**	**1.11**	**(1.01, 1.21)**	**0.02**	**5.1**	**77**

Table 6.5. Fully adjusted RR and 95% CI for loneliness in relation to all-cause mortality before and after adjustment for SCI score and in combination with SCI score.

	Model 1			Model 2			Model 3				
							Not Lonely		Lonely		
	RR	95% CI	p for hetero-geneity	RR	95% CI	p for hetero-geneity	RR	95% CI	RR	95% CI	p for inter-action
SCI Score											
Less Isolated, n=3,745	1.00	(-)	<0.0001	1.00	(-)	<0.0001	1.00	(-)	1.00	(-)	0.83
Most Isolated, n=724	1.29	(1.19, 1.40)		1.28	(1.18, 1.39)		1.29	(1.17, 1.41)	1.26	(1.06, 1.49)	
Loneliness											
Not Lonely, n=3,808	1.00	(-)	0.02	1.00	(-)	0.10	-	-	-	-	
Lonely, n=661	1.11	(1.01, 1.21)		1.08	(0.99, 1.18)		-	-	-	-	

Notes**:** Model 1: Loneliness in relation to all-cause mortality adjusted for personal characteristics, health behaviours, physiological factors, and psychological factors; Model 2: Model 1 additionally adjusted for SCI score; Model 3: Sub-group analysis of SCI score in relation to all-cause mortality within strata of loneliness and adjusted for personal characteristics, health behaviours, physiological factors, and depressed mood.

Table 6.6. Minimally and fully adjusted RR and 95% CI for relationship satisfaction in relation to all-cause mortality.

ALL-CAUSE MORTALITY	Satisfied	Not Fully Satisfied	p for heterogeneity
No. of deaths	1,164	71	
Minimally adjusted	1.00 (-)	1.15 (0.91, 1.47)	0.26
Fully adjusted	1.00 (-)	1.13 (0.88, 1.44)	0.35

Notes: Minimally adjusted for age and gender and region of recruitment; Fully adjusted for additional personal characteristics, health behaviours, physiological factors, and depressed mood.

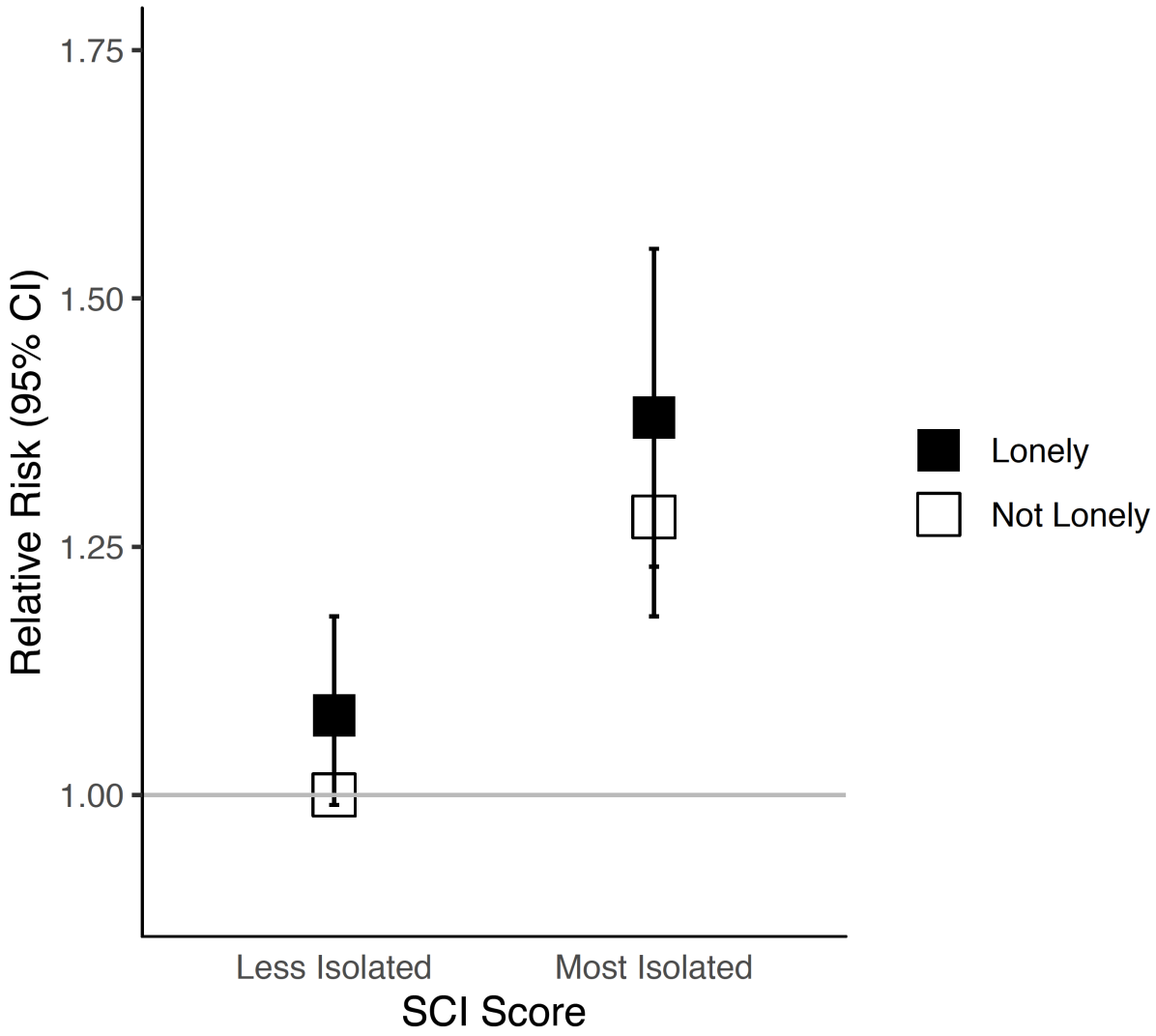


Figure 6.3. Fully adjusted RR and 95% CI for linear combination of regression coefficients from Model 3 for each level of SCI score and loneliness in relation to all-cause mortality.

6.1.3.3 Depression as an Explanatory Factor for Structural Isolation

Another reason SCI score was included in the current analysis was to assess the degree to which depressive symptoms explain associations between structural isolation and mortality (Table A6.2, pp.230). After minimal adjustment for age, gender, and region of recruitment, compared to less isolated participants, the most isolated had 43% increased mortality (Table A6.2, *RR*=1.43, *95% CI*: 1.32-1.55, $p<0.0001$). After full adjustment, the most isolated participants had 29% greater mortality than less isolated participants (Table A6.2, *RR*=1.29, *95% CI*: 1.19-1.40, $p<0.0001$). Overall, personal characteristics, health behaviours, physiological factors, and depressed mood, explained 50% of the minimally adjusted association. Health behaviours and personal characteristics accounted for 36% and 23% attenuation in the minimally adjusted associations, respectively. Depressed mood explained 4% of the minimally adjusted association.

6.1.4 Discussion

Among 284,579 adults without vascular disease, cancer, and fair or poor self-rated health, the current analysis examined functional, perceived, and structural dimensions of social isolation in relation to all-cause mortality. Functional isolation was assessed using a measure of confiding support availability. After adjustment for explanatory factors and structural isolation (i.e. SCI score), lacking confiding support remained associated with approximately 15% excess mortality compared to those with confiding support. Perceived isolation was assessed using measures of loneliness and relationship satisfaction. Loneliness was not associated with mortality after adjustment for explanatory factors and structural isolation. In minimally and fully adjusted analyses, satisfaction with family relationships and friendships was not associated with mortality. Depressed mood tended to explain a much larger proportion of the minimally adjusted association between loneliness and mortality than associations between structural and functional isolation and mortality. No statistically significant interaction between structural isolation and either functional or perceived isolation was observed. Therefore, there was little evidence that combined exposure to structural and functional or structural and perceived isolation was associated with increased mortality risk over and above the mortality risk associated with each measure independently. These findings have implications for how social isolation is measured, current understandings of how social isolation may affect mortality, and directions for future research.

Functional Isolation – Confiding Support

The current analysis found that never or almost never being able to confide in someone close to be associated with 15% increased mortality compared to those who were able to confide at least sometimes. A previous meta-analysis of 74 studies similarly found that after adjusting for potential explanatory factors, those who lacked emotional social support had 15% increased mortality compared to those with some emotional social support (Shor *et al.*, 2013). Previous research has used a variety of measures to assess social support (Shor *et al.*, 2013). Heterogeneity in measurement methods may contribute to inconsistency in the findings of studies published after the meta-analysis search strategy timeframe (Stringhini *et al.*, 2012; Barger, 2013). More recent studies present inconsistent findings. In their longitudinal analysis of Whitehall II participants (waves two, five, and seven), Stringhini and colleagues (2012) examined an index of seven questions from the Close Persons Questionnaire to assess confiding support. They observed lower all-cause mortality among women within the lowest quartile of confiding support compared to higher quartiles of support (*HR*=0.68, *95% CI*: 0.49-0.93) and no associations among men (Stringhini *et al.*, 2012). Barger (2013) analysed the American National Health Interview Study cohort (adults 18 years and older). This analysis examined emotional support using the following question: "How often do you get the social or emotional support you need – always, usually, sometimes, rarely, or never?" No associations with all-cause mortality were observed across levels of emotional support among men nor women (Barger, 2013). In both of the aforementioned analyses, it is unclear whether sufficient cases were observed across levels of social support to detect associations, particularly if as found in the current analysis, confiding support has a weak association with mortality. Due to the size of the current analysis and approaches taken to account for reverse causation and confounding, the associations observed are believed to be robust. However, given that it measured one dimension of social support it remains unclear what specific factors explain the association between confiding support and mortality independent of SCI score.

Explanations for how social support may influence mortality remain inconclusive (Reblin and Uchino, 2008; Berkman and Krishna, 2014). As discussed in Sections 3.4 and 4.4, the availability of someone who can assist another in seeking care during an emergency may be one mechanism explaining increased mortality among more isolated people and/or those lacking support. Confidants are also believed to provide appraisal support which may encourage someone to proactively seek health services (e.g. preventative health services), adopt health behaviours, and adhere to treatment regimens (Reblin and Uchino, 2008; Berkman and Krishna, 2014; Stafford *et al.*, 2018). Emotional support is believed to be particularly important

for maintaining psychological well-being and self-managing symptoms and treatment regimens after major health events like diagnosis of myocardial infarction, stroke, or cancer (Barth, Schneider and von Kanel, 2010; Foster and Fenlon, 2011; Northcott *et al.*, 2016). Social support is also believed to buffer adverse physiological sequelae of distress from life circumstances and illness (Uchino *et al.*, 1999). However, the findings of research examining such physiological pathways and the buffering effects of social support are inconsistent (Reblin and Uchino, 2008). Further research is needed to evaluate the delays in seeking care pathway, and other hypothesised pathways linking social support and mortality, particularly physiological and psychological.

Perceived Isolation - Loneliness

After adjusting for explanatory factors and structural isolation (i.e. SCI score), and when combined with SCI score, there was little evidence of association between loneliness and all-cause mortality. While this finding contrasts the aggregate results of previous meta-analytic research, several studies support the current findings. In their meta-analysis of 13 studies which adjusted for covariates, Holt-Lunstad and colleagues (2015) estimated that compared to those who were less lonely, those who were more lonely had 26% greater mortality (*OR*=1.26, *95%* CI: 1.04-1.53). An important limitation of this estimate is that the studies examined tended to be small, included participants from clinical settings (e.g. people with cancer or awaiting coronary artery bypass grafting), and used several different measures of loneliness. Studies analysing larger cohorts (1,500 to 6,500 participants) and adjusting for multiple explanatory factors (e.g. baseline health condition, personal characteristics, health behaviours, depression), tended not to observe statistically significant associations between loneliness and all-cause mortality (Sugisawa, Liang and Liu, 1994; Penninx *et al.*, 1997; Patterson and Veenstra, 2010; Steptoe *et al.*, 2013; Stessman *et al.*, 2014). More recent analyses of the UK Biobank (Elovainio *et al.*, 2017) and older men in the Netherlands (Julsing *et al.*, 2016) also did not observe statistically significant associations between loneliness and all-cause mortality after adjusting for explanatory factors.

While coming to similar conclusions, there are a few differences between the current analysis of loneliness and Elovainio and colleagues (2017) which merit discussion. First the prevalence of loneliness in the previous UK Biobank analysis (6.0%) was lower than that observed in the current analysis (12.5%). This is likely because people were categorised as lonely if they often/always felt lonely and never/almost never were able to confide in someone close. The rationale provided for aggregating confiding support and loneliness was that similar measures

are included in the revised UCLA Loneliness Scale (Elovainio *et al.*, 2017). Associations between loneliness and mortality may have been underestimated in the previous analysis because individuals who were lonely but had support, and those who were not lonely but lacked support were grouped together with those who were not lonely and had support. This may have increased the baseline hazard of the reference group and thus decreased the differences in baseline hazard compared to the comparison group. Further, as in the current analysis, Elovainio and colleagues (2017) found that depressive symptoms explained larger proportions of associations between loneliness and mortality than structural isolation (i.e. SCI score) and mortality. A larger degree of attenuation may have been observed in Elovainio and colleagues (2017) after adjustment for depressive symptoms because beyond depressed mood, their analyses additionally adjusted for frequency of feelings of un-enthusiasm/disinterest, tenseness/restlessness, and tiredness/lethargy. Given that people of poor or fair self-rated health were included in their cohort, adjustment for these additional indicators of depression may have been accounting for variation attributed to sub-clinical illness rather than depression alone. For example, the percentage of excess risk mediated by depressive symptoms may be inflated because lethargy may be reflective of a range of other physical health conditions. In summary, the current analysis builds upon Elovainio and colleagues (2017), by conceptually distinguishing between functional and perceived dimensions of isolation, and adjusting for a more specific indicator of depression.

Holt-Lunstad and colleagues (2015) hypothesised that the combination of loneliness and social isolation would result in stronger associations than each exposure individually. However, in the current analysis, no statistically significant interaction was observed. When SCI score and loneliness exposure variables were combined, isolated participants who were lonely had similar mortality rates as those who were not lonely. This finding is consistent with two previous analyses of structural and perceived isolation (Steptoe *et al.*, 2013; Tanskanen and Anttila, 2016). In summary, previous claims of an association between loneliness and mortality may be based on evidence biased by small samples, confounding, and reverse causation. If indeed a causal association exists, structural dimensions of social isolation may be more relevant to preventing premature mortality than perceived dimensions.

Perceived Isolation – Relationship Satisfaction

The current analysis represents the largest general assessment of relationship satisfaction in relation to mortality in the UK. No associations between satisfaction with relationships and mortality were observed, however further research is needed to assess the replicability of these

findings and relevance of other outcomes. Merely 6.3% of UK Biobank participants were unsatisfied with either family or friendships. It is unclear to what degree this is reflective of the general population. A survey conducted by the charity, Relate, polled 5,071 of approximately 800,000 YouGov survey participants (16 years and older) and observed that 3.0% of respondents were "not satisfied at all" with their relationship with their partner (Marjoribanks and Darnell Bradley, 2017). However, these results should be interpreted with caution as few details related to selection of participants and survey methods were provided in their report (Marjoribanks and Darnell Bradley, 2017).

In the current analysis, after adjusting for age, gender and recruitment region, relationship satisfaction was not statistically significantly associated with all-cause mortality. This may suggest that relationship satisfaction is not associated with mortality, or the current analysis was underpowered to detect any association. Indeed, only 71 deaths were observed among those who were not fully satisfied with family relationships or friendships. Other indicators of relationship satisfaction may include negative aspects of social relationships (e.g. intimate partner violence) which along with loneliness may be associated with mental health outcomes such as depression (Devries *et al.*, 2013; Wang *et al.*, 2018) and cause-specific mortality (e.g. suicide [Fässberg *et al.*, 2012]). Given that this is the first and largest analysis of general relationship satisfaction in relation to all-cause mortality, further studies of similar scale are needed to assess if and to what degree indicators of relationship satisfaction are associated with mortality and broader health outcomes.

Explanatory Factors

Compared to all other participant characteristics, the most marked differences across participants were observed for depressed mood. Depressed mood was considerably more prevalent among those who were lonely, not fully satisfied with relationships, and to a lesser degree those who lacked confiding support. As hypothesised in Section 1.4.4, for SCI score and confiding support, depressed mood only explained 4% and 8% of minimally adjusted associations with mortality, respectively. Consistent with Chapters 3 and 4, personal characteristics and health behaviours explained the largest degree of these associations between SCI score, confiding support, and mortality. Depressed mood explained a larger degree of the minimally adjusted association between loneliness and mortality. While personal characteristics and health behaviours each accounted for 40% and 48% attenuation in the minimally adjusted LR χ^2, depressed mood explained 30% attenuation. This finding was consistent with other UK Biobank analyses (Elovainio *et al.*, 2017). The current analysis

suggests that depression may be an important explanatory pathway linking loneliness and mortality. Given that the current analysis measured loneliness and depressed mood at one point in time, it remains unclear whether depression represents a confounder or mediator of this association. However, evidence from the longitudinal Chicago Health, Aging, and Social Relations Study suggest that changes in loneliness predicts changes in depressive symptomatology but not vice versa (Cacioppo *et al.*, 2010). The current analysis suggests that psychological pathways linking social relationships and health are more relevant to perceived dimensions of isolation than functional and structural dimensions, while health behaviours remain important pathways for all dimensions. Further research is needed examining the role of physiological pathways explaining these associations with mortality.

Implications for Measuring Social Isolation

The excess mortality observed among those lacking confiding support suggests that adding functional measures of isolation to structural indices of isolation may be useful for predicting mortality. The Lubben Social Network Scale is one example of an index which measures structural and functional measures of isolation (Lubben, 1988; Ceria *et al.*, 2001; Lubben *et al.*, 2006). However, there may be little utility in expanding the structural indices of social isolation to account for perceived isolation. Given that loneliness was moderately correlated with depression, weakly correlated with SCI score, and weakly attenuated associations between SCI score and mortality, loneliness may be more appropriately studied as a psychological explanatory factor for associations between structural isolation and mortality (Berkman *et al.*, 2000).

Limitations

In addition to limitations discussed in Section 4.4, response bias merits further consideration for the current analysis. Single-item assessments of perceived isolation were commonly used in previous studies (Holt-Lunstad *et al.*, 2015). However, direct questions with explicit reference to loneliness are vulnerable to underreporting due to stigma associated with these experiences (Gierveld, 1998). Social desirability bias may thus have contributed to misclassification of loneliness and the underestimation of associations. However, one previous study examining structural and perceived isolation using multi-item scales for loneliness (without explicit vocabulary related to loneliness) generated consistent findings as the current analysis (Steptoe *et al.*, 2013). Given that there is consistency with previous research and that questions were asked via self-administered electronic questionnaire, social desirability bias is not believed to impact the current findings significantly (Bowling, 2005).

6.2 Part 2 – Comparing Smoking and Social Isolation

6.2.1 Background

It is difficult to assess the accuracy of claims that associations between social isolation and mortality are comparable to associations between smoking and all-cause mortality. This is because previous studies compare the magnitude of association for social isolation to that of smoking from analyses of different cohorts using different methods of analysis (House *et al.*, 1988; Kawachi *et al.*, 1996; Holt-Lunstad *et al.*, 2010). The one study which estimated social isolation and smoking effect estimates within the same cohort may be biased by measurement error as the binary smoking status variable examined grouped those who never smoked with former smokers (Pantell *et al.*, 2013). Given that compared to never smokers, former smokers tend to have higher mortality for at least 20 years after cessation, such categorisations can reduce the relative difference in mortality across those who do and do not currently smoke and thus underestimate effect estimates (Pirie *et al.*, 2013).

In their narrative review of five prospective studies, House and colleagues (1988) compared associations between social isolation and all-cause mortality (Most Isolated compared to least isolated, *RR range*= 1.08 to 4.00) to smoking effect estimates summarised in the 1964 report of the U.S. Surgeon General's Advisory Committee on Smoking and Health (U.S. Public Health Service, 1964). The U.S. Surgeon General's report summarised analyses of seven large prospective cohorts from the UK, USA, and Canada on smoking and mortality including those later cited by Kawachi and colleagues (1996). Within these cohorts, 44% to 83% higher mortality was observed among current smokers compared to non-smokers (U.S. Public Health Service, 1964). Compared to non-smokers, mortality rate ratios ranged from 6% to 55% higher among those who smoked less than 10 cigarettes per day, and 83% to 150% higher among those who smoked 40 or more cigarettes per day (U.S. Public Health Service, 1964). However, effect estimates from these earlier studies of smoking and mortality are believed to be underestimated due in part to grouping former smokers with never smokers and relatively short follow-up periods (less than five years) (U.S. Public Health Service, 1964).

Holt-Lunstad and colleagues (2010) reference a meta-analysis of 15 prospective studies examining cigarette consumption in relation to all-cause mortality (Shavelle *et al.*, 2008). Compared to never smokers, smoking up to 15 cigarettes per day was associated with 47% to 50% higher mortality for men and women respectively. Among both men and women, 15 to 25 cigarettes per day was associated with 102% higher mortality. Smoking over 25 cigarettes per day was associated with 138% to 166% higher mortality among men and women

respectively (Shavelle *et al.*, 2008). It is difficult to assess the quality of these meta-analysed studies, as their characteristics were only described in brief. To make their comparison with social isolation, Holt-Lunstad and colleagues (2010) transformed pooled estimates for smoking less than 15 cigarettes per day and plotted these estimates alongside transformed estimates for social isolation from their meta-analysis (Original estimates: Social relationships overall, *OR*=1.50, *95% CI*: 1.42-1.59; High versus low social support, *OR*=1.46, *95% CI*: 1.28-1.66; Complex measures of social integration [i.e most similar to social contact index], *OR*=1.91, *95% CI*: 1.63-2.23; Transformed estimates presented in Figure 6.4). However, the methods used by Holt-Lunstad and colleagues (2010) to transform estimates for smoking and social isolation were not described. Nonetheless, this study is often referred to when associations between social isolation and mortality are equated to the effects of smoking 15 cigarettes per day on mortality (AgeUK, 2017; CBC News, 2017; Morrison, 2018; Tate, 2018; Coughlan, 2019; Mahder-Bashi and Savage, 2019).

More recently, Thun and colleagues (2013) conducted a pooled analysis of individual data from seven prospective cohorts of American adults 50 years old and older who were followed for eight to ten years. Within five contemporary cohorts (i.e. recruited from the years 2000 to 2010), after adjusting for potential confounders and baseline health status, and compared to never smokers, former smokers had 44% higher mortality (*multivariable adjusted RR*= 1.45, *95% CI*: 1.43-1.48) and current smokers had 176% increased mortality (*multivariable adjusted RR*= 2.76, *95% CI*: 2.69-2.84). Among approximately 1.2 million UK women over 40 years old who were followed for 12 years, Pirie and colleagues (2013) found similar associations for current smokers compared to never smokers (*adjusted RR*= 2.76, *95% CI*: 2.71-2.81). Mortality increased substantially depending on the amount smoked. After adjusting for potential confounders and baseline health status, compared to never smokers, participants who smoked under 10 cigarettes per day had 98% higher mortality (*adjusted RR*= 1.98, *95% CI:* 1.91–2.04), those who smoked ten to 20 cigarettes per day had 180% higher mortality (*adjusted RR*= 2.80, *95% CI:* not reported [NR]) and over 20 cigarettes per day had 270% increased mortality (*adjusted RR*= 3.70, *95% CI:* NR) (Pirie *et al.*, 2013). Similar increases in mortality were observed across cigarette consumption among 205,000 Australian adults 45 years of age and older (Banks *et al.*, 2015).

Popular media outlets, well-recognised organisations, and the UK Government have made and referenced claims that associations between social isolation and mortality equate those for smoking and mortality (National Health Service, 2015; AgeUK, 2017; CBC News, 2017; Department for Digital Culture Media and Sport, 2018a; Tate, 2018; Coughlan, 2019; Mahder-

Bashi and Savage, 2019). These claims also often conflate structural isolation with perceived isolation. However, research has yet to rigorously examine whether associations between structural, functional, or perceived dimensions of social isolation and mortality are comparable to cigarette smoking.

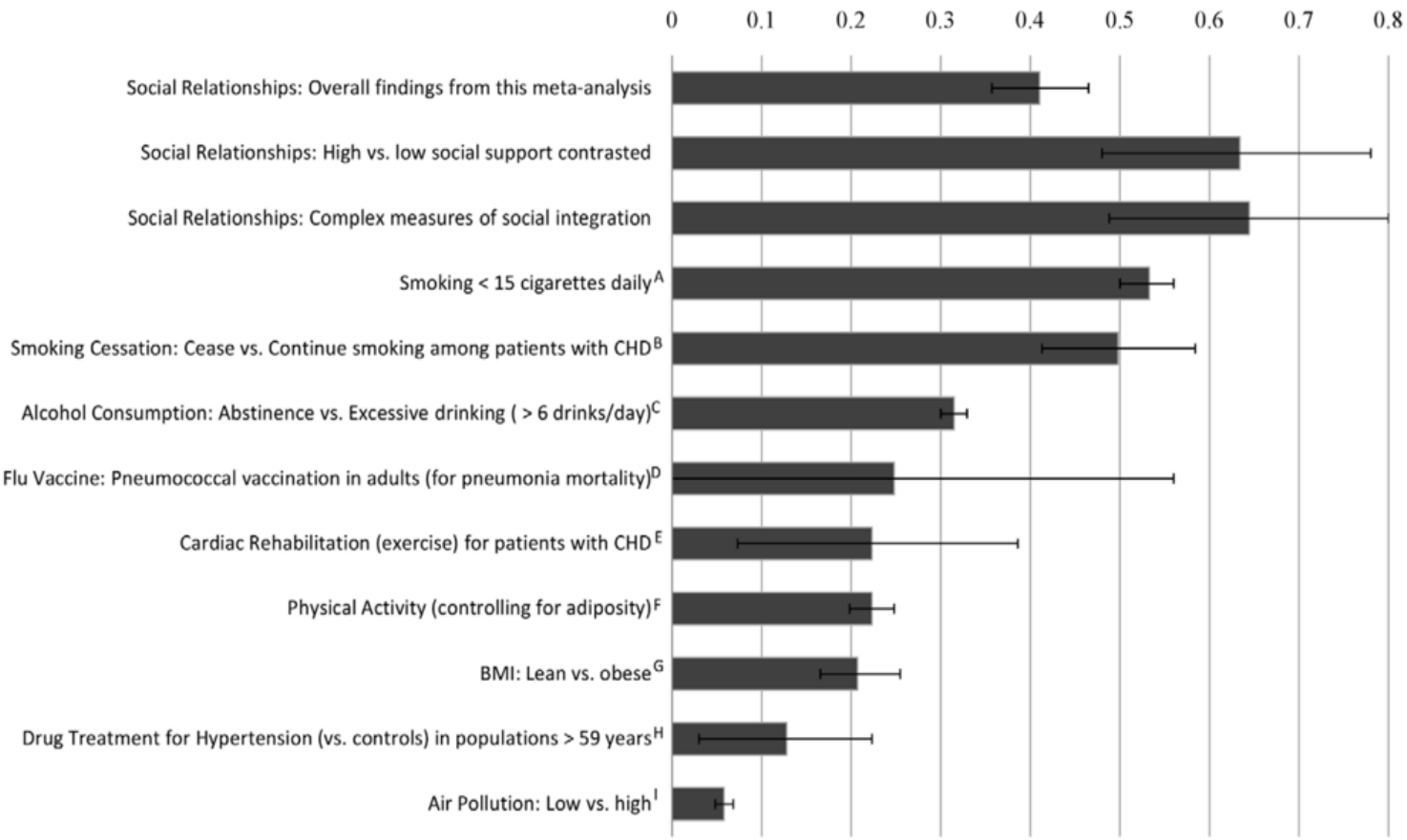


Figure 6. Comparison of odds (lnOR) of decreased mortality across several conditions associated with mortality. Note: Effect size of zero indicates no effect. The effect sizes were estimated from meta analyses: ; A = Shavelle, Paculdo, Strauss, and Kush, 2008 [205]; B = Critchley and Capewell, 2003 [206]; C = Holman, English, Milne, and Winter, 1996 [207]; D = Fine, Smith, Carson, Meffe, Sankey, Weissfeld, Detsky, and Kapoor, 1994 [208]; E = Taylor, Brown, Ebrahim, Jollife, Noorani, Rees et al., 2004 [209]; F, G = Katzmarzyk, Janssen, and Ardern, 2003 [210]; H = Insua, Sacks, Lau, Lau, Reitman, Pagano, and Chalmers, 1994 [211]; I = Schwartz, 1994 [212].
doi:10.1371/journal.pmed.1000316.g006

Figure 6.4. Figure presented in Holt-Lunstad *et al.* (2010) often cited for its comparison of associations between social isolation and smoking up to 15 cigarettes per day.

173

6.2.1.1 Objective

The primary objective was to examine associations between cigarette consumption and all-cause mortality and compare these associations with those for social isolation.

6.2.2 Methods

6.2.2.1 Study Design and Participants

The current analysis examined a similar cohort as in the Part 1 analyses of confiding support and loneliness, however additionally excluded participants with missing data for cigarette consumption (*n*=9,605).

6.2.2.2 Exposures

At baseline, UK Biobank participants were asked about whether they currently smoked tobacco (Figure 6.5A). Those who reported not being current smokers were asked about past smoking status (Figure 6.5B). Participants who reported being current smokers were additionally asked to enter the average number of cigarettes they consume per day (Figure 6.5C). Responses less than one (i.e. responses entered as opposed to the option clicked) and greater than 150 were rejected by the touchscreen questionnaire. A categorical cigarette consumption variable was used to create separate groups for those who never smoked, former smokers, current smokers consuming up to 15 cigarettes per day, and current smokers consuming over 15 cigarettes per day. "Never smokers" were defined as those who responded "I have never smoked" to the past smoking status question. "Former smokers" were defined as those who responded, "smoked on most or all days," "smoked occasionally," or "just tried once or twice." For the cigarette consumption question, those who selected "less than one per day" or entered a value from zero to 15 were grouped as smoking "up to 15" cigarettes per day. Those who entered a value from 16 to 149 were grouped as smoking "over 15" cigarettes per day. Fifteen cigarettes was used as the threshold because this was the threshold used by Holt-Lunstad and colleagues (2010) in their comparison of social isolation and smoking.

The dichotomised SCI score variable described in Section 6.1.2.2 was used to measure structural isolation. The combined variables were also included for comparison because reports often conflate structural and perceived isolation when referencing Holt-Lunstad and colleagues' (2010) claim.

A. Current Smoking Status

Do you smoke tobacco now?
☐ Yes, on most or all days ☐ Only occasionally ☐ No ☐ Prefer not to answer

B. Past Smoking Status

In the past, how often have you smoked tobacco?
☐ Smoked on most or all days ☐ Smoked occasionally ☐ Just tried once or twice ☐ I have never smoked ☐ Prefer not to answer

C. Cigarette Consumption

About how many cigarettes do you smoke on average each day?

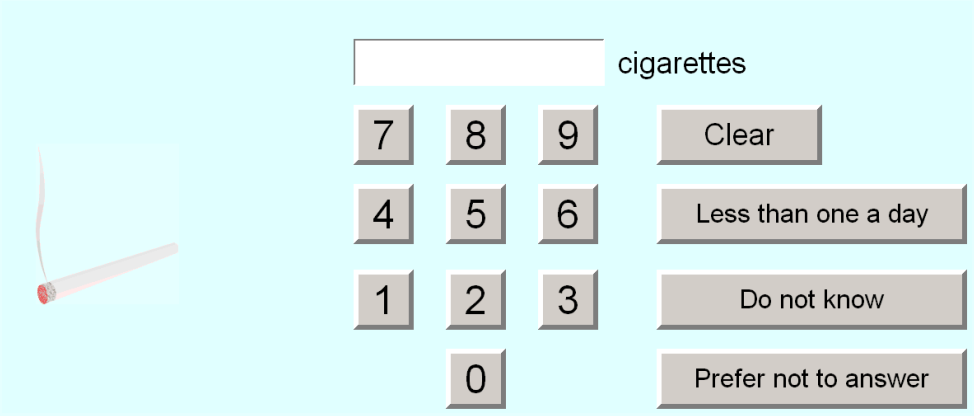


Figure 6.5. Cigarette smoking questions as they appear in the UK Biobank touchscreen questionnaire.

6.2.2.3 Outcomes

The all-cause mortality outcome described in Section 6.1.2.3 was used.

6.2.2.4 Explanatory Factors

The explanatory factors described in Section 6.1.2.4 were used with one exception. As opposed to smoking status, the cigarette consumption variable presented in Section 6.2.2.2 was used for analyses of structural, functional, and perceived isolation.

6.2.2.5 Statistical Analysis

Fully adjusted Cox regression models were used to examine SCI score, confiding support, loneliness, and cigarette consumption in relation to all-cause mortality. These models simultaneously adjusted for personal characteristics, health behaviours, physiological factors and depressed mood. The LR test of heterogeneity was used to assess the statistical significance of any associations.

6.2.3 Results

In total, 274,974 participants (*mean age*=56 years, *SD*: 8.1) without previous vascular disease, cancer, or fair/poor self-rated health, and with complete information for social isolation, loneliness, confiding support and cigarette consumption were included in the analysis. Over a mean follow-up period of 6.9 years (*SD*: 0.9), 4,239 deaths were observed. Approximately 34.0% of participants (*n*=95,119) were former smokers, 3.5% smoked up to 15 cigarettes per day (*n*=9,765), and 1.7% smoked over 15 cigarettes per day (*n*=4,771).

6.2.3.1 Prospective Analysis of Cigarette Consumption and Mortality

After full adjustment, compared to participants who never smoked, former smokers had 27% increased risk of death, those who smoked up to 15 cigarettes had 145% increased risk of death, and those who smoked over 15 cigarettes per day had 285% greater risk of death (Figure 6.6, Former: *RR*=1.27, *95% CI*: 1.19-1.36; Up to 15 cigarettes: *RR*=2.45, *95% CI*: 2.15-2.79; Over 15 cigarettes: *RR*=3.85, *95% CI*: 3.35-4.43, $p<0.0001$). Associations between SCI score, confiding support, loneliness, and all-cause mortality were consistent with those presented in Tables 6.3 and Table 6.5.

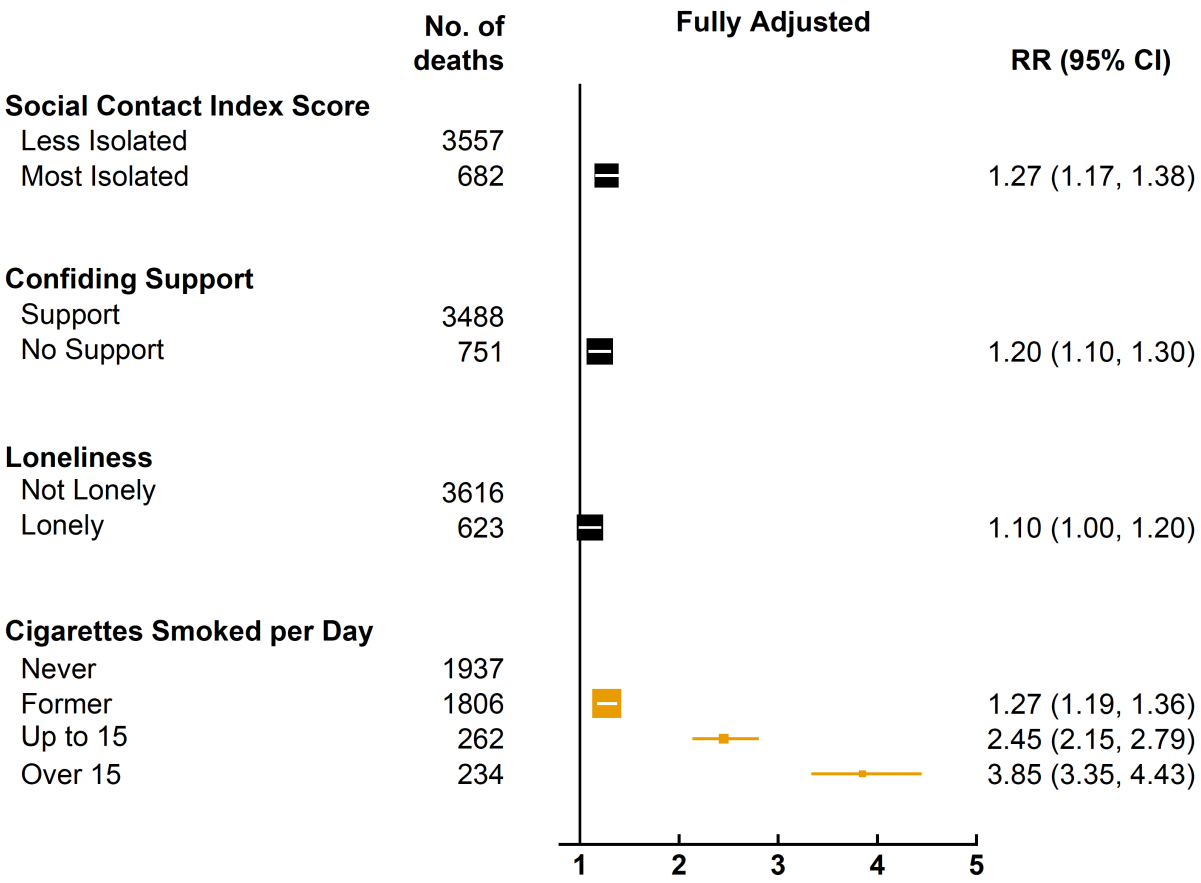


Figure 6.6. Fully Adjusted RR and 95% CI for cigarette consumption, SCI score, and combined social isolation measures in relation to all-cause mortality.

6.2.4 Discussion

Using data from the UK Biobank, the current analysis tested the highly-cited claim that the association between social isolation and all-cause mortality has the same magnitude as that of smoking up to 15 cigarettes per day. Among 274,974 participants without previous vascular disease, cancer, or fair or poor self-rated health, smoking up to and more than 15 cigarettes per day had much stronger associations with all-cause mortality than social isolation. This finding was consistent across structural, functional, and perceived dimensions of social isolation. Equating social isolation and smoking as health risk factors is challenged by differences in their prevalence, the magnitude of associations each share with mortality, and robustness of evidence explaining how each are related to health. Investigating popular health claims is important for effectively communicating health hazards to the public, and for policymakers, appropriately prioritising the allocation of scarce public health resources.

Comparing Social Isolation and Smoking - Prevalence and Magnitude of Associations

One reason it is inaccurate to equate social isolation and smoking as health risk factors is because more people are likely exposed to smoking across there lifetime than social isolation, and smoking is more strongly associated with mortality than social isolation.

Approximately 20.0% of adults in the UK smoke (Reitsma *et al.*, 2017). Smoking is most common among those aged 25 to 34 (20.0% to 28.0%) and decreases to approximately 10.0% among adults of 65 years or older (Cancer Research UK, 2014). Nine to 14.0% of UK adults 40 years and older are believed to be isolated (Beach and Bamford, 2014; Elovainio *et al.*, 2017). Prevalence estimates for social isolation among adults under 40 years of age are scarce. Within the current analysis cohort, only approximately 5.0% of participants were current smokers and 12.5% were among the most isolated. The low proportion of current smokers may represent evidence of selection bias. Despite this, effect estimates for both exposures observed were consistent with those observed in other large prospective studies (Jha *et al.*, 2013; Pirie *et al.*, 2013; Thun *et al.*, 2013; Banks *et al.*, 2015; Elovainio *et al.*, 2017; Section 3.3.5).

Those who smoked up to 15 cigarettes per day compared to those who never smoked, had excess mortality approximately five times higher than the most isolated participants when compared to less isolated. Excess mortality among those who smoked over 15 cigarettes per day was approximately ten times higher than that for the most isolated compared to less isolated participants. While social isolation was more prevalent than smoking at the time of the UK Biobank baseline assessment, the population prevalence estimates are more informative for

assessing smoking's importance as a risk factor because the health damaging effects of smoking accrue and persist over decades (International Agency for Research on Cancer, 2004; U.S. Centers for Disease Control and Prevention, U.S. National Center for Chronic Disease Prevention and Health Promotion and U.S. Office on Smoking and Health, 2010). Further longitudinal research is needed to assess whether duration of exposure to isolation over the life course changes the strength of association of social isolation and mortality. However, even if so, smoking likely remains a greater burden to population health than social isolation. Approximately 11.5% of global deaths (6.4 million) were attributable to smoking in 2015 (Reitsma *et al.*, 2017). Estimating how many deaths globally are attributable to social isolation is not yet possible because it remains unclear what factors explain associations with mortality.

Comparing Social Isolation and Smoking - Explanatory Factors

Mechanisms explaining associations between social isolation and mortality are not as well defined as they are for smoking. The cigarette as a vector for disease is more objectively quantified in terms of chemical composition, means of consumption, and intensity and duration of exposure. These properties have helped researchers delineate causal pathways linking toxins in and by-products of smoked tobacco to biological changes which cause various diseases (International Agency for Research on Cancer, 2004; U.S. Centers for Disease Control and Prevention *et al.*, 2010). This thesis and previous research has not produced robust evidence of causal associations between social isolation and health (Berkman and Krishna, 2014; Kim and Kawachi, 2018). It remains unclear if and exactly how structural and functional aspects of social isolation affect behavioural, psychological, and physiological processes which cause disease or death. As discussed in Sections 1.4.4, 3.4, and 4.4, there are several potential mechanisms explaining associations between social isolation and health outcomes, but they are not conclusive. This is particularly the case for physiological mechanisms (Section 1.4.4). Confounding and reverse causation biases remain important limitations for inferring causation from previous and the current analyses of social isolation and mortality. In contrast, cigarette smoking is recognized as a cause of several cancers, cardiovascular diseases, pulmonary diseases, nicotine addiction, reproductive conditions, and other conditions (International Agency for Research on Cancer, 2004; U.S. Centers for Disease Control and Prevention *et al.*, 2010)

Implications of Health Claims for People and Policymaking

Communicating simple and relatable messages to general audiences is an effective means of raising awareness about health hazards within a population (Glik, 2007). However, the

simplicity and inaccuracy of claims comparing social isolation and smoking as health risk factors may also distort people's perception of risk; potentially leading them to overestimate the consequences of social isolation or underestimate the consequences of smoking. Emotional and behavioural responses to health hazards is shaped by risk perception as opposed to actual risk (Glik, 2007). Addressing popular health claims are important as they may trigger undue distress among consumers of this information, and they may misinform evidence-based policymaking processes.

The absolute frequency, and to a lesser degree the prevalence, of single-occupant households is increasing across nations in Europe and North America (Office for National Statistics, 2018b; Eurostat, 2019; Tang *et al.*, 2019; U.S. Census Bureau, 2019). It could be argued that these statistics indicate that societies are becoming increasingly isolated. However, these statistics do not measure other dimensions of isolation such as people's frequency of contact with family, friends or social groups, and they don't reflect the preferences of those living alone. Many older adults for example, may prefer living in their own homes later in life even in spite of living alone (Reher and Requena, 2018). Among those who prefer to live alone or enjoy lifestyles with less frequent social contact, a perception that their preferred lifestyle is actively harming their health to the same degree as smoking may trigger distress. This may particularly be the case when the claims are framed within the context of a supposed crisis such as the "loneliness epidemic" (Glik, 2007; Holt-Lunstad, 2018a). To avoid causing undue distress among consumers of their research findings, scientists must carefully consider the accuracy of claims coming from their research, current attitudes and beliefs about the topic of their claim, and the potential impact that changing risk perceptions may have on consumers of their health claim.

Priority setting is necessary and inevitable in public health policymaking and is influenced by a myriad of factors (Lomas, 2000). Popular health claims that capture public and policymaker attention can impact the decision making environment, with implications for prioritization and funding (Lavis *et al.*, 2002; Green and Bennett, 2007). Addressing the potential health implications of social isolation and loneliness was justification for the UK Government's recent £30 million pledge to support its first ever loneliness strategy (Department for Digital Culture Media and Sport, 2018a). Indeed in her foreword to the strategy, the Prime Minister stated, "research now shows that loneliness is as damaging to our physical health as smoking" (Department for Digital Culture Media and Sport, 2018a). This strategy is focused on the following three objectives: To support research on loneliness and social isolation; support initiatives aimed at reducing stigma around loneliness; and to consider loneliness within government's policymaking and to invest in interventions supporting people during times of

increased vulnerability to loneliness (e.g. migration, job loss, illness) (Department for Digital Culture Media and Sport, 2018a). Policies and investments stemming from this strategy may indeed make important contributions to the health and wellbeing of UK society. However, investments aimed at addressing loneliness in the UK also coincide with broader reductions in funding for public health.

Spending at the local authority level on smoking cessation services and wider tobacco control decreased by an estimated £41 million between 2015 and 2018 despite evidence of the effectiveness of such programs (Iacobucci, 2018; National Institute for Health and Care Excellence, 2018a, 2018b). Funding reductions in the central government's public health grant is believed to be a primary contributor to local authorities' reduced spending (Cancer Research UK and Action on Smoking and Health, 2019). Herein lies another potential consequence of inaccurate comparisons of social isolation and smoking. Such claims may lead policy makers to underestimate the hazards of smoking and the benefits of cessation. Without a robust understanding of the magnitude of smoking's health effects, policymakers may be more inclined to reallocate scarce public health resources away from smoking cessation.

Limitations

Compared to population-level estimates, the low proportion of current smokers within the sample examined suggests that smokers may be underrepresented within the UK Biobank cohort. Furthermore, while self-reported cigarette smoking measures are generally valid within general populations, risk of response and recall bias may still affect the accuracy of the cigarette consumption measure examined (Patrick *et al.*, 1994). Associations between cigarette consumption and mortality may be underestimated as a result of selection, response, and recall bias. However, this limitation is not believed to be significant given the consistency of associations observed in the current analysis with those from similar large prospective analyses of smoking and mortality (Pirie *et al.*, 2013; Banks *et al.*, 2015)

6.3 Conclusion

This was among the first analyses to estimate associations with mortality within specific categories of functional, perceived, and structural isolation. It was also the first to test the widely cited claim that associations between structural and perceived isolation are comparable to smoking up to 15 cigarettes per day. After accounting for explanatory factors and structural isolation, functional isolation remained associated with 15% excess risk of all-cause mortality, whereas perceived isolation was not associated with mortality. Compared to never having

smoked, cigarette smoking was associated with five to ten-fold greater mortality than structural, functional and perceived social isolation. Depression explained a greater degree of the association between perceived isolation and mortality than that between functional and structural isolation and mortality. Among those who were less isolated and most isolated, there were no statistically significant increases in mortality according to whether they also lacked support or were lonely. Expanding the concept of social isolation to include structural and functional dimensions may strengthen future research examining social isolation and health. However, at least for examining mortality, the current analysis found little evidence to suggest that indices of structural isolation would be strengthened by including measures of perceived isolation. These findings may have important implications for the measurement of social isolation, public perceptions of social isolation as a hazard to health, and evidence-based public health policymaking.

7 Summary and Implications of Findings

7.1 Main Findings

Within two large and generally healthy adult cohorts from the Million Women Study and the UK Biobank, this thesis generated evidence of strong associations between social isolation and vascular disease mortality and all-cause mortality but only weak evidence in relation to vascular disease incidence. These studies were the first analyses of social isolation, with vascular disease incidence, and vascular disease mortality to focus on people without previously diagnosed vascular disease, cancer, and/or fair or poor self-rated health in order to reduce the risk of reverse causation bias. The associations observed were consistent across age groups and gender, and in contrast to popular claims, associations with all-cause mortality were five to ten-fold weaker than associations between cigarette smoking and all-cause mortality.

The findings of Chapters 3, 4, and 6 offer little support for social isolation as a risk factor for vascular disease aetiology and point to delays in seeking care as a potentially important but unmeasured explanatory factor for associations with vascular disease mortality. The weak and inconsistent associations observed between social isolation and vascular disease incidence may draw into question the hypothesis that psychosocial stress from social isolation causes vascular inflammation which increases one's risk of incident vascular disease. Further research on large prospective cohorts is needed to examine the validity of vascular inflammation as physiological explanatory factor. The personal characteristics, health behavioural, and physiological explanatory factors adjusted for in this thesis explained only a small proportion of the associations between social isolation and vascular disease mortality than all-cause mortality and vascular disease incidence. While it was not possible to measure the degree to which the most isolated participants experienced delays in seeking care after having suffered an acute vascular disease event, this thesis provides some support for the hypothesis. For example, among structural dimensions of social isolation, living alone had the strongest and most consistent associations with mortality outcomes. Furthermore, even after accounting for structural dimensions, functional dimensions, namely lacking confiding social support, also exhibited independent associations with all-cause mortality. Future research is needed to examine the degree to which delays in seeking care explain associations between social isolation and mortality outcomes.

This thesis also generated novel findings which may advance the conceptualisation of social isolation within epidemiologic research. These were among the first and largest individual studies to examine independent and joint associations between specific structural, functional, and perceived dimensions of social isolation and mortality. After accounting for structural dimensions no statistically significant evidence of association was observed between loneliness nor relationship satisfaction and mortality (i.e. perceived dimensions of isolation). Also, no statistically significant interaction was observed between structural and functional or structural and perceived dimensions of social isolation. Given the aforementioned independent associations observed between functional isolation and mortality, these findings suggest that using indices of social isolation constituting structural and functional dimensions may be useful when examining mortality outcomes. However, perceived dimensions of isolation may be more appropriately characterised in these analyses as psychological explanatory factors. This thesis was also the first to utilize data on neighbourhood socioeconomic deprivation, crime, greenspace availability, and geographic distance to services to examine whether these factors modify associations between social isolation, vascular disease, and mortality. Chapter 5 found little evidence of effect modification among these neighbourhood factors. While neighbourhood factors may help identify people who are more likely to be isolated, there is insufficient evidence to suggest that intervening on these factors will prevent vascular disease or mortality by way of reducing social isolation.

This concluding chapter provides a detailed summary of the analyses each chapter presented in (Section 7.2), and then discuss the implications for future research (Section 7.3) and policy and intervention (Section 7.4).

7.2 Detailed Summary of Analyses

Chapter 2 reviewed 23 prospective studies published between 1979 and 2018 examining indices of structural social isolation in relation to vascular disease incidence and mortality and all-cause mortality among general adult populations. This narrative review found stronger evidence of associations between social isolation and vascular disease mortality and all-cause mortality than vascular disease incidence. These findings contrasted a highly cited meta-analysis examining social isolation in relation to vascular disease incidence. For vascular disease mortality, after adjusting for explanatory factors, estimates of association ranged from 20% to 76% increased mortality among the most isolated participants compared to least isolated. For all-cause mortality, after adjusting for explanatory factors, estimates of association ranged from 26% to 80% increased mortality among the most isolated participants

compared to least isolated. Few studies were identified that examined social isolation in relation to stroke incidence and mortality. The findings of these studies were mixed in terms of the magnitude and statistical significance of associations.

Most studies sought to address reverse causation bias by adjusting for baseline health, and many additionally excluded participants with vascular disease at baseline. Not one study further excluded participants based on self-rated health. Small sample size was a limitation of many studies likely preventing the use of more thorough cohort exclusion criteria and limiting their capacity to examine CHD and stroke-specific mortality. Most studies adjusted regression analyses for multiple personal characteristics (e.g. age, gender, socioeconomic position) and health behavioural factors (e.g. smoking, alcohol intake, physical activity, body mass index). Fewer studies adjusted for physiological factors (e.g. blood pressure, serum cholesterol, inflammatory biomarkers). While multiple studies compared associations across age and gender sub-groups, only two formally assessed effect modification with one finding statistically significant evidence of effect modification by gender. This narrative review indicated that further large prospective analyses examining social isolation, vascular disease, and mortality using more thorough exclusion criteria was warranted.

Using a summative index of frequency of contact with family or friends, frequency of contact with social groups, and living alone (i.e. social contact index [SCI]), Chapter 3 examined structural social isolation in relation to vascular disease incidence, vascular disease mortality, and all-cause mortality within the Million Women Study 12-year re-survey cohort. Among 326,169 women without previous vascular disease, cancer, or fair/poor self-rated health at baseline, there was stronger evidence of associations between social isolation and mortality than vascular disease incidence. For vascular disease mortality, after adjusting for explanatory factors (i.e. personal characteristics, health behavioural factors, and physiological factors), the most isolated women had 80% (41% to 131%) greater CHD mortality, 71% (34% to 118%) greater stroke mortality, and 32% (24% to 40%) greater all-cause mortality respectively compared to least isolated. After adjustment for explanatory factors the most isolated women had 7% (1% to 14%) greater CHD incidence and 28% (19% to 38%) greater stroke incidence respectively compared to the least isolated women. This finding may however be explained by residual confounding. Among the explanatory factors, health behaviours, particularly smoking, explained the largest proportions of minimally adjusted associations, while physiological factors explained the lowest proportions of associations. Among the constituent measures of isolation, living alone had the strongest and most consistent associations with stroke incidence

and mortality outcomes. There were no statistically significant evidence of effect modification by attained age (i.e. under or over 75 years old).

Using data from the UK Biobank, Chapter 4 examined the reproducibility of findings from Chapter 3 within a younger cohort of men and women. Among 296,913 participants without previous vascular disease, cancer, or fair/poor self-rated health at baseline, there was again stronger evidence of associations between social isolation and mortality than between social isolation and vascular disease incidence. For vascular disease mortality, after adjusting for explanatory factors, the most isolated participants had 68% (28% to 121%) greater CHD mortality, 92% (32% to 181%) greater stroke mortality, and 38% (27% to 51%) greater all-cause mortality compared to the least isolated. After adjustment for explanatory factors the most isolated participants had 23% (9% to 40%) increased stroke incidence compared to the least isolated participants. Social isolation was not associated with CHD incidence in minimally nor fully adjusted analyses. Again, health behaviours tended to explain the largest proportions of minimally adjusted associations for each outcome, and among the constituent measures of social isolation, living alone was most consistently associated with increased mortality. There was no evidence of effect modification by gender.

Chapters 3 and 4 make important and novel contributions to the field. First, the large sample size enabled these analyses to be restricted to generally health adult populations, and to examine cause-specific mortality. These methods generated robust evidence of associations between social isolation, and vascular disease mortality, and all-cause mortality. By assessing changes in the goodness of fit of models adjusted for specific explanatory factors, these chapters' findings reinforce prior evidence suggesting that health behaviours, particularly smoking, are important factors explaining associations between social isolation, vascular disease, and mortality. Contrastingly, physiological factors were not found to be strong explanatory factors. This may be due to measurement error in the variables adjusted for or may indicate that potentially relevant physiological factors such as inflammatory biomarkers (e.g. c reactive protein) were not measured. When considered alongside the weak evidence of association between social isolation and vascular disease incidence, these findings may challenge the belief that social isolation triggers physiological processes, which promote inflammation and cardiometabolic changes that lead to the development of vascular disease. Based on the degree to which adjustment for explanatory factors attenuated minimally adjusted associations, it is more likely that residual confounding explains associations observed for stroke incidence and potentially all-cause mortality. The consistent associations observed between living alone and vascular disease mortality suggest that delays in seeking medical care

may at least in-part explain the excess mortality observed among the most isolated people. These analyses also present strong evidence that the strength of association between social isolation, vascular disease, and mortality does not vary meaningfully by age and gender.

The focus of Chapter 5 was to understand whether any associations between structural social isolation, vascular disease, and mortality in the Million Women Study and UK Biobank cohorts vary according to broader characteristics of one's neighbourhood. Using the Index of Multiple Deprivation 2010 and Generalised Land Use Database 2005, these analyses examined effect modification by neighbourhood socioeconomic deprivation, crime rates, distance to services, and greenspace availability. Social isolation was more prevalent in neighbourhoods with greater deprivation, higher crime, and less greenspace. Contrary to what was hypothesised, there was a greater prevalence of social isolation in neighbourhoods that were closer to services. Effect modification analyses suggested that associations between social isolation, vascular disease, and mortality are likely not influenced by the neighbourhood factors examined. These were the largest analyses to examine neighbourhood deprivation as an effect modifier on social isolation, and was the first to examine neighbourhood crime rates, distance to services, and greenspace availability.

Chapter 6 was presented in two parts. Among 284,579 UK Biobank participants, Part 1 examined whether structural, functional, and perceived dimensions of social isolation were independently and jointly associated with all-cause mortality. After adjustment for explanatory factors including depressed mood and SCI score (i.e. structural isolation), participants lacking confiding support (i.e. functional isolation) had 15% (6% to 24%) greater mortality than those with confiding support. Loneliness (i.e. perceived isolation) was not associated with mortality after adjustment for explanatory factors and SCI score. Within a subsample of 101,223 UK Biobank participants, relationship satisfaction (i.e. perceived isolation) was not associated with mortality in minimally nor fully adjusted analyses. No statistically significant interaction was observed between structural and functional isolation nor structural and perceived isolation. The results suggest that expanding the concept of social isolation to include functional dimensions such as social support may have utility for measuring and studying social isolation in relation to mortality. This finding also lends support to the potential role of delays in seeking care representing an explanatory factor explaining excess mortality among the most isolated. This analysis also suggests that perceived isolation may be more appropriately studied as a psychological explanatory factor for social isolation and mortality. Part 2 examined the popular claim that social isolation is as bad for health as smoking 15 cigarettes per day. Among participants studied in Part 1 that had complete data for cigarette consumption (N=274,974),

smoking up to 15 cigarettes per day was associated with five to ten-fold greater excess mortality than structural social isolation. The effect estimates observed for smoking were consistent with other large prospective analyses.

Chapter 6 analyses were the first to examine joint associations between multiple dimensions of social isolation and mortality, and to investigate the claim equating associations between social isolation to that of cigarette smoking. These analyses have implications for how social isolation is conceptualized in epidemiology, how it is communicated as a health risk factor, and how policy makers and practitioners approach intervening on social isolation.

7.3 Implications for Future Research

This thesis research revealed several opportunities for future research related to examining explanatory factors, addressing unmeasured confounding, and effect modification on an additive scale.

Delays in Seeking Care Explanatory Factors

In theory, those who are more isolated have a greater probability of being alone when vascular disease events occur. Without others in the vicinity to alert emergency medical services and/or take a stroke victim to hospital, they may be less likely to get to hospital in time to receive life-saving therapy. This delay in seeking care may in part explain the excess mortality observed among the most isolated and those living alone. Future research could examine this explanation indirectly using Million Women Study or UK Biobank data. One potential analysis could compare the magnitude of associations between social isolation and vascular disease mortality across those whose location of death was at home without preceding hospitalization and those who died in hospital. Secondary outcomes of this research could be time from symptom onset to arrival to the emergency department and receipt of thrombolytic treatment.

Physiological Explanatory Factors

As discussed in Section 1.4.4, it is difficult to infer that associations between social isolation and health are causal in part because research on physiological explanatory factors remains inconclusive. Further research is needed to understand the degree to which physiological factors such as vascular inflammation and cellular ageing explain associations between social isolation and health (Berkman and Krishna, 2014; Kim and Kawachi 2018). The UK Biobank data could be used to assess cross-sectional associations between social isolation and inflammatory biomarkers (e.g. c reactive protein), proteins implicated in oxidative stress (e.g.

gamma-glutamyltransferase), and other metabolic biomarkers (e.g. serum cholesterol, glycated haemoglobin) (UK Biobank, 2015). In the future, data on telomere length will also be available (UK Biobank, 2019). A noteworthy advantage of UK Biobank data sources is that the size and diversity of data collected enables researchers to more rigorously account for reverse causation and confounding biases. While smaller than the UK Biobank, the Understanding Society (i.e. the UK Household Longitudinal Study) resource is another rich data source. Understanding Society is a longitudinal cohort study of approximately 20,000 UK adults and children with repeated measures on social relationships, personal characteristics, health behaviours, psychological factors, and physiological factors (Understanding Society, 2019b). Among the physiological factors include inflammatory biomarkers (e.g. c reactive protein, fibrinogen), hormones (e.g. testosterone, insulin-like growth factor-1), metabolic biomarkers (e.g. cholesterol, glycated haemoglobin, creatinine) (Benzeval *et al.*, 2014). Understanding Society can also facilitate analyses of epigenetic factors such as DNA methylation within a subsample of 1,200 participants (Understanding Society, 2019a). Where statistically significant evidence of associations between social isolation and these biomarkers exist, percentage attenuation in the LR χ^2 test statistic could then be used to assess the degree to which these factors explain associations with health outcomes.

Confounding

Analyses in this thesis and in most previous studies rely on measures of social isolation and explanatory factors taken at one point in time. These analyses assume that levels of exposure to social isolation and potentially confounding or mediating factors remain constant over the observation period and in the time preceding the observation period. These assumptions may be unreasonable because non-communicable diseases such as CHD and ischaemic stroke develop over decades. One could argue that if social isolation is causally related to vascular disease incidence and mortality through biological mechanisms, a person would need to be exposed to isolation over similarly extended periods of time. Methods from life course epidemiology may prove useful in future research on social isolation and health. Using longitudinal designs over multiple stages of life (e.g. childhood, adolescence, and young and older adulthood) future research may be better able to examine factors which may increase one's propensity to become more or less isolated over time, and account for time-varying exposure to explanatory factors. The Understanding Society and National Longitudinal Study of Adolescent to Adult Health (Add Health Study) may be valuable data resources for this research. This research will help clarify the degree to which associations observed in the current and previous research can be explained by confounding, and the degree to which personal

characteristics, health behaviours, physiological factors, and psychological factors represent confounders versus effect mediators.

Effect Modification and Interaction Analyses

Within this thesis research, effect modification was only tested on a multiplicative scale by comparing models which did and did not include an interaction term between social isolation and the potential modifiers in question (e.g. age, gender, neighbourhood factors). As discussed in Sections 5.4 and 5.5, future research may be strengthened by examining modifiers of associations between social isolation and mortality on additive and multiplicative scales. A challenge with multiplicative interaction is that baseline risk can vary between different subgroups, and thus risk ratios could be based on different baseline risks (VanderWeele and Knol, 2014). Given that with absolute probabilities risk can be observed across all combinations of two interacting variables, the difference in probabilities across the affected groups (over and above the probability among those who are unaffected) can be used to estimate how many lives could be affected by intervention upon one or both factors. This is a key reason that effect modification on an additive scale is believed to be of greater relevance for public health (VanderWeele and Knol, 2014). Additive hazards modelling is one method for modelling an exposure and covariates (including interaction terms) using time-to-event data (Rod *et al.*, 2012). This method can generate estimates of the number of additional events one can expect given combined exposure to two or more factors (Rod *et al.*, 2012). Using effect estimates from traditional linear, logistic and Cox regression, more general inferences can be made using post-hoc measures such as relative excess risk due to interaction, synergy index, and attributable proportion due to interaction (Li and Chambless, 2007; VanderWeele and Knol, 2014). In order to make effect modification analyses more relevant and actionable for researchers and public health officials, VanderWeele and Knol (2014) advocate for examining effect modification on both additive and multiplicative scales. However, it should be noted that these measures of additive effect modification may be biased in the presence of confounding (Skrondal, 2003; Rod *et al.*, 2012). Also, assumptions of causation are inherent in the interpretation of results from additive effect modification analysis. Therefore, it may be inappropriate to apply these methods when examining associations between social isolation and mortality. Nonetheless, only one study identified examined multiplicative and additive effect modification in relation to social isolation and mortality and found complementary results (Marcus *et al.*, 2016). Further research may help reinforce or challenge the utility of examining both forms of effect modification when examining social isolation and health.

7.4 Implications for Policy and Intervention

Defining the Purpose and Outcomes of Social Isolation Interventions

Calls-to-action for "tackling" social isolation often cite associations between social isolation and health as a rationale for intervention (Age UK, 2011; Department for Digital, Culture, Media and Sport, 2018a). If the purpose of interventions for mitigating social isolation is to improve health, it is essential that specific health outcomes are defined at the design-stage of intervention. This thesis research suggests that interventions which address structural dimensions of social isolation may not have any impact on people's risk of developing vascular disease. If the goal is to reduce mortality, those designing interventions should consider that the structural dimensions of isolation associated with mortality in this thesis still may not be causally associated and thus intervention may not affect mortality. If causal associations do exist, Chapters 3, 4, and 6 suggest that living alone and emotional support may be appropriate avenues for intervention. Given that social isolation has been associated with other health, healthcare, and general well-being outcomes, many reasons for intervening to prevent social isolation may have merit (Leigh-Hunt *et al.*, 2017; Valtorta, Collingridge Moore, *et al.*, 2018; Wang *et al.*, 2018). However, to ensure that resources are invested appropriately, those tasked with designing and implementing strategies to prevent isolation must carefully consider the purpose and what evidence suggests are realistic outcomes of intervention.

Who and what to Target through Intervention

Effect modification and interaction analyses can be useful for identifying high-risk sub-groups of a population that may particularly benefit from intervention. However, Chapters 3, 4, 5, and 6 found that excess mortality among those who were isolated was generally consistent across age, gender, neighbourhood characteristics. The current research suggests that while neighbourhood factors may be useful for identifying individuals who are more likely to be isolated, changing these factors may not influence vascular disease incidence and mortality through changes in the prevalence of social isolation. This point is important because the perceived health benefits of preventing social isolation are often used as rationale for intervening on neighbourhood factors (e.g. by reducing crime, and improving walkability and access to transportation) (Equal Opportunities Committee, 2015; Holt-Lunstad, 2018b; Mahder-Bashi and Savage, 2019). It should be noted that there are many benefits to reducing poverty, lowering crime rates, making communities more pedestrian-friendly, and preserving greenspace. However, currently there is little evidence to suggest that reductions in social isolation explain the health benefits of interventions which achieve these goals. Rather than

potential effect modifiers, Chapters 3, 4, and 6 suggest that explanatory factors like smoking may represent key factors warranting intervention. Cigarette smoking explained considerable proportions of associations between social isolation, vascular disease, and mortality. These results suggest that social isolation may be a useful indicator of people who may particularly benefit from smoking cessation interventions.

Measuring Social Isolation in Society

To better judge whether the prevalence of social isolation is changing in UK society and whether it indeed represents a public health crisis, better measurement is needed. Currently, Public Health England measures and monitors the percentage of adult social care users and caregivers that have as much social contact as they would like. However these measurements are not generalizable to the wider UK population and are difficult to compare with traditional indicators of structural isolation such as frequency of contact, living alone, and marital status (Public Health England, 2017). The Census has coverage for the population however, it only includes measures of household occupancy, marital status, and family structure (Office for National Statistics, 2019). The nationally representative Community Life Survey includes measures of frequency of contact with family or friends, and social group participation; however it does not include measures of marital status or living alone (Department for Digital, Culture, Media and Sport, 2018). One seemingly pragmatic way to improve a nation's measurement of social isolation would be to include a single question in the Census similar to those used in this thesis (e.g. How frequently do you have contact with the following: family or friends [outside the household]; social groups [e.g. religious community, volunteer organisations, recreation or fitness, education]). It remains unclear whether any nations currently include related questions in their Census. However, like employment, family relationships, friendships, and connection with broader communities bring meaning and purpose to people's lives. Social relationships and interaction are fundamental to society. For this reason, one might argue that they are as important to measure systematically as aspects of life which are already measured such as employment and means of transport.

7.5 Concluding Statement

Findings from this thesis and their discussion in relation to previous research provides novel and robust evidence that will inform future research, public discourse, and policy responses to social isolation in society.

References

Abraham, A., Sommerhalder, K. and Abel, T. (2010) 'Landscape and well-being: a scoping study on the health-promoting impact of outdoor environments', *International Journal of Public Health*, 55(1), pp. 59–69. doi: 10.1007/s00038-009-0069-z.

Adams, J., Ryan, V. and White, M. (2005) 'How accurate are Townsend Deprivation Scores as predictors of self-reported health? A comparison with individual level data', *Journal of Public Health*, 27(1), pp. 101–106. Available at: http://dx.doi.org/10.1093/pubmed/fdh193.

AgeUK (2011) *Safeguarding the Convoy: A Call to Action from the Campaign to End Loneliness*. Abingdon, UK. Available at: https://campaigntoendloneliness.org/wp-content/uploads/downloads/2011/07/safeguarding-the-convey_-_a-call-to-action-from-the-campaign-to-end-loneliness.pdf.

AgeUK (2017) *No one should have no one*, *ageUK Oxfordshire*. Available at: https://www.ageuk.org.uk/oxfordshire/about-us/news/articles/2017/no_one_should_have_no_one/ (Accessed: 20 May 2019).

Alcaraz, K. I. *et al.* (2018) 'Social Isolation and Mortality in US Black and White Men and Women', *American Journal of Epidemiology*, pp. kwy231–kwy231. Available at: http://dx.doi.org/10.1093/aje/kwy231.

Banks, E. *et al.* (2015) 'Tobacco smoking and all-cause mortality in a large Australian cohort study: findings from a mature epidemic with current low smoking prevalence', *BMC Medicine*, 13(1), p. 38. doi: 10.1186/s12916-015-0281-z.

Barefoot, J. C. *et al.* (2005) 'Social Network Diversity and Risks of Ischemic Heart Disease and Total Mortality: Findings from the Copenhagen City Heart Study', *American Journal of Epidemiology*, 161(10), pp. 960–967. Available at: http://dx.doi.org/10.1093/aje/kwi128.

Barger, S. D. (2013) 'Social integration, social support and mortality in the US National Health Interview Survey', *Psychosomatic medicine*, 75(5), p. 510. doi: 10.1097/PSY.0b013e318292ad99.

Barth, J., Schneider, S. and von Kanel, R. (2010) 'Lack of social support in the etiology and the prognosis of coronary heart disease: a systematic review and meta-analysis.',

Psychosomatic medicine. United States, 72(3), pp. 229–238. doi: https://dx.doi.org/10.1097/PSY.0b013e3181d01611.

Beach, B. and Bamford, S.-M. (2014) *Isolation: The Emerging Crisis for Older Men*. London. Available at: www.independentage.org.

Benzeval, M. *et al.* (2014) *Understanding Society: The UK Household Longitudinal Study Biomarker User Guide and Glossary*. Essex. Available at: https://www.understandingsociety.ac.uk/sites/default/files/downloads/documentation/health/user-guides/7251-UnderstandingSociety-Biomarker-UserGuide-2014.pdf (Accessed: 10 July 2019).

Berkman, L. F. (1977) *Social networks, host resistance, and mortality: A follow-up study of Alameda County residents.* University of California, Berkley.

Berkman, L. F. *et al.* (2000) 'From social integration to health: Durkheim in the new millennium', *Social Science and Medicine*, 51(6), pp. 843–857. doi: http://dx.doi.org/10.1016/S0277-9536%2800%2900065-4.

Berkman, L. F. *et al.* (2004) 'Social integration and mortality: a prospective study of French employees of Electricity of France-Gas of France: the GAZEL Cohort.', *American journal of epidemiology*. United States, 159(2), pp. 167–174. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med5&NEWS=N&AN=14718219.

Berkman, L. F. and Krishna, A. (2014) 'Social Network Epidemiology', in Berkman, Lisa F;, Kawachi, I., and Glymour, M. M. (eds) *Social Epidemiology*. Second. New York: Oxford University Press, pp. 234–289.

Berkman, L. F. and Syme, S. L. (1979) 'Social Networks, Host Resistance, and Mortality: a Nine-Year Follow-up Study of Alameda County Residents', *American Journal of Epidemiology*, 109(2), pp. 186–204. Available at: http://dx.doi.org/10.1093/oxfordjournals.aje.a112674.

Bhatnagar, P. *et al.* (2016) 'Trends in the epidemiology of cardiovascular disease in the UK', *Heart*, 102(24), pp. 1945 LP – 1952. Available at: http://heart.bmj.com/content/102/24/1945.abstract.

Bland, J. M. and Altman, D. G. (1995) 'Multiple significance tests: the Bonferroni method', *BMJ*, 310(6973), p. 170. doi: 10.1136/bmj.310.6973.170.

Bowling, A. (2005) 'Mode of questionnaire administration can have serious effects on data

quality', *Journal of Public Health*, 27(3), pp. 281–291. doi: 10.1093/pubmed/fdi031.

British Heart Foundation (2017) 'Chapter 2: Morbitity, Table 2.1, Inpatient episodes by main diagnosis in NHS hospitals, by gender, England, Scotland, Wales, Northern Ireland and United Kingdom latest', in *BHF CVD Statistics Compendium 2017*. Oxford, UK: British Heart Foundation.

British Heart Foundation (2018a) *BHF CVD Statistics Compendium 2018*. Oxford, UK: British Heart Foundation.

British Heart Foundation (2018b) 'Chapter 1: Mortality, Table 1.1, Deaths by cause, by gender and age, United Kingdom 2016', in *BHF CVD Statistics Compendium 2018*. Oxford, UK: British Heart Foundation.

British Heart Foundation (2018c) 'Chapter 1: Mortality, Table 1.16, Number of deaths and age-standardised death rates for coronary heart disease (CHD), all ages, by region and country, United Kingdom 2014/16', in *BHF CVD Statistics Compendium 2018*. Oxford, UK: British Heart Foundation.

British Heart Foundation (2018d) 'Chapter 2: Morbidity, Table 2.3, Prevalence of selected cardiovascular conditions by nation and region, United Kingdom Latest Year', in *BHF CVD Statistics Compendium 2018*. Oxford, UK: British Heart Foundation.

British Heart Foundation (2018e) 'Chapter 2: Mortality, Table 1.18, Numbers of deaths and age-standardised death rates from stroke in men and women, all ages, by region and nation, United Kingdom 2014/16', in *BHF CVD Statistics Compendium 2018*. Oxford, UK: British Heart Foundation.

Brody, J. E. (2013) *Shaking Off Loneliness*, *New York Times*. Available at: https://well.blogs.nytimes.com/2013/05/13/shaking-off-loneliness/ (Accessed: 20 May 2019).

Brooks, K. P. *et al.* (2014) 'Social relationships and allostatic load in the MIDUS study', *Health Psychology*, 33(11), p. 1373. doi: 10.1037/a0034528.

Cacioppo, J. T. *et al.* (2015) 'The Neuroendocrinology of Social Isolation', *Annu. Rev. Psychol*, 66, pp. 733–67. doi: 10.1146/annurev-psych-010814-015240.

Cacioppo, J. T., Hawkley, L. C. and Thisted, R. A. (2010) 'Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study', *Psychology and Aging*, 25(2), p. 453. doi: 10.1037/a0017216.

Campaign to End Loneliness (2014) *The Care Act 2014 and Loneliness*. London. Available at: https://campaigntoendloneliness.org/guidance/wp-content/uploads/2015/06/The-Care-Act-2014-and-Loneliness.pdf.

Campaign to End Loneliness (2017) *Threat to health*, *Campaign to End Loneliness*. Available at: https://www.campaigntoendloneliness.org/threat-to-health/ (Accessed: 20 May 2019).

Cancer Research UK (2014) *Cigarette Smoking Prevalence, by Age, UK, 2013*, *Cancer Research UK*. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/tobacco#heading-Two (Accessed: 6 June 2019).

Cancer Research UK and Action on Smoking and Health (2019) *A Changing Landscape for Stop Smoking Services and Tobacco Control in England*. London. Available at: http://ash.org.uk/wp-content/uploads/2019/03/2019-LA-Survey-Report.pdf (Accessed: 8 June 2019).

Canvin, K. *et al.* (2018) 'Seeking assistance in later life: how do older people evaluate their need for assistance?', *Age and Ageing*, 47(3), pp. 466–473. Available at: http://dx.doi.org/10.1093/ageing/afx189.

Cattan, M. *et al.* (2005) 'Preventing social isolation and loneliness among older people: a systematic review of health promotion interventions', *Ageing and Society*. 2005/01/10. Cambridge University Press, 25(1), pp. 41–67. doi: DOI: 10.1017/S0144686X04002594.

CBC News (2017) *Why loneliness can be as unhealthy as smoking 15 cigarettes a day*, *CBC*. Available at: https://www.cbc.ca/news/health/loneliness-public-health-psychologist-1.4249637 (Accessed: 20 May 2019).

Ceria, C. D. *et al.* (2001) 'The relationship of psychosocial factors to total mortality among older Japanese-American men: the Honolulu Heart Program.', *Journal of the American Geriatrics Society*. United States, 49(6), pp. 725–731. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=11454110.

Chaix, B. (2009) 'Geographic Life Environments and Coronary Heart Disease: A Literature Review, Theoretical Contributions, Methodological Updates, and a Research Agenda', *Annual Review of Public Health*. (Annual Review of Public Health), 30, pp. 81–105. doi: 10.1146/annurev.publhealth.031308.100158.

Chang, S.-C. *et al.* (2017) 'Social Integration and Reduced Risk of Coronary Heart Disease in

Women: The Role of Lifestyle Behaviors', *Circulation Research*, 120(12), pp. 1927–1937. Available at: http://circres.ahajournals.org/content/early/2017/03/30/CIRCRESAHA.116.309443.abstract.

Chiang, J. J. *et al.* (2012) 'Negative and competitive social interactions are related to heightened proinflammatory cytokine activity', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 109(6), pp. 1878–1882. doi: 10.1073/pnas.1120972109.

Christakis, N. A. and Fowler, J. H. (2007) 'The Spread of Obesity in a Large Social Network over 32 Years', *New England Journal of Medicine*, 357(4), pp. 370–379. doi: 10.1056/NEJMsa066082.

Christakis, N. A. and Fowler, J. H. (2008) 'The Collective Dynamics of Smoking in a Large Social Network', *The New England Journal of Medicine*, 358(21), pp. 2249–2258. doi: 10.1056/NEJMsa0706154.

Christakis, N. A. and Fowler, J. H. (2013) 'Social contagion theory: examining dynamic social networks and human behavior', *Statistics in Medicine*. Wiley Online Library, 32(4), pp. 556–577. doi: 10.1002/sim.5408.

Cotterell, N., Buffel, T. and Phillipson, C. (2018) 'Preventing social isolation in older people', *Maturitas*, 113, pp. 80–84. doi: 10.1016/j.maturitas.2018.04.014.

Coughlan, S. (2019) *Loneliness more likely to affect young people*, *BBC News*. Available at: https://www.bbc.co.uk/news/education-43711606 (Accessed: 20 May 2019).

Courtin, E. and Knapp, M. (2017) 'Social isolation, loneliness and health in old age: a scoping review', *Health & Social Care in the Community*. Wiley Online Library, 25(3), pp. 799–812. doi: 10.1111/hsc.12311.

Coyle, C. E. and Dugan, E. (2012) 'Social Isolation, Loneliness and Health Among Older Adults', *Journal of Aging and Health*, 24(8), pp. 1346–1363. doi: 10.1177/0898264312460275.

Department for Communities and Local Government (2007) *Generalised Land Use Database Statistics for England 2005*. West Yorkshire.

Department for Digital Culture Media and Sport (2018a) *A connected society: A strategy for tackling loneliness - laying the foundations for change*. London. Available at: www.nationalarchives.gov.uk/doc/open-government- (Accessed: 9 April 2019).

Department for Digital Culture Media and Sport (2018b) *Community Life Survey: 2017-18*. London. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/734726/Community_Life_Survey_2017-18_statistical_bulletin.pdf (Accessed: 11 July 2019).

DeVon, H. A. *et al.* (2010) 'Time to Treatment for Acute Coronary Syndromes: The Cost of Indecision', *The Journal of cardiovascular nursing*, 25(2), pp. 106–114. doi: 10.1097/JCN.0b013e3181bb14a0.

Devries, K. M. *et al.* (2013) 'Intimate Partner Violence and Incident Depressive Symptoms and Suicide Attempts: A Systematic Review of Longitudinal Studies', *PLOS Medicine*. Public Library of Science, 10(5), p. e1001439. Available at: https://doi.org/10.1371/journal.pmed.1001439.

Dickens, A. P. *et al.* (2011) 'Interventions targeting social isolation in older people: a systematic review', *BMC Public Health*. BioMed Central, 11, p. 647. doi: 10.1186/1471-2458-11-647.

Diez Roux, A. V and Mair, C. (2010) 'Neighborhoods and health', *Annals of the New York Academy of Sciences*. Blackwell Publishing Inc, 1186(1), pp. 125–145. doi: 10.1111/j.1749-6632.2009.05333.x.

Donaldson, C. A. and Ware, J. E. (1982) *The qualification of social contacts and resources*. Santa Monica, CA.

Easton, M. (2018) *How should we tackle the loneliness epidemic?*, *BBC News*. Available at: https://www.bbc.co.uk/news/uk-42887932 (Accessed: 28 June 2019).

Elovainio, M. *et al.* (2017) 'Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study', *The Lancet Public Health*. Elsevier, 2(6), pp. e260–e266. doi: 10.1016/S2468-2667(17)30075-0.

Eng, P. M. *et al.* (2002) 'Social Ties and Change in Social Ties in Relation to Subsequent Total and Cause-specific Mortality and Coronary Heart Disease Incidence in Men', *American Journal of Epidemiology*, 155(8), pp. 700–709. doi: 10.1093/aje/155.8.700.

Equal Opportunities Committee (2015) *Age and Social Isolation, 5th Report, 2015*. Edinburgh, Scotland. Available at: http://www.parliament.scot/S4_EqualOpportunitiesCommittee/Reports/EOS042015R05.pdf.

Eurostat (2019) *Household composition statistics*, *European Union - Eurostat*. Available at: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Household_composition_statistics&stable=0&redirect=no#Household_types (Accessed: 8 June 2019).

Faiz, K. W. *et al.* (2014) 'Factors Related to Decision Delay in Acute Stroke', *Journal of Stroke and Cerebrovascular Diseases*. W.B. Saunders, 23(3), pp. 534–539. doi: 10.1016/J.JSTROKECEREBROVASDIS.2013.05.007.

Fässberg, M. M. *et al.* (2012) 'A systematic review of social factors and suicidal behavior in older adulthood', *International journal of environmental research and public health*. 2012/03/01. MDPI, 9(3), pp. 722–745. doi: 10.3390/ijerph9030722.

Finlay, J. M. and Kobayashi, L. C. (2018) 'Social isolation and loneliness in later life: A parallel convergent mixed-methods case study of older adults and their residential contexts in the Minneapolis metropolitan area, USA', *Social Science & Medicine*, 208, pp. 25–33. doi: 10.1016/j.socscimed.2018.05.010.

Flanders, W. *et al.* (1992) 'Assessing the Direction of Causality in Cross-sectional Studies', *American Journal of Epidemiology*. Baltimore, Md., 135(8), p. 926. doi: 10.1093/oxfordjournals.aje.a116388.

Floud, S. *et al.* (2014) 'Marital status and ischemic heart disease incidence and mortality in women: a large prospective study', *BMC Medicine*, 12(42). doi: 10.1186/1741-7015-12-42.

Floud, S. *et al.* (2015) 'Social participation and coronary heart disease risk in a large prospective study of UK women', *European Journal of Preventive Cardiology*. SAGE Publications, 23(9), pp. 995–1002. doi: 10.1177/2047487315607056.

Floud, S. *et al.* (2016) 'The role of health-related behavioural factors in accounting for inequalities in coronary heart disease risk by education and area deprivation: prospective study of 1.2 million UK women', *BMC Medicine*, 14(1), p. 145. doi: 10.1186/s12916-016-0687-2.

Floud, S. *et al.* (2017) 'Disability and participation in breast and bowel cancer screening in England: A large prospective study', *British Journal of Cancer*, 117(11), pp. 1711–1714. doi: 10.1038/bjc.2017.331.

Fonarow, G. C. *et al.* (2011) 'Improving Door-to-Needle Times in Acute Ischemic Stroke', *Stroke*, 42(10), pp. 2983 LP – 2989. Available at: http://stroke.ahajournals.org/content/42/10/2983.abstract.

Ford, D. W. *et al.* (2014) 'The associations between diet quality, Body Mass Index (BMI) and Health and Activity Limitation Index (HALex) in the Geisinger Rural Aging Study (GRAS)', *The journal of nutrition, health & aging*, 18(2), pp. 167–170. doi: 10.1007/s12603-014-0016-4.

Ford, E. S., Loucks, E. B. and Berkman, L. F. (2006) 'Social Integration and Concentrations of C-Reactive Protein Among US Adults', *Annals of Epidemiology*, 16(2), pp. 78–84. doi: https://doi.org/10.1016/j.annepidem.2005.08.005.

Foster, C. and Fenlon, D. (2011) 'Recovery and self-management support following primary cancer treatment', *British Journal Of Cancer*. The Author(s), 105, p. S21. Available at: https://doi.org/10.1038/bjc.2011.419.

Fry, A. *et al.* (2017) 'Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those of the General Population', *American Journal of Epidemiology*, 186(9), pp. 1026–1034. Available at: http://dx.doi.org/10.1093/aje/kwx246.

GBD 2013 Mortality and Causes of Death Collaborators (2015) 'Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013', *The Lancet*, 385(9963), pp. 117–171. doi: https://doi.org/10.1016/S0140-6736(14)61682-2.

Gierveld, J. de J. (1998) 'A review of loneliness: concept and definitions, determinants and consequences', *Reviews in Clinical Gerontology*. 1998/02/01. Cambridge University Press, 8(1), pp. 73–80. doi: DOI: 10.1017/S0959259898008090.

Glik, D. C. (2007) 'Risk Communication for Public Health Emergencies', *Annual Review of Public Health*. Annual Reviews, 28(1), pp. 33–54. doi: 10.1146/annurev.publhealth.28.021406.144123.

Green, A. and Bennett, S. (2007) 'Building evidence-informed policy environments', in *Sound Choices: Enhancing Capacity for Evidence-Informed Health Policy*. Geneva: World Health Organization, pp. 23–36. Available at: http://www.mcc.gov/selection/index.php (Accessed: 9 June 2019).

Green, J. *et al.* (2018) 'Cohort Profile: the Million Women Study', *International Journal of Epidemiology*, pp. dyy065–dyy065. Available at: http://dx.doi.org/10.1093/ije/dyy065.

Greenland, S., Mansournia, M. A. and Altman, D. G. (2016) 'Sparse data bias: a problem

hiding in plain sight', *BMJ*, 352, p. i1981. doi: 10.1136/bmj.i1981.

Groce, N. E. and Mont, D. (2017) 'Counting disability: emerging consensus on the Washington Group questionnaire', *The Lancet Global Health*. Elsevier, 5(7), pp. e649–e650. doi: 10.1016/S2214-109X(17)30207-3.

Hakulinen, C. *et al.* (2018) 'Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women', *Heart*. Available at: http://heart.bmj.com/content/early/2018/03/16/heartjnl-2017-312663.abstract.

Hassen, N. and Kaufman, P. (2016) 'Examining the role of urban street design in enhancing community engagement: A literature review', *Health & Place*, 41, pp. 119–132. doi: 10.1016/j.healthplace.2016.08.005.

Hawkley, L. C. and Cacioppo, J. T. (2010) 'Loneliness Matters: A Theoretical and Empirical Review of Consequences and Mechanisms', *Annals of Behavioral Medicine*, 40(2), pp. 218–227. doi: 10.1007/s12160-010-9210-8.

Health Quality Ontario (2008) 'Social Isolation in Community-Dwelling Seniors: An Evidence-Based Analysis', *Ontario Health Technology Assessment Series*. Medical Advisory Secretariat, 8(5), pp. 1–49. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3377559/.

Hirdes, J. P. and Forbes, W. F. (1992) 'The importance of social relationships, socioeconomic status and health practices with respect to mortality among healthy Ontario males.', *Journal of clinical epidemiology*. United States, 45(2), pp. 175–182. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=1573434.

Holt-Lunstad, J. *et al.* (2015) 'Loneliness and Social Isolation as Risk Factors for Mortality: a Meta-Analytic Review', *Perspectives on Psychological Science*. SAGE Publications, 10(2), pp. 227–237. doi: 10.1177/1745691614568352.

Holt-Lunstad, J. (2018a) 'The Potential Public Health Relevance of Social Isolation and Loneliness: Prevalence, Epidemiology, and Risk Factors', *Public Policy & Aging Report*, 27(4), pp. 127–130. doi: 10.1093/ppar/prx030.

Holt-Lunstad, J. (2018b) 'Why Social Relationships Are Important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection', *Annual Review of Psychology*. Annual Reviews, 69(1), pp. 437–458. doi: 10.1146/annurev-psych-122216-011902.

Holt-Lunstad, J., Smith, T. B. and Layton, J. B. (2010) 'Social Relationships and Mortality Risk: A Meta-analytic Review', *PLOS Medicine*. Public Library of Science, 7(7), p. e1000316. Available at: https://doi.org/10.1371/journal.pmed.1000316.

House, J. S., Landis, K. R. and Umberson, D. (1988) 'Social Relationships and Health', *Science*. American Association for the Advancement of Science, 241(4865), pp. 540–545. Available at: http://www.jstor.org/stable/1701736.

House, J. S., Robbins, C. and Metzner, H. L. (1982) 'The association of social relationships and activities with mortality: Prospective evidence from the Techcumseh Community Health Study', *American Journal of Epidemiology*, 116(1), pp. 123–140. Available at: http://dx.doi.org/10.1093/oxfordjournals.aje.a113387.

Hughes, M. E. *et al.* (2004) 'A Short Scale for Measuring Loneliness in Large Surveys: Results From Two Population-Based Studies', *Research on aging*, 26(6), pp. 655–672. doi: 10.1177/0164027504268574.

Iacobucci, G. (2018) 'Stop smoking services: BMJ analysis shows how councils are stubbing them out', *BMJ*, 24 August, p. k3649. doi: 10.1136/bmj.k3649.

International Agency for Research on Cancer (2004) *Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 83: Tobacco Smoke and Involuntary Smoking*. Lyon. Available at: http://monographs.iarc.fr/ (Accessed: 30 May 2019).

Jetten, J. *et al.* (2014) 'How groups affect our health and well-being: The path from theory to policy', *Social Issues and Policy Review*, 8(1), pp. 103–130. doi: 10.1111/sipr.12003.

Jha, P. *et al.* (2013) '21st-Century Hazards of Smoking and Benefits of Cessation in the United States', *The New England Journal of Medicine*, 368(4), pp. 341–350. doi: 10.1056/NEJMsa1211128.

Jopling, K. and Vasileiou, K. (2015) *Promising approaches to reducing loneliness and isolation in later life*. London. Available at: https://www.campaigntoendloneliness.org/wp-content/uploads/Promising-approaches-to-reducing-loneliness-and-isolation-in-later-life.pdf.

Jordan, H., Roderick, P. and Martin, D. (2004) 'The Index of Multiple Deprivation 2000 and accessibility effects on health', *Journal of Epidemiology and Community Health*. BMJ Group, 58(3), pp. 250–257. doi: 10.1136/jech.2003.013011.

Julsing, J. E. *et al.* (2016) 'Loneliness and All-Cause, Cardiovascular, and Noncardiovascular Mortality in Older Men: The Zutphen Elderly Study', *The American Journal of*

Geriatric Psychiatry, 24(6), pp. 475–484. doi: https://doi.org/10.1016/j.jagp.2016.01.136.

Kaplan, G. A. *et al.* (1988) 'Social connections and mortality from all causes and from cardiovascular disease: prospective evidence from eastern Finland.', *American journal of epidemiology*. United States, 128(2), pp. 370–380. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med3&NEWS=N&AN=3394703.

Kawachi, I. *et al.* (1996) 'A prospective study of social networks in relation to total mortality and cardiovascular disease in men in the USA.', *Journal of epidemiology and community health*. England, 50(3), pp. 245–251. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=8935453.

Keating, N. L. *et al.* (2011) 'Minimal social network effects evident in cancer screening behavior', *Cancer*. John Wiley & Sons, Ltd, 117(13), pp. 3045–3052. doi: 10.1002/cncr.25849.

Khamis, R. Y., Ammari, T. and Mikhail, G. W. (2016) 'Gender differences in coronary heart disease', *Heart*, 102(14), pp. 1142 LP – 1149. Available at: http://heart.bmj.com/content/102/14/1142.abstract.

Kim, J.-H. *et al.* (2016) 'Influence of Social Engagement on Mortality in Korea: Analysis of the Korean Longitudinal Study of Aging (2006-2012).', *Journal of Korean medical science*. Korea (South), 31(7), pp. 1020–1026. doi: https://dx.doi.org/10.3346/jkms.2016.31.7.1020.

Kim, Y. and Kawachi, I. (2018) 'Social Networks', in Kivimaki, M. et al. (eds) *The Routledge International Handbook of Psychosocial Epidemiology*. New York: Routledge, pp. 49–84.

Krieger, N. (2001) 'Theories for social epidemiology in the 21st century: an ecosocial perspective', *International Journal of Epidemiology*, 30(4), pp. 668–677. Available at: http://dx.doi.org/10.1093/ije/30.4.668.

Kubzansky, L. D., Seeman, T. E. and Glymour, M. M. (2014) 'Biological Pathways Linking Social Conditions and Health', in Berkman, L. F., Kawachi, I., and Glymour, M. M. (eds) *Social Epidemiology*. Second. New York: Oxford University Press, pp. 512–561.

Kullar, D. (2016) *How Social Isolation is Killing Us*, *New York Times*. Available at:

https://www.nytimes.com/2016/12/22/upshot/how-social-isolation-is-killing-us.html (Accessed: 28 June 2019).

Laugesen, K. *et al.* (2018) 'Social isolation and all-cause mortality: a population-based cohort study in Denmark', *Scientific Reports*, 8(1), p. 4731. doi: 10.1038/s41598-018-22963-w.

Lavis, J. N. *et al.* (2002) 'Examining the Role of Health Services Research in Public Policymaking', *The Milbank Quarterly*. [Wiley, Milbank Memorial Fund], 80(1), pp. 125–154. Available at: http://ezproxy-prd.bodleian.ox.ac.uk:2084/stable/3350497.

Leigh-Hunt, N. *et al.* (2017) 'An overview of systematic reviews on the public health consequences of social isolation and loneliness', *Public Health*, 152, pp. 157–171. doi: 10.1016/j.puhe.2017.07.035.

Li, R. and Chambless, L. (2007) 'Test for Additive Interaction in Proportional Hazards Models', *Annals of Epidemiology*, 17(3), pp. 227–236. doi: https://doi.org/10.1016/j.annepidem.2006.10.009.

Liu, B. *et al.* (2017) 'Does happiness itself directly affect mortality? The prospective UK Million Women Study', *The Lancet*. Elsevier, 387(10021), pp. 874–881. doi: 10.1016/S0140-6736(15)01087-9.

Liu, B. and Floud, S. (2017) 'Unravelling the associations between social isolation, loneliness, and mortality', *The Lancet Public Health*, pp. e248–e249. doi: 10.1016/S2468-2667(17)30090-7.

Lomas, J. (2000) 'Connecting research and policy', *Canadian Journal of Policy Research*, 1(1), pp. 140–144.

Loucks, E. B., Berkman, L. F., *et al.* (2006) 'Relation of Social Integration to Inflammatory Marker Concentrations in Men and Women 70 to 79 Years', *The American Journal of Cardiology*, 97(7), pp. 1010–1016. doi: 10.1016/j.amjcard.2005.10.043.

Loucks, E. B., Sullivan, L. M., *et al.* (2006) 'Social Networks and Inflamatory Markers in the Framingham Heart Study', *Journal of Biosocial Science*. 2006/01/27. Cambridge University Press, 38(6), pp. 835–842. doi: DOI: 10.1017/S0021932005001203.

Lubben, J. *et al.* (2006) 'Performance of an abbreviated version of the Lubben Social Network Scale among three European community-dwelling older adult populations', *The Gerontologist*, 46(4), p. 503. doi: 10.1093/geront/46.4.503.

Lubben, J. E. (1988) 'Assessing social networks among elderly populations.', *Family &*

Community Health: The Journal of Health Promotion & Maintenance. US: Lippincott Williams & Wilkins, pp. 42–52. doi: 10.1097/00003727-198811000-00008.

Madsen, T. E. *et al.* (2017) 'Gender, Social Networks, and Stroke Preparedness in the Stroke Warning Information and Faster Treatment Study', *Journal of Stroke and Cerebrovascular Diseases*. W.B. Saunders, 26(12), pp. 2734–2741. doi: 10.1016/J.JSTROKECEREBROVASDIS.2017.06.046.

Mahder-Bashi, A. and Savage, R. (2019) *Look at all the lonely people: A lack of connection is a public-health problem - The Globe and Mail*, *The Globe and Mail*. Available at: https://www.theglobeandmail.com/opinion/article-look-at-all-the-lonely-people-a-lack-of-connection-is-a-public-health/ (Accessed: 20 May 2019).

Marcus, A. F. *et al.* (2015) 'How Neighborhood Poverty Structures Types and Levels of Social Integration', *American Journal of Community Psychology*. Springer US, 56(1–2), pp. 134–144. doi: 10.1007/s10464-015-9732-0.

Marcus, A. F. *et al.* (2016) 'The joint contribution of neighborhood poverty and social integration to mortality risk in the United States', *Annals of Epidemiology*. Elsevier, 26(4), pp. 261–266. doi: 10.1016/J.ANNEPIDEM.2016.02.006.

Marcus, A. F. *et al.* (2017) 'Relationships between social isolation, neighborhood poverty, and cancer mortality in a population-based study of US adults', *PLOS ONE*. Edited by M. Buchowski. Public Library of Science, 12(3), p. e0173370. doi: 10.1371/journal.pone.0173370.

Marit, K. *et al.* (2012) 'Facing the challenge of adapting to a life "alone" in old age: the influence of losses', *Journal of Advanced Nursing*. Wiley/Blackwell (10.1111), 69(2), pp. 394–403. doi: 10.1111/j.1365-2648.2012.06018.x.

Marjoribanks, D. and Darnell Bradley, A. (2017) *The Way We Are Now-The state of the UK's relationships*. Doncaster. Available at: https://www.relate.org.uk/sites/default/files/the_way_we_are_now_-_it_takes_two.pdf (Accessed: 3 June 2019).

Matsuoka, R. H. and Kaplan, R. (2008) 'People needs in the urban landscape: Analysis of Landscape And Urban Planning contributions', *Landscape and Urban Planning*, 84(1), pp. 7–19. doi: 10.1016/j.landurbplan.2007.09.009.

McGuinness, L. A. (2019) 'robvis: An R package and web application for visualising risk-of-bias assessments'. Available at: https://github.com/mcguinlu/robvis.

McLennan, D. *et al.* (2011) *The English Indices of Deprivation 2010*, *Department for Communities and Local Government*. London, United Kingdom. doi: http://dx.doi.org/http://www.communities.gov.uk/publications/corporate/statistics/indices2010technicalreport.

Menec, V. *et al.* (2015) 'Making Rural and Remote Communities More Age-Friendly: Experts' Perspectives of Issues, Challenges, and Priorities', *Journal of Aging & Social Policy*. Routledge, 27(2). doi: 10.1080/08959420.2014.995044.

Menec, V. H. *et al.* (2019) 'Examining individual and geographic factors associated with social isolation and loneliness using Canadian Longitudinal Study on Aging (CLSA) data', *PLOS ONE*. Public Library of Science, 14(2), p. e0211143. Available at: https://doi.org/10.1371/journal.pone.0211143.

Meschia, J. F. *et al.* (2014) 'Guidelines for the Primary Prevention of Stroke', *Stroke*, 45(12), pp. 3754–3832. doi: 10.1161/STR.0000000000000046.

Ministry of Housing Communities and Local Government (2011) *English indices of deprivation 2010*. Available at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010 (Accessed: 22 September 2018).

Morrison, J. (2018) *Social isolation should be a public health priority*, *The Guardian*. Available at: https://www.theguardian.com/social-care-network/2018/feb/23/social-isolation-public-health-priority (Accessed: 20 May 2019).

Nagayoshi, M. *et al.* (2014) 'Social Network, Social Support, and Risk of Incident Stroke', *Stroke*, 45(10), pp. 2868 LP – 2873. Available at: http://stroke.ahajournals.org/content/45/10/2868.abstract.

National Health Service (2015) *Loneliness 'increases risk of premature death'*, *NHS*. Available at: https://www.nhs.uk/news/mental-health/loneliness-increases-risk-of-premature-death/ (Accessed: 20 May 2019).

National Institute for Health and Care Excellence (2018a) *Smoking cessation interventions and services [A] Evidence reviews for stop smoking services*. London: NICE. Available at: https://www.nice.org.uk/guidance/ng92/evidence/a-stop-smoking-services-pdf-4788920846 (Accessed: 8 June 2019).

National Institute for Health and Care Excellence (2018b) *Smoking cessation interventions and services [B] Evidence reviews for interventions to aid smoking cessation: behavioural support and pharmacotherapy*. London: NICE. Available at: https://www.nice.org.uk/guidance/ng92/evidence/b-interventions-to-aid-smoking-

cessation-behavioural-support-and-pharmacotherapy-pdf-4788920847 (Accessed: 8 June 2019).

National Seniors Council (2014) *Report on the Social Isolation of Seniors*. Ottawa, Canada. Available at: https://www.canada.ca/en/national-seniors-council/programs/publications-reports/2014/social-isolation-seniors.html.

Nicholson, N. R. (2009) 'Social isolation in older adults: An evolutionary concept analysis.', *Journal of Advanced Nursing*. Edited by B. Ackley Bassuk, Berkman, Berkman, Berkman, Berkman, Berkman, Biordi, Boden-Albala, Bondevik, Brummett, Cattan, Cohen, Eng, Faulkner, Findlay, Fioto, Fleury, Fowles, Fratiglioni, Gist, Grundy, Hagerty, Hanson, Havens, Howat, LaVeist, Lien-Gieschen, Locher,. Nicholson, Nicholas R., Jr., Nicholas.Nicholson@yale.edu: Wiley-Blackwell Publishing Ltd., 65(6), pp. 1342–1352. doi: http://dx.doi.org/10.1111/j.1365-2648.2008.04959.x.

Nicholson, N. R. (2012) 'A review of social isolation: an important but underassessed condition in older adults', *The Journal of Primary Prevention*. N.R. Nicholson, School of Nursing, Quinnipiac University, 275 Mount Carmel Ave. N1-HSC, Hamden, CT, USA., 33(2–3), pp. 137–152. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed13&NEWS=N&AN=366362636.

Northcott, S. *et al.* (2016) 'A systematic review of the impact of stroke on social support and social networks: associated factors and patterns of change.', *Clinical rehabilitation*. England, 30(8), pp. 811–831. doi: https://dx.doi.org/10.1177/0269215515602136.

O'Donnell, M. J. *et al.* (2016) 'Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study', *The Lancet*, 388(10046), pp. 761–775. doi: https://doi.org/10.1016/S0140-6736(16)30506-2.

Office for National Statistics (2013) *What Does the 2011 Census Tell Us About Older People?* London.

Office for National Statistics (2014) *2011 Census Analysis: Do the Demographic and Socio-Economic Characteristics of those Living Alone in England and Wales Differ from the General Population?* London. Available at: http://webarchive.nationalarchives.gov.uk/20160107120943/http://www.ons.gov.uk/ons/dcp171776_387694.pdf.

Office for National Statistics (2018a) *Avoidable Mortality in the UK: 2016*, *Office for*

National Statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/avoidablemortalityinenglandandwales/2016 (Accessed: 1 June 2018).

Office for National Statistics (2018b) *Trends in living arrangements including families (with and without dependent children), people living alone and people in shared accommodation, broken down by size and type of household.*, *Families and Households: 2017*. London. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/families/bulletins/familiesandhouseholds/2017 (Accessed: 8 June 2019).

Office for National Statistics (2019) *2011 Census*, *Office for National Statistics*. Available at: https://www.ons.gov.uk/census/2011census (Accessed: 11 July 2019).

Office of National Statistics (2016) *ONS Postcode Directory*. Available at: http://ons.maps.arcgis.com/home/item.html?id=d7fe815217504f4eac0cb07170747094 (Accessed: 23 January 2017).

Office of National Statistics (2017) *Enumeration Districts*, *Census geography*. Available at: https://www.ons.gov.uk/methodology/geography/ukgeographies/censusgeography#enumeration-district-ed (Accessed: 3 August 2017).

Ordnance Survey (2017a) *OS MasterMap Greenspace Layer Product Technical Specification V1.0*. Southampton. Available at: www.os.uk (Accessed: 26 March 2019).

Ordnance Survey (2017b) *OS MasterMap Greenspace Product guide*. Southampton. Available at: https://www.ordnancesurvey.co.uk/docs/product-guides/osmm-greenspace-product-guide.pdf (Accessed: 26 March 2019).

Orth-Gomer, K. and Johnson, J. V (1987) 'Social network interaction and mortality. A six year follow-up study of a random sample of the Swedish population.', *Journal of chronic diseases*. England, 40(10), pp. 949–957. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=3611293.

Orth-Gomér, K. and Johnson, J. V (1987) 'Social network interaction and mortality: A six year follow-up study of a random sample of the swedish population', *Journal of Chronic Diseases*, 40(10), pp. 949–957. doi: https://doi.org/10.1016/0021-9681(87)90145-7.

Palomeras Soler, E. and Casado Ruiz, V. (2010) 'Epidemiology and Risk Factors of Cerebral Ischemia and Ischemic Heart Diseases: Similarities and Differences', *Current*

Cardiology Reviews, 6(3), pp. 138–149. doi: 10.2174/157340310791658785.

Pantell, M. *et al.* (2013) 'Social Isolation: A Predictor of Mortality Comparable to Traditional Clinical Risk Factors', *American Journal of Public Health*. American Public Health Association, 103(11), pp. 2056–2062. doi: 10.2105/AJPH.2013.301261.

Parish, S. *et al.* (2009) 'The joint effects of apolipoprotein B, apolipoprotein A1, LDL cholesterol, and HDL cholesterol on risk: 3510 cases of acute myocardial infarction and 9805 controls†', *European Heart Journal*, 30(17), pp. 2137–2146. doi: 10.1093/eurheartj/ehp221.

Patrick, D. L. *et al.* (1994) 'The validity of self-reported smoking: a review and meta-analysis.', *American Journal of Public Health*. American Public Health Association, 84(7), pp. 1086–1093. doi: 10.2105/AJPH.84.7.1086.

Patterson, A. C. (2016) 'Does the mortality risk of social isolation depend upon socioeconomic factors?', *Journal of Health Psychology*. London, England, 21(10), pp. 2420–2433. doi: 10.1177/1359105315578302.

Patterson, A. C. and Veenstra, G. (2010) 'Loneliness and risk of mortality: a longitudinal investigation in Alameda County, California.', *Social Science & Medicine*, 71(1), pp. 181–186. doi: https://dx.doi.org/10.1016/j.socscimed.2010.03.024.

Penninx, B. W. *et al.* (1997) 'Effects of social support and personal coping resources on mortality in older age: the Longitudinal Aging Study Amsterdam', *American Journal of Epidemiology*, 146(6), p. 510. doi: 10.1093/oxfordjournals.aje.a009305.

Perlman, D. and Vangelisti, A. L. (2006) *Personal Relationships: An Introduction*, *The Cambridge Handbook of Personal Relationships*. Edited by D. Perlman and A. L. Vangelisti. New York: Cambridge University Press.

Pirie, K. *et al.* (2013) 'The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK', *The Lancet*. Elsevier, 381(9861), pp. 133–141. doi: 10.1016/S0140-6736(12)61720-6.

Portacolone, E. *et al.* (2018) '"I Feel Trapped": The Tension Between Personal and Structural Factors of Social Isolation and the Desire for Social Integration Among Older Residents of a High-Crime Neighborhood', *The Gerontologist*, 58(1), pp. 79–88. doi: 10.1093/geront/gnw268.

Public Health England (2016) *Indicator Definitions and Supporting Information*, *Public Health Outcomes Framework*. Available at:

https://fingertips.phe.org.uk/profile/public-health-outcomes-framework/data#page/6/gid/1000041/pat/6/par/E12000004/ati/102/are/E06000015/iid/90280/age/168/sex/4.

Public Health England (2017) *Indicator Definitions and Supporting Information: 1.18i-Social Isolation*, *Public Health Outcomes Framework*. Available at: https://fingertips.phe.org.uk/profile/public-health-outcomes-framework/data#page/6/gid/1000041/pat/6/par/E12000004/ati/102/are/E06000015/iid/90280/age/168/sex/4.

Pun, V. C., Manjourides, J. and Suh, H. H. (2018) 'Association of neighborhood greenness with self-perceived stress, depression and anxiety symptoms in older U.S adults', *Environmental Health*, 17(1), p. 39. doi: 10.1186/s12940-018-0381-2.

Reblin, M. and Uchino, B. N. (2008) 'Social and emotional support and its implication for health', *Current Opinion in Psychiatry*, pp. 201–205. doi: 10.1097/YCO.0b013e3282f3ad89.

Reed, D. *et al.* (1983) 'Social networks and coronary heart disease among Japanese men in Hawaii.', *American journal of epidemiology*. United States, 117(4), pp. 384–396. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med2&NEWS=N&AN=6837553.

Reher, D. and Requena, M. (2018) 'Living Alone in Later Life: A Global Perspective', *Population and Development Review*. John Wiley & Sons, Ltd (10.1111), 44(3), pp. 427–454. doi: 10.1111/padr.12149.

Reitsma, M. B. *et al.* (2017) 'Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: a systematic analysis from the Global Burden of Disease Study 2015', *The Lancet*. Elsevier, 389(10082), pp. 1885–1906. doi: 10.1016/S0140-6736(17)30819-X.

Robles, T. F. *et al.* (2014) 'Marital quality and health: a meta-analytic review.', *Psychological bulletin*. United States, 140(1), pp. 140–187. doi: https://dx.doi.org/10.1037/a0031859.

Rod, N. H. *et al.* (2012) 'Additive Interaction in Survival Analysis: Use of the Additive Hazards Model', *Epidemiology*, 23(5), pp. 733–737. Available at: https://journals.lww.com/epidem/Fulltext/2012/09000/Additive_Interaction_in_Survival_Analysis__Use_of.14.aspx.

Rodriguez-Laso, A., Zunzunegui, M. V. and Otero, A. (2007) 'The effect of social relationships on survival in elderly residents of a Southern European community: a cohort study.', *BMC geriatrics*. England, 7, p. 19. doi: https://dx.doi.org/10.1186/1471-2318-7-19.

Seeman, T. *et al.* (2004) 'Social relationships and allostatic load in Taiwanese elderly and near elderly', *Social Science and Medicine*, 59(11), pp. 2245–2257. doi: 10.1016/j.socscimed.2004.03.027.

Seeman, T. E. *et al.* (2002) 'Social relationships, gender, and allostatic load across two age cohorts.', *Psychosomatic medicine*. United States, 64(3), pp. 395–406. Available at: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=med4&NEWS=N&AN=12021414.

Shankar, A. *et al.* (2011) 'Loneliness, Social Isolation, and Behavioral and Biological Health Indicators in Older Adults', *Health Psychology*. Edited by A. Shankar, 30(4), pp. 377–385. doi: 10.1037/a0022826.

Shavelle, R. M. *et al.* (2008) 'Smoking Habit and Mortality: A Meta-analysis', *Journal of Insurance Medicine*, 40, pp. 170–178.

Shavers, V. L. (2007) 'Measurement of socioeconomic status in health disparities research.', *Journal of the National Medical Association*. National Medical Association, 99(9), pp. 1013–1023. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2575866/.

Shor, E. and Roelfs, D. J. (2015) 'Social contact frequency and all-cause mortality: A meta-analysis and meta-regression', *Social Science & Medicine*. Pergamon, 128, pp. 76–86. doi: 10.1016/J.SOCSCIMED.2015.01.010.

Shor, E., Roelfs, D. J. and Yogev, T. (2013) 'The strength of family ties: A meta-analysis and meta-regression of self-reported social support and mortality', *Social Networks*, 35(4), pp. 626–638. doi: 10.1016/j.socnet.2013.08.004.

Siegler, V., Njeru, R. and Thomas, J. (2015) *Inequalities in Social Capital by Age and Sex, July 2015*. London. Available at: http://webarchive.nationalarchives.gov.uk/20160105172209/http://www.ons.gov.uk/ons/rel/wellbeing/measuring-national-well-being/inequalities-in-social-capital-by-age-and-sex/art.html.

Skrondal, A. (2003) 'Interaction as Departure from Additivity in Case-Control Studies: A Cautionary Note', *Am J Epidemiol*, (158), pp. 251–258.

Smith, K. P. and Christakis, N. A. (2008) 'Social Networks and Health', *Annual Review of Sociology*, 34(1), pp. 405–429. doi: 10.1146/annurev.soc.34.040507.134601.

Smith, S. G. *et al.* (2018) 'Social Isolation, Health Literacy, and Mortality Risk: Findings From the English Longitudinal Study of Ageing.', *Health Psychology*. United States, 37(2), pp. 160–169. doi: https://dx.doi.org/10.1037/hea0000541.

Smith, T. *et al.* (2015) *The English Indices of Deprivation 2015 Research Report*. London. Available at: http://forms.communities.gov.uk/orwritetousat: (Accessed: 27 November 2018).

Stafford, M. *et al.* (2018) 'Social connectedness and engagement in preventive health services: an analysis of data from a prospective cohort study.', *The Lancet Public health*. Elsevier, 3(9), pp. e438–e446. doi: 10.1016/S2468-2667(18)30141-5.

StataCorp (2015) 'Stata Statistical Software: Release 14', *2015*. doi: 10.2307/2234838.

StataCorp (2017) 'Stata Statistical Software: Release 15'. College Station, TX: StataCorp LLC.

Steptoe, A. *et al.* (2013) 'Social isolation, loneliness, and all-cause mortality in older men and women.', *Proceedings of the National Academy of Sciences of the United States of America*. United States, 110(15), pp. 5797–5801. doi: https://dx.doi.org/10.1073/pnas.1219686110.

Stessman, J. *et al.* (2014) 'Loneliness, health, and longevity.', *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*. United States, 69(6), pp. 744–750. doi: https://dx.doi.org/10.1093/gerona/glt147.

Stewart, J., Manmathan, G. and Wilkinson, P. (2017) 'Primary prevention of cardiovascular disease: A review of contemporary guidance and literature', *JRSM Cardiovascular Disease*, 6, p. 204800401668721. doi: 10.1177/2048004016687211.

Stringhini, S. *et al.* (2012) 'Socioeconomic status, structural and functional measures of social support, and mortality: The British Whitehall II Cohort Study, 1985-2009', *American Journal of Epidemiology*, 175(12), pp. 1275–1283. doi: 10.1093/aje/kwr461.

Sudlow, C. *et al.* (2015) 'UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age', *PLOS Medicine*. Public Library of Science, 12(3), pp. e1001779-. Available at: https://doi.org/10.1371/journal.pmed.1001779.

Sugisawa, H., Liang, J. and Liu, X. (1994) 'Social Networks, Social Support, and Mortality Among Older People in Japan', *Journal of Gerontology*. St. Louis, Mo., 49(1), p. 3. doi: 10.1093/geronj/49.1.S3.

Talen, E. and Koschinsky, J. (2014) 'Compact, Walkable, Diverse Neighborhoods: Assessing Effects on Residents', *Housing Policy Debate*, 24(4), pp. 717–750. doi: 10.1080/10511482.2014.900102.

Tang, J., Galbraith, N. and Truong, J. (2019) *Living Alone in Canada*. Ottawa.

Tanskanen, J. and Anttila, T. (2016) 'A Prospective Study of Social Isolation, Loneliness, and Mortality in Finland.', *American journal of public health*. United States, 106(11), pp. 2042–2048. doi: https://dx.doi.org/10.2105/AJPH.2016.303431.

Tate, N. (2018) *Loneliness Rivals Obesity, Smoking as Health Risk*, *WebMD*. Available at: https://www.webmd.com/balance/news/20180504/loneliness-rivals-obesity-smoking-as-health-risk (Accessed: 20 May 2019).

Thun, M. J. *et al.* (2013) '50-Year Trends in Smoking-Related Mortality in the United States', *New England Journal of Medicine*. Massachusetts Medical Society , 368(4), pp. 351–364. doi: 10.1056/NEJMsa1211127.

Thurber, A., Bohmann, C. R. and Heflinger, C. A. (2018) 'Spatially integrated and socially segregated: The effects of mixed-income neighbourhoods on social well-being', *Urban Studies*, 55(9), pp. 1859–1874. doi: 10.1177/0042098017702840.

Thurley, D. and McInnes, R. (2018) *Increases in the State Pension age for women born in the 1950s*, *Parliament of the United Kingdom, House of Commons Library*. Available at: https://researchbriefings.parliament.uk/ResearchBriefing/Summary/CBP-7405 (Accessed: 2 January 2019).

Townsend, P., Beattie, A. and Phillimore, P. (1988) *Health and deprivation : inequality and the north*. London: Croom Helm.

Turtzo, L. C. and McCullough, L. D. (2008) 'Sex Differences in Stroke', *Cerebrovascular Diseases*, 26(5), pp. 462–474. Available at: https://www.karger.com/DOI/10.1159/000155983.

U.S. Census Bureau (2019) *Figure HH-4: The rise of living alone*, *Current Population Survey, Annual Social and Economic Supplements, 1960 to 2018*. Available at: https://www.census.gov/content/dam/Census/library/visualizations/time-series/demo/families-and-households/hh-4.pdf (Accessed: 8 June 2019).

U.S. Centers for Disease Control and Prevention, U.S. National Center for Chronic Disease Prevention and Health Promotion and U.S. Office on Smoking and Health (2010) 'Introduction, Evaluation of Evidence on Mechanisms of Disease Production, and Summary', in *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services. Available at: https://www.ncbi.nlm.nih.gov/books/NBK53019/ (Accessed: 6 June 2019).

U.S. Public Health Service (1964) *U.S. Surgeon General's Advisory Committee on Smoking and Health, Smoking and Health*. Washington, DC.

Uchino, B. N., Uno, D. and Holt-Lunstad, J. (1999) 'Social Support, Physiological Processes, and Health', *Current Directions in Psychological Science*. SAGE Publications Inc, 8(5), pp. 145–148. doi: 10.1111/1467-8721.00034.

Udell, J. A. *et al.* (2012) 'Living alone and cardiovascular risk in outpatients at risk of or with atherothrombosis.', *Archives of internal medicine*. United States, 172(14), pp. 1086–1095. doi: https://dx.doi.org/10.1001/archinternmed.2012.2782.

UK Biobank (2007) *UK Biobank: Protocol for a large-scale prospective epidemiological resource*. Stockport, UK. doi: 10.1126/science.311.5767.1535c.

UK Biobank (2015) *Table 1. Biomarkers currently included in the panel*. Stockport. Available at: http://www.ukbiobank.ac.uk/wp-content/uploads/2018/11/BCM023_ukb_biomarker_panel_website_v1.0-Aug-2015-edit-2018.pdf (Accessed: 11 July 2019).

UK Biobank (2017) *Access matter: representativeness of the UK Biobank resource*. Oxford. Available at: http://www.ukbiobank.ac.uk/wp-content/uploads/2017/03/access-matters-representativeness-1.pdf (Accessed: 6 April 2019).

UK Biobank (2018) *Resources*. Available at: https://www.ukbiobank.ac.uk/resources/ (Accessed: 4 October 2018).

UK Biobank (2019) *Biomarkers*, *UK Biobank*. Available at: https://www.ukbiobank.ac.uk/uk-biobank-biomarker-panel/ (Accessed: 11 July 2019).

Umberson, D., Crosnoe, R. and Reczek, C. (2010) 'Social Relationships and Health Behavior Across the Life Course', *Annual Review of Sociology*. Annual Reviews, 36(1), pp. 139–157. doi: 10.1146/annurev-soc-070308-120011.

Understanding Society (2019a) *Biomarkers, Genetics & Epigenetics*, *Understanding*

Society. Available at: https://www.understandingsociety.ac.uk/research/themes/biomarkers-genetics-and-epigenetics (Accessed: 10 July 2019).

Understanding Society (2019b) *Understanding Society: About the study*, *Understanding Society*. Available at: https://www.understandingsociety.ac.uk/about/about-the-study (Accessed: 10 July 2019).

Valtorta, N. K., Kanaan, M., Gilbody, S. and Hanratty, B. (2016) 'Loneliness, social isolation and social relationships: what are we measuring? A novel framework for classifying and comparing tools', *BMJ Open*, 6(4), p. e010799. doi: 10.1136/bmjopen-2015-010799.

Valtorta, N. K., Kanaan, M., Gilbody, S., Ronzi, S., *et al.* (2016) 'Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies', *Heart*, 102(13), pp. 1009–1016. doi: 10.1136/heartjnl-2015-308790.

Valtorta, N. K., Kanaan, M., *et al.* (2018) 'Loneliness, social isolation and risk of cardiovascular disease in the English Longitudinal Study of Ageing', *European Journal of Preventive Cardiology*. SAGE Publications Ltd STM, 25(13), pp. 1387–1396. doi: 10.1177/2047487318792696.

Valtorta, N. K., Collingridge Moore, D., *et al.* (2018) 'Older Adults' Social Relationships and Health Care Utilization: A Systematic Review', *American Journal of Public Health*, 108(4), p. e1. doi: 10.2105/AJPH.2017.304256.

Valtorta, N. K. and Hanratty, B. (2012) 'Loneliness, isolation and the health of older adults: Do we need a new research agenda?', *Journal of the Royal Society of Medicine*, 105, pp. 518–522. doi: 10.1258/jrsm.2012.120128.

Valtorta, N. K. and Hanratty, B. (2016) 'P36 Loneliness, social isolation and health: "What's the problem represented to be?" in the United Kingdom?', *Journal of Epidemiology and Community Health*, 70(Suppl 1), p. A69. Available at: http://jech.bmj.com/content/70/Suppl_1/A69.2.abstract.

VanderWeele, T. J. and Knol, M. J. (2014) 'A Tutorial on Interaction', *Epidemiologic Methods*, 3(1), pp. 33–72. doi: 10.1515/em-2013-0005.

Victor, C. R. (2005) *Loneliness, Social Isolation and Living Alone in Later Life: ESRC Full Research Report, L480254042*. Swindon.

Victor, C. R. and Bowling, A. (2012) ‘A Longitudinal Analysis of Loneliness Among Older People in Great Britain’, *The Journal of Psychology*, 146(3), pp. 313–331. doi: 10.1080/00223980.2011.609572.

Wang, J. *et al.* (2018) ‘Associations between loneliness and perceived social support and outcomes of mental health problems: a systematic review’, *BMC Psychiatry*, 18(156), pp. 1–16. doi: 10.1186/s12888-018-1736-5.

Webb, P. and Bain, C. (2010) ‘Healthy research: study designs for public health’, in *Essential Epidemiology: An Introduction for Students and Health Professionals.* 2nd edn. Cambridge: Cambridge University Press (Ebook central), pp. 98–9.

Wheeler, B. (2016) *UK Biobank Project 15374: Documentation of environmental indicators attributed to participants based on home location grid references*. Oxford. Available at: http://biobank.ctsu.ox.ac.uk/showcase/docs/App15374Docs.pdf (Accessed: 26 March 2019).

Williams, R. (1995) ‘Product-limit survival functions with correlated survival times’, *Lifetime Data Analysis*. Dordrecht, 1(2), pp. 171–186. doi: 10.1007/BF00985768.

Williams, R. L. (2000) ‘A Note on Robust Variance Estimation for Cluster-Correlated Data’, *Biometrics*. Oxford, UK, 56(2), pp. 645–646. doi: 10.1111/j.0006-341X.2000.00645.x.

Wilson, D. M. *et al.* (2010) ‘Upstream thinking and health promotion planning for older adults at risk of social isolation’, *International Journal of Older People Nursing*. Wiley/Blackwell (10.1111), 6(4), pp. 282–288. doi: 10.1111/j.1748-3743.2010.00259.x.

Winterton, R. and Warburton, J. (2011) ‘Does place matter? Reviewing the experience of disadvantage for older people in rural Australia’, *Rural Society*. Routledge, 20(2), pp. 187–197. doi: 10.5172/rsj.20.2.187.

Wister, A. *et al.* (2019) ‘Development and Concurrent Validity of a Composite Social Isolation Index for Older Adults Using the CLSA’, *Canadian Journal on Aging / La Revue canadienne du vieillissement*. 2019/01/11. Cambridge University Press, 38(2), pp. 180–192. doi: DOI: 10.1017/S0714980818000612.

World Health Organisation (2010) *International Statistical Classification of Diseases and Related Health Problems 10th Revision*, *World Health Organisation*. Available at: http://apps.who.int/classifications/icd10/browse/2010/en.

World Health Organization (2015) *World Report on Ageing and Health*. Geneva, Switzerland. Available at: http://apps.who.int/iris/bitstream/10665/186463/1/9789240694811_eng.pdf?ua=1.

Yang, Y. C. *et al.* (2013) 'Social Isolation and Adult Mortality The Role of Chronic Inflammation and Sex Differences', *Journal of Health and Social Behavior*, 54(2), pp. 183–203. doi: 10.1177/0022146513485244.

Yang, Y. C. *et al.* (2016) 'Social relationships and physiological determinants of longevity across the human life span', *Proceedings of the National Academy of Sciences*. National Academy of Sciences, 113(3), pp. 578–583. doi: 10.1073/PNAS.1511085112.

Yusuf, S. *et al.* (2004) 'Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study', *The Lancet*, 364(9438), pp. 937–952. doi: https://doi.org/10.1016/S0140-6736(04)17018-9.

Zavaleta, D., Samuel, K. and Mills, C. (2014) *Social Isolation: A Conceptual and Measurement Proposal*, *OPHI Working Paper 67*. Oxford: Oxford Department of International Development. Available at: http://www.ophi.org.uk/social-isolation-a-conceptual-and-measurement-proposal/.

Zavaleta, D., Samuel, K. and Mills, C. T. (2017) 'Measures of Social Isolation', *Social Indicators Research*, 131(1), pp. 367–391. doi: 10.1007/s11205-016-1252-2.

Appendix A: Supplementary Tables and Figures

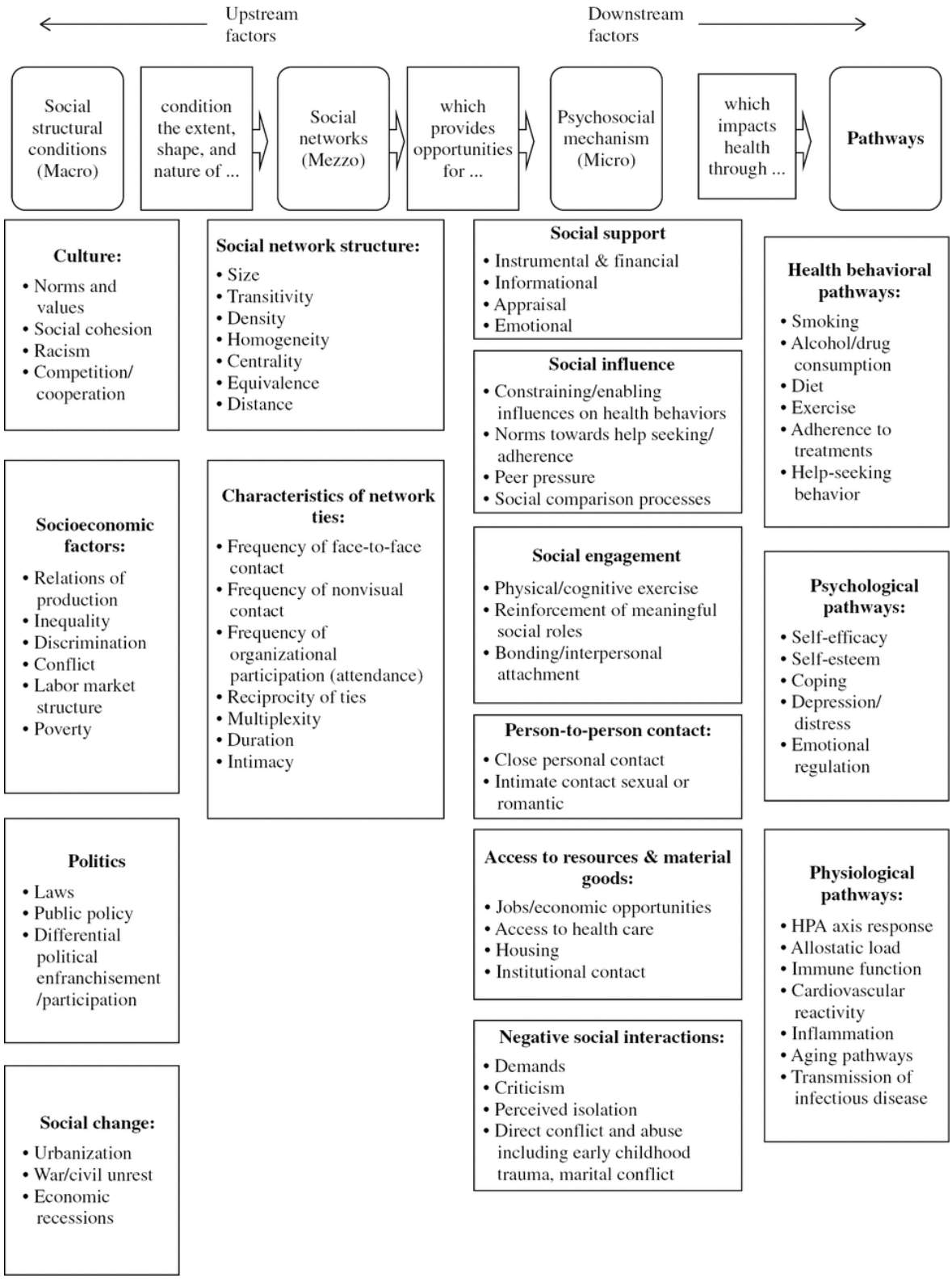


Figure A1.1. Berkman and Krishna's conceptual model of social networks and their influence on health (Berkman and Krishna, 2014).

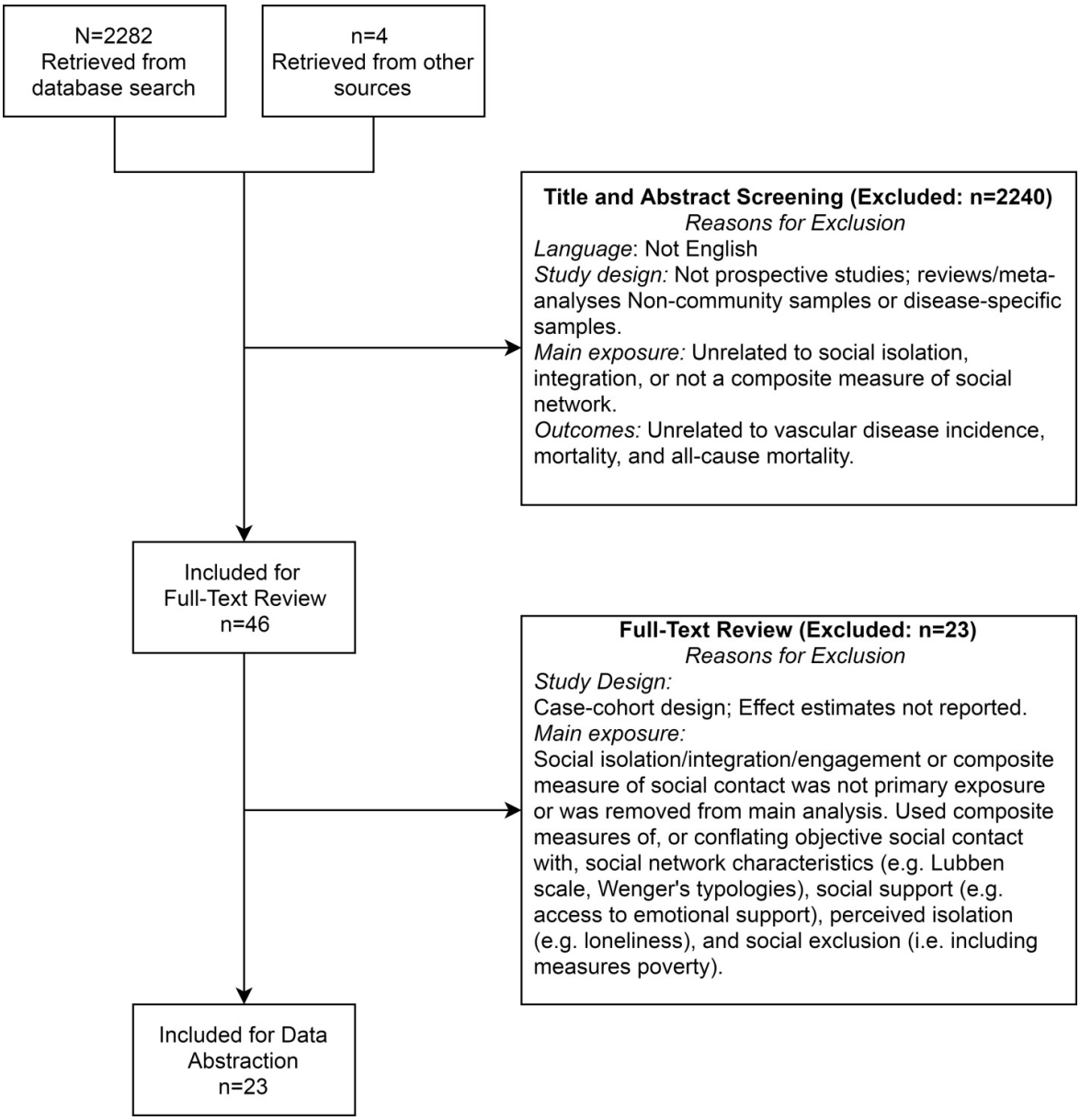


Figure A2.1. Flowchart of literature search results as of 2 November 2018 and the number of articles screened, included, and rationale for exclusions.

Table A2.1. Original Medline database literature search strategy executed on 1 December 2017.

1. exp heart arrest/ or exp myocardial ischemia/
2. angina.mp.
3. atheroscler*.mp.
4. ((heart or coronary or artery or ischem* or ischaem* or myocard*) adj3 (disease or attack or event or infarct*)).mp.
5. cerebrovasc*.mp.
6. exp Stroke/ or stroke.mp.
7. exp mortality/ or exp Death/ or mortality.mp.
8. social isolation.mp. or exp Social Isolation/
9. exp Social Support/ or exp Interpersonal Relations/ or social integration.mp.
10. ((longitudinal adj (study or studies)) or (follow up adj (study or studies)) or (prospective adj (study or studies)) or (retrospective adj (study or studies)) or (observational adj (study or studies))).mp.
11. (cohort analy$ or (cohort adj (study or studies))).mp. or exp Cohort Studies/
12. meta analysis.mp. or exp Meta-Analysis/
13. (system* adj3 review*).mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7
15. 8 or 9
16. 10 or 11 or 12 or 13
17. 14 and 15 and 16
18. limit 17 to yr="1979 -Current"

Note: Addition condition added on 2 November 2018 limiting to searches published from 2017 to 2 November 2018.

Table A2.2. Summary of indices used to measure social isolation in the reviewed studies.

Study	Measure of Social Isolation	Index Constituent Measures
Alcaraz *et al*., 2018	Modified Berkman-Syme social network index	Marital status; Number of close relatives or friends; Frequency of participation in religious organisation; Frequency of participation in club meetings or group activities
Barefoot *et al.,* 2005	Social contact diversity index	Frequency of any social contact (parents, children, other family, friends, spouse/partner, work colleagues [outside working hours], or neighbours); Frequency of contact with intimate contacts (parents, children, other family, spouse/partner)
Berkman and Syme, 1979; Kawachi et al., 1996	Berkman-Syme social network index	Marital status; Number of close relatives and friends; Frequency of contact with family and friends; Church membership; Formal/informal participation with associations or social organisations
Berkman *et al*., 2004	Modified Berkman-Syme social network index	Marital status; Frequency of contact with family and close friends; Participation with social organisations
Chang *et al.,* 2017	Modified Berkman-Syme social network index	Marital status; Number of close friends; Attendance at religious services; Participation in community or volunteer groups or other organisations (e.g. church-connected groups/self-help group/charity/public service)
Elovainio *et al.,* 2017; Hakulinen et al., 2018	Social isolation scale	Living alone; Frequency of contact family and friends; Frequency of social group participation
Eng *et al.,* 2002	Modified Berkman-Syme social network index	Marital status; Frequency of contact with family and friends; Religious group affiliation; Membership in other social or community organisations

Hirdes and Forbes, 1992	Social relationships index	Marital status; Number of children; Frequency of contact with family members; Voluntary association participation
House *et al.,* 1982	Social integration index	Marital status; Frequency of visits with friends and relatives; Going on pleasure drives and picnics; Formal organisational involvement outside of work (e.g. church attendance or voluntary association participation); Active and relatively social leisure (e.g. going to classes or lectures, movies, plays, fairs, museums); Passive and relatively solitary leisure (e.g. watching television, listening to the radio, reading)
Kaplan *et al.,* 1988	Social connections index	Marital status; Frequency of seeking contact with family/friends; No. of different homes of family/friends visited per month; Frequency of receiving any social contact; Frequency of participation in social organisations
Kim *et al.,* 2016	Social engagement index	Frequency of contact with friends; Frequency of contact with mutual benevolence group meetings; Frequency of attendance at leisure, culture, and sports activities; Frequency of religious attendance; Frequency of contact with an alumni meeting, or hometown alumni and clan gatherings
Laugesen *et al.,* 2018	Modified Berkman-Syme social network index	Marital status; Frequency of family and friends; Frequency of participation in religious organisation; Frequency of participation in any of several social groups/activities
Orth-Gomér and Johnson, 1987	Social network interaction index	Marital status; Frequency of contact with parents, children, siblings, friends, friends from youth, neighbours, co-workers, co-workers at work; Exchange of assistance with neighbours; Frequency of casual neighbourhood interaction
Pantell *et al*. 2013; Yang *et al.* 2013	Modified Berkman-Syme social network index	Marital status; Frequency of contact with family/friends/neighbours; Religious service attendance; Participation in other social organisations

Reed *et al.,* 1983	Social network index	Proximity of parents or wife's parents; Marital status; No. of living children; Household occupancy; Frequency of social activity participation; Frequency of discussing serious personal problems; Frequency of religious service attendance; No. of social organisations regularly attended
Rodriguez-Laso *et al.,* 2007	Family ties index	Marital status; Frequency of contact with children; Frequency of contact with sibling, niece/nephew or grand-child
Steptoe et al., 2013; Smith *et al.,* 2017	Social isolation index	Marital status; Frequency of contact with children; Frequency of contact with other family members; Frequency of contact with friends; Participation with social organisations
Tanskanen and Anttila, 2016	Social isolation index	Living alone; Frequency of contact with non-co-inhabiting family (parents, children, and siblings not belonging to the same household); Frequency of contact with friends or co-workers outside the work place; Participation in social organisations or neighbourhood activities
Valtorta *et al.,* 2018	Social isolation scale	Living alone; Frequency of contact with their children outside the household; Frequency of contact with other relatives outside the household; Frequency of contact with friends; Frequency of participation in any organisations, religious groups, or committees; Not currently employed

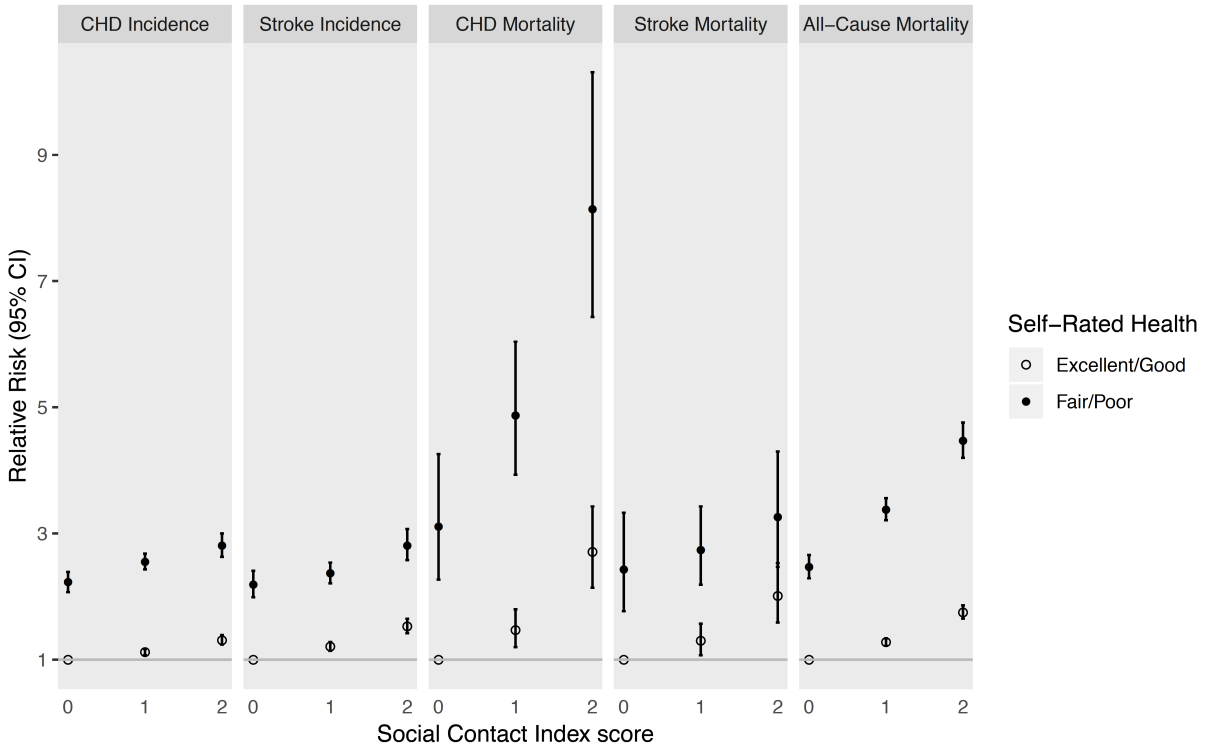


Figure A3.1. Minimally adjusted RR and 95% CI of vascular disease incidence and mortality, and all-cause mortality according to self-rated health and social contact index score.

Table A3.1. Fully adjusted RR and 95% CI of social isolation in relation to CHD and stroke sub-types.

	No. of Cases	RR	95% CI	p for hetero-geneity
INCIDENCE				
Acute Myocardial Infarction				
Least Isolated	902	1.00	(-)	0.20
Moderately Isolated	1,383	0.99	(0.91, 1.08)	
Most Isolated	453	1.10	(0.97, 1.23)	
Ischaemic Stroke				
Least Isolated	795	1.00	(-)	<0.001
Moderately Isolated	1,335	1.11	(1.01, 1.21)	
Most Isolated	462	1.28	(1.14, 1.44)	
Haemorrhagic Stroke				
Least Isolated	369	1.00	(-)	0.04
Moderately Isolated	495	1.00	(0.87, 1.15)	
Most Isolated	169	1.25	(1.04, 1.52)	
MORTALITY				
Acute Myocardial Infarction				
Least Isolated	71	1.00	(-)	0.02
Moderately Isolated	128	1.06	(0.78, 1.42)	
Most Isolated	65	1.61	(1.12, 2.30)	
Ischaemic Stroke				
Least Isolated	8	1.00	(-)	0.01
Moderately Isolated	22	1.72	(0.76, 3.92)	
Most Isolated	15	3.43	(1.40, 8.41)	
Haemorrhagic Stroke				
Least Isolated	95	1.00	(-)	<0.01
Moderately Isolated	145	1.09	(0.84, 1.42)	
Most Isolated	65	1.73	(1.24, 2.41)	

Table A3.2. RRs and 95% CIs for social isolation and each outcome before and after excluding first two years of follow-up.

	Fully Adjusted				Fully Adjusted excluding two years follow-up			
	n	RR	95% CI	p-value[a]	n	RR	95% CI	p-value[a]
CHD Incidence								
Least Isolated	3,728	1.00	(-)	0.04	2,713	1.00	(-)	0.22
Moderately Isolated	5,491	1.00	(0.96, 1.04)		3,985	1.00	(0.95, 1.06)	
Most Isolated	1,657	1.07	(1.01, 1.14)		1,176	1.06	(0.99, 1.14)	
Stroke Incidence								
Least Isolated	1,957	1.00	(-)	<0.0001	1,526	1.00	(-)	<0.0001
Moderately Isolated	3,218	1.11	(1.05, 1.17)		2,495	1.11	(1.04, 1.19)	
Most Isolated	1,106	1.28	(1.19, 1.38)		832	1.25	(1.15, 1.37)	
CHD Mortality								
Least Isolated	140	1.00	(-)	<0.0001	102	1.00	(-)	<0.0001
Moderately Isolated	280	1.20	(0.97, 1.47)		222	1.35	(1.06, 1.71)	
Most Isolated	139	1.80	(1.41, 2.31)		111	2.10	(1.58, 2.79)	
Stroke Mortality								
Least Isolated	163	1.00	(-)	<0.001	135	1.00	(-)	0.02
Moderately Isolated	296	1.21	(1.00, 1.47)		236	1.17	(0.94, 1.45)	
Most Isolated	128	1.71	(1.34, 2.18)		93	1.51	(1.15, 2.00)	
All-Cause Mortality								
Least Isolated	2,886	1.00	(-)	<0.0001	2,436	1.00	(-)	<0.0001
Moderately Isolated	4,976	1.11	(1.06, 1.16)		4,136	1.10	(1.05, 1.16)	
Most Isolated	1,805	1.32	(1.24, 1.40)		1,491	1.31	(1.22, 1.40)	

Note: [a] p for heterogeneity

Table A3.3. RR and 95% CI for SCI constituent measures in relation to all outcomes while mutually adjusting for each other constituent measure.

	Fully Adjusted			p for hetero-geneity
	n	RR	95% CI	
CHD INCIDENCE				
Contact with Family or Friends				
Almost daily	7,332	1.00	(-)	0.36
Weekly	3,295	0.98	(0.94, 1.02)	
At most monthly	249	1.07	(0.94, 1.22)	
Frequency of Contact with Groups				
At least weekly	5,308	1.00	(-)	0.41
Less than weekly	5,568	1.02	(0.98, 1.06)	
Living Alone				
No	7,852	1.00	(-)	0.15
Yes	3,024	1.03	(0.99, 1.08)	
STROKE INCIDENCE				
Contact with Family or Friends				
Almost daily	4,042	1.00	(-)	<0.01
Weekly	2,070	1.08	(1.02, 1.14)	
At most monthly	169	1.25	(1.07, 1.45)	
Frequency of Contact with Groups				
At least weekly	3,012	1.00	(-)	<0.01
Less than weekly	3,269	1.08	(1.03, 1.14)	
Living Alone				
No	4,253	1.00	(-)	<0.0001
Yes	2,028	1.18	(1.11, 1.24)	
CHD MORTALITY				
Contact with Family or Friends				
Almost daily	367	1.00	(-)	0.27
Weekly	172	1.03	(0.86, 1.24)	
At most monthly	20	1.48	(0.94, 2.34)	
Frequency of Contact with Groups				
At least weekly	235	1.00	(-)	0.04
Less than weekly	324	1.2	(1.00, 1.43)	
Living Alone				
No	337	1.00	(-)	<0.0001
Yes	222	1.51	(1.27, 1.80)	
STROKE MORTALITY				
Contact with Family or Friends				
Almost daily	360	1.00	(-)	0.03
Weekly	208	1.22	(1.03, 1.45)	
At most monthly	19	1.51	(0.95, 2.41)	
Frequency of Contact with Groups				
At least weekly	267	1.00	(-)	0.02
Less than weekly	320	1.22	(1.03, 1.45)	
Living Alone				
No	370	1.00	(-)	<0.001
Yes	217	1.37	(1.15, 1.63)	

Continued

Continuation	n	RR	95% CI	p for hetero-geneity
ALL-CAUSE MORTALITY				
Contact with Family or Friends				
Almost daily	6,216	1.00	(-)	<0.0001
Weekly	3,158	1.08	(1.04, 1.13)	
At most monthly	293	1.35	(1.20, 1.52)	
Frequency of Contact with Groups				
At least weekly	4,396	1.00	(-)	<0.0001
Less than weekly	5,271	1.11	(1.07, 1.16)	
Living Alone				
No	6,581	1.00	(-)	<0.0001
Yes	3,086	1.16	(1.11, 1.21)	

Table A4.1. RRs and 95% CIs for social isolation and each outcome before and after excluding first two years of follow-up.

	Fully Adjusted				Fully Adjusted excluding two years follow-up			
	n	RR	95% CI	p-value[a]	n	RR	95% CI	p-value[a]
CHD Incidence								
Least Isolated	3,428	1.00	(-)	0.10	2,539	1.00	(-)	0.03
Moderately Isolated	2,709	0.95	(0.90, 1.00)		1,960	0.93	(0.87, 0.98)	
Most Isolated	891	0.94	(0.88, 1.02)		668	0.95	(0.87, 1.04)	
Stroke Incidence								
Least Isolated	1,034	1.00	(-)	<0.01	823	1.00	(-)	<0.01
Moderately Isolated	908	1.05	(0.96, 1.15)		680	0.99	(0.90, 1.10)	
Most Isolated	345	1.23	(1.09, 1.40)		273	1.24	(1.07, 1.42)	
CHD Mortality								
Least Isolated	167	1.00	(-)	<0.001	131	1.00	(-)	<0.01
Moderately Isolated	190	1.34	(1.09, 1.66)		144	1.29	(1.02, 1.64)	
Most Isolated	83	1.68	(1.28, 2.21)		62	1.58	(1.16, 2.16)	
Stroke Mortality								
Least Isolated	79	1.00	(-)	<0.01	67	1.00	(-)	0.05
Moderately Isolated	79	1.14	(0.83, 1.56)		67	1.14	(0.81, 1.61)	
Most Isolated	45	1.92	(1.32, 2.81)		34	1.72	(1.12, 2.62)	
All-Cause Mortality								
Least Isolated	2,003	1.00	(-)	<0.0001	1,751	1.00	(-)	<0.0001
Moderately Isolated	1,918	1.14	(1.07, 1.21)		1,641	1.11	(1.04, 1.19)	
Most Isolated	773	1.38	(1.27, 1.51)		665	1.37	(1.25, 1.50)	

Note: [a] p for heterogeneity

Table A5.1. Literature search strategy and results for reviews on neighbourhood factors and social relationships, and studies examining these factors in relation to health.

Databases	Search Terms	Abstracts Screened	Full-Text Review	Articles Included
Ovid MEDLINE Epub ahead of print, in-process and other non-indexed citations, Ovid MEDLINE Daily and Ovid MEDLINE (1946-present)/Embase (1974 to present)/PsycINFO(1806 to present)	1. social integration.mp. or exp Social Integration/ 2. exp Social Isolation/ or exp Interpersonal Interaction/ or social isolat*.mp. or social contact.mp. 3. exp POVERTY AREAS/ 4. exp Neighborhoods/ or exp Urban Environments/ or exp Rural Environments/ or exp Built Environment/ or exp Transportation/ or exp Walking/ or walkability.mp. or exp Deprivation/ or exp Social Deprivation/ or socioeconomic deprivation.mp. 5. exp VIOLENT CRIME/ or exp CRIME/ or crime.mp. 6. (review or systematic review or meta analysis).mp. [mp=tx, bt, ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, px, rx, ui, sy, tc, id, tm] 7. 1 and 2 8. 3 or 4 or 5 9. 6 and 7 and 8 10. 7 and 8 11. limit 10 to english language 12. limit 11 to yr="2000 -Current	398	8	2
Web of Science	1.TS=(social isolat* OR social integ* OR social contact OR social interact*) DocType=All document types; Language=All languages; 2.TS=(neighbourhoods OR urban environments OR rural environments OR built environment OR transportation OR walk* OR depriv* OR soci* depriv* OR poverty OR impoverish* OR crime) DocType=All document types; Language=All languages; 3.(PY=(2000-2018)) AND LANGUAGE: (English) DocType=All document types; Language=All languages; 4.(TI=(review* OR systematic review*)) AND LANGUAGE: (English) DocType=All document types; Language=All languages; 5.(TS=(review* OR systematic review*)) AND LANGUAGE: (English) DocType=All document types; Language=All languages; 6. #5 OR #4 DocType=All document types; Language=All languages; 7. #6 AND #3 AND #2 AND #1 DocType=All document types; Language=All languages;	1653	14	9
Google Scholar	neighborhood, social isolation; neighbourhoods, health	n/a	2	1
Other	Text books and reference list searching	n/a	2	2
			Total:	14

Table A5.2. Baseline characteristics for Million Women Study and UK Biobank participants according to social isolation status.

Characteristics	A. Million Women Study			B. UK Biobank		
	Overall N=322,588	Less Isolated n=284,074 (88.1%)	Most Isolated n=38,514 (11.9%)	Overall N=272,596	Less Isolated n=238,113 (87.3%)	Most Isolated n=34,483 (12.6%)
Mean Age (SD)	67.7 (4.5)	67.5 (4.4)	68.7 (4.9)	56.1 (8.1)	56.2 (8.1)	55.7 (7.9)
Female (%)	100	100	100	55.9	56.6	51.1
Educational attainment						
No educational qualifications (%)	27.9	26.4	39.3	-	-	-
Less than secondary (%)	-	-	-	13.4	13.2	14.9
Disability						
At least one disability (%)	13.6	12.8	19.3	-	-	-
Receipt of disability allowance (%)	-	-	-	1.6	1.6	2.2
Frequency of contact with:						
Family or friends (% at most monthly)	1.9	0.4	13.1	21.7	14.1	74.2
Social groups (% at most monthly)	48.1	41.2	99.2	-	-	-
Social groups (% less than weekly)	-	-	-	27.8	19.7	83.6
Living alone (%)	23.6	14.6	90.0	16.5	11.6	49.9
Current smoker (%)	5.5	4.7	11.6	8.2	7.7	11.9
Alcohol intake						
≥7 units per week (%)	31.6	32.3	26.7	-	-	-
≥5 days per week (%)	-	-	-	21.8	21.9	20.7
Rarely/never exercise (%)	7.2	6.8	10.6	9.5	8.7	15.8
BMI ≥30 kg/m^2 (%)	16.9	16.7	19.1	18.4	18.2	20.1
History of hypertension (%)	19.0	18.7	21.3	20.3	20.2	20.9
History of diabetes (%)	3.3	3.1	4.4	2.6	2.6	3.2

Notes: Percentages calculated based on participants with complete information for each specific variable.

Table A5.3. Results of follow-up for vascular disease and mortality outcomes among Million Women Study and UK Biobank participants.

	A. Million Women Study	B. UK Biobank
Incident CHD events (n)	**10,819**	**6,439**
Mean years of follow-up per person (SD)	5.8(1.3)	6.8(1.0)
Person-years (1000s)	1,879	1,845
Incident Stroke events (n)	**6,234**	**2,068**
Mean years of follow-up per person (SD)	5.9(1.2)	6.8(0.9)
Person-years (1000s)	1,895	1,861
CHD deaths (n)	**555**	**405**
Mean years of follow-up per person (SD)	5.9(1.1)	6.8(0.9)
Person-years (1000s)	1907	1867
Stroke deaths (n)	**584**	**180**
Mean years of follow-up per person (SD)	5.9(1.1)	6.8(0.9)
Person-years (1000s)	1,907	1,867
All-cause deaths (n)	**9,561**	**4,253**
Mean years of follow-up per person (SD)	5.9(1.1)	6.8(0.9)
Person-years (1000s)	1,907	1,867

Table A5.4. Fully adjusted RR and 95% CI estimated using robust standard errors for social isolation and all-cause mortality by neighbourhood socioeconomic deprivation tertile.

	Least Deprived		Moderately Deprived		Most Deprived	
	n	RR 95% CI	n	RR 95% CI	n	RR 95% CI
A. Million Women Study						
All-Cause Mortality						
Less Isolated	3,795	1.00 (-)	2828	1.00 (-)	1,151	1.00 (-)
Most Isolated	706	1.30 (1.24, 1.37)	610	1.09 (1.03, 1.15)	471	1.36 (1.23, 1.49)
B. UK Biobank						
All-Cause Mortality						
Less Isolated	1,735	1.00 (-)	1,172	1.00 (-)	653	1.00 (-)
Most Isolated	274	1.29 (1.17, 1.44)	223	1.25 (1.11, 1.41)	196	1.33 (1.18, 1.50)

Table A6.1. Description of variables adjusted for in Cox regression analyses.

Covariate Group	Variables	Values/Categories
Personal Characteristics	Age	Date of birth to date of censoring
	Gender	Female, Male
	Region of Recruitment	East Anglia, East midlands, London, North east, North west, South east, South west, Wales, West midlands, Yorkshire & Humber
	Socioeconomic deprivation (Townsend deprivation index)	Least deprived Moderately deprived Most deprived
	Educational attainment	Tertiary Secondary Less than secondary
	Receipt of disability or mobility allowance	Yes, No
Health Behavioural Factors	Frequency of strenuous or moderate exercise	Rarely/never Sometimes (1-3 days/week) Most Days (4-6 days/week) Daily
	Smoking status	Current Never Former
	Alcohol intake	0 days per week 1-5 days per week ≥5 days per week
	Body Mass Index	Desirable (<25 kg/m^2) Overweight (25-29.9 kg/m^2) Obese (≥30 kg/m^2)
Physiological Factors	Self-reported history of hypertension	Yes, No
	Self-reported history of diabetes	Yes, No
	Taking cholesterol lowering medication	Yes, No
Psychological Factors	Self-reported depressed mood within past two weeks	Yes, No

Table A6.2. RR and 95% CI for SCI score in relation to all-cause mortality after adjustment for each group of covariates.

ALL-CAUSE MORTALITY	Less Isolated		Most Isolated		p for hetero-geneity	LR χ^2	% Attenuation in LR χ^2
No. of deaths	3,745		724				
Age, gender, region (minimally adjusted)	**1.00**	**(-)**	**1.43**	**(1.32, 1.55)**	**<0.0001**	**70.7**	**-**
Age, gender, region, personal characteristics	**1.00**	**(-)**	**1.37**	**(1.26, 1.48)**	**<0.0001**	**54.7**	**23**
Age, gender, region, deprivation	1.00	(-)	1.38	(1.27, 1.50)	<0.0001	57.9	18
Age, gender, region, education	1.00	(-)	1.42	(1.31, 1.54)	<0.0001	67.8	4
Age, gender, region, disability	1.00	(-)	1.42	(1.31, 1.53)	<0.0001	67.3	5
Age, gender, region, health behaviour factors	**1.00**	**(-)**	**1.33**	**(1.23, 1.44)**	**<0.0001**	**45.5**	**36**
Age, gender, region, smoking	1.00	(-)	1.36	(1.26, 1.48)	<0.0001	53.4	24
Age, gender, region, alcohol	1.00	(-)	1.42	(1.31, 1.54)	<0.0001	67.8	4
Age, gender, region, physical activity	1.00	(-)	1.41	(1.30, 1.53)	<0.0001	65.2	8
Age, gender, region, body mass index	1.00	(-)	1.42	(1.31, 1.54)	<0.0001	68.5	3
Age, gender, region, physiological factors	**1.00**	**(-)**	**1.42**	**(1.31, 1.53)**	**<0.0001**	**67.6**	**4**
Age, gender, region, hypertension	1.00	(-)	1.42	(1.32, 1.54)	<0.0001	69.7	1
Age, gender, region, diabetes	1.00	(-)	1.42	(1.31, 1.54)	<0.0001	68.4	3
Age, gender, region, cholesterol medications	1.00	(-)	1.43	(1.32, 1.55)	<0.0001	70.8	0
Age, gender, region, depressed mood	**1.00**	**(-)**	**1.42**	**(1.31, 1.54)**	**<0.0001**	**68.1**	**4**
Fully adjusted	**1.00**	**(-)**	**1.29**	**(1.19, 1.40)**	**<0.0001**	**35.6**	**50**

Appendix B: Million Women Study 12-year Re-Survey Questionnaire

THE MILLION WOMEN STUDY

Confidential National Study of Women's Health

The Million Women Study is a major national study of women's health supported by public funds.
(see enclosed leaflet and/or www.millionwomenstudy.org)

Over the past few years you have filled out one or more questionnaires to help with the study. Now we are asking for your help again. All information provided will be treated with absolute confidentiality and used for medical research only.

Any questions? Ring Freephone 0800 262 872

QUESTIONS ABOUT YOU AND YOUR HEALTH. Please use a BLACK PEN if possible.
We know it may be difficult to answer some questions, but an approximate answer is better than none.

1. **What is your date of birth?** d d m m 1 9 y y

2. **What is today's date?** d d m m 2 0 y y

3. **In general, how would you now rate your:**
(please cross [X] the relevant boxes)

	excellent	good	fair	poor
overall health?	☐	☐	☐	☐
memory?	☐	☐	☐	☐
quality of life?	☐	☐	☐	☐
quality of sleep?	☐	☐	☐	☐
physical fitness?	☐	☐	☐	☐
eyesight (with glasses, if worn)?	☐	☐	☐	☐
hearing (best ear, with any aids)?	☐	☐	☐	☐

4. **Do you:**

	No	Yes
have difficulty bathing or dressing yourself?	☐	☐
have difficulty walking up a flight of stairs?	☐	☐
have a disability allowance, attendance allowance or blue badge?	☐	☐

5. **How often do you contact (eg phone, meet, email):**

	rarely/ never	monthly	weekly/ fortnightly	most days
family?	☐	☐	☐	☐
friends?	☐	☐	☐	☐
groups (eg religious, WI, fitness, adult education)?	☐	☐	☐	☐

6. **In the last 5 years have you experienced:**

	No	Yes
death of a spouse or partner?	☐	☐
death of any other close relative or friend?	☐	☐
divorce or permanent separation?	☐	☐

7. **How often do you feel:**

	rarely/ never	some-times	often	almost always
tired during the day?	☐	☐	☐	☐
in control?	☐	☐	☐	☐
happy?	☐	☐	☐	☐

8. **How many people live in your household?** ☐ number of people (incl. you)

9. **How many cars or vans are available for use in your household?** ☐ number of vehicles

10. **Is your household accommodation:**
☐ rented? ☐ owned (or mortgaged)? ☐ other?

11. **When you were about 10 years old,**
- was your household accommodation:
☐ rented? ☐ owned (or mortgaged) by your family? ☐ other?

- did your household then have: *(you can cross both boxes)*
☐ running hot water? ☐ an indoor toilet?

- how many people usually slept in your bedroom? (when you were 10 years old) ☐ number of people (incl. you)

12. **Has your doctor ever said you had:**

	Yes	Age first diagnosed
Breast cancer?	☐	☐☐ years old
Bowel (intestinal) cancer?	☐	☐☐ years old
Malignant melanoma?	☐	☐☐ years old
Cervix cancer/precancer?	☐	☐☐ years old
Womb (endometrial) cancer?	☐	☐☐ years old
Diabetes?	☐	☐☐ years old
High blood pressure?	☐	☐☐ years old
Osteoporosis?	☐	☐☐ years old

13. **In the last 5 years have you had any broken/fractured bones?**
☐ No ☐ Yes - once ☐ Yes - more than once

If Yes,
- which bones? *(you can cross more than one box)*
☐ wrist ☐ arm ☐ spine ☐ hip
☐ ankle ☐ foot ☐ leg ☐ other

- about when was your most recent fracture? m m y y y y

- did your most recent fracture result from a fall?
☐ No ☐ Yes

14. **How many recent falls have you had?** ☐☐ falls in past year *(0 if none)*

Supported by Cancer Research UK, the Medical Research Council and the Health and Safety Executive

LIFESTYLE

15. Have you ever regularly worked at night, or on night shifts?
(at any time between midnight and 6am, for at least 3 nights per month)

☐ No ☐ Yes

If Yes,
- over how many years in total? ☐☐ total years *(0 if less than one)*

- when did you last work at night? ☐☐ years ago *(0 if you still work at night)*

16. When do you usually go to sleep? ☐☐ : ☐☐
(eg for ten-forty-five put 10:45)

17. When do you usually get up? ☐☐ : ☐☐

18. How much actual sleep do you get a night? ☐☐ hours

19. When you sleep at night, is the room usually:

☐ very dark? ☐ dark? ☐ dimly lit? ☐ lit?

20. Do you:

	rarely/ never	monthly	weekly/ fortnightly	most days
take medication to sleep?	☐	☐	☐	☐
have trouble falling asleep?	☐	☐	☐	☐
wake up too early in the morning and cannot fall asleep again?	☐	☐	☐	☐
feel refreshed in the morning?	☐	☐	☐	☐

21. Do you consider yourself to be:

☐ a morning person? ☐ more morning than evening?

☐ an evening person? ☐ more evening than morning?

22. How often do you usually nap? ☐ naps per week *(0 if less than one)*

- for about how long? ☐☐☐ minutes per nap (usually)

23. In a typical week, how much VIGOROUS activity do you do?
eg running, fast swimming or cycling, heavy lifting
Please state both how many days and the total hours a week (0 if less than one)

- summer: ☐ DAYS a week **AND** ☐☐ HOURS a week

- winter: ☐ DAYS a week **AND** ☐☐ HOURS a week

In a typical week, how much MODERATE activity do you do?
eg brisk walking, ordinary swimming or cycling, gym, heavy housework or gardening *(0 if less than one)*

- summer: ☐ DAYS a week **AND** ☐☐ HOURS a week

- winter: ☐ DAYS a week **AND** ☐☐ HOURS a week

24. How would you describe your usual walking pace?

☐ brisk ☐ average ☐ slow ☐ cannot walk

25. In a typical SINGLE DAY, how much LIGHT activity do you do?
eg walking, shopping, cooking, general housework, yoga

summer ☐☐ hours per day **winter** ☐☐ hours per day

26. On a typical WEEKDAY (not weekends) how long do you:

watch TV ☐☐ hours — use a computer (include at work) ☐☐ hours

read ☐☐ hours — look after sick relatives ☐☐ hours

MEDICATIONS

27. Have you ever used HRT? ☐ No ☐ Yes

If Yes,
- how many years in total? ☐☐ total years of use *(0 if less than one)*

- are you still using HRT?

☐ No, stopped - if so, when? ☐☐ years ago

☐ Yes, still using

28. Have you EVER used any of these osteoporosis drugs?
(you can cross more than one box)

☐ Alendronate 10mg (daily)	☐ Fosamax (daily)	☐ Actonel (daily)
☐ Alendronate 70mg (weekly)	☐ Fosamax Once Weekly	☐ Actonel Once a Week
☐ Bonviva tablets	☐ Fosavance	☐ Actonel Combi
☐ Bonviva injection	☐ Didronel	☐ Didronel PMO

Please write the name(s) of any other osteoporosis drugs you have used, eg Aclasta

For office use only ☐☐☐☐☐

29. If you EVER used any of the drugs listed in question 28,

- for how long? ☐☐ total years of use of all types added together *(0 if less than one)*

- are you still using any of them?

☐ No, stopped - if so, when? ☐☐ years ago

☐ Yes, still using

30. Do you regularly take any of the following?
(you can cross more than one box)

☐ Aspirin	☐ Insulin injections
☐ Prednisolone	☐ Glucophage
☐ Thyroxine	☐ Avandia
☐ a statin for cholesterol eg Lipitor, Zocor, Lipostat	☐ other drugs for diabetes

SCREENING

31. About how many years is it since you last had:
(0 if screened less than one year ago; cross box if never screened)

a cervical smear test? ☐☐ years ago **OR** ☐ never

a breast cancer screen? ☐☐ years ago **OR** ☐ never

a bowel cancer screen? ☐☐ years ago **OR** ☐ never

32. Have you had a bone mineral density (eg DEXA) scan?

☐ No ☐ Yes ☐ not sure

- If Yes, were you told your bone density was:

☐ low? ☐ normal? ☐ not sure

33. Have you had your blood pressure taken in the last 5 years?

☐ No ☐ Yes ☐ not sure

- If Yes, were you told it was:

☐ high? ☐ normal? ☐ low? ☐ not sure

- what was your blood pressure?

☐☐☐ / ☐☐☐ eg 130 / 90 *(leave blank if not sure)*

YOUR DIET

34. Any major changes to your diet in the past 5 years?

☐ No ☐ Yes - because of illness ☐ Yes - for some other reason

35. Please cross the box(es) if in the past 5 years you:

☐ never ate fish ☐ never ate meat or poultry ☐ never ate dairy products ☐ never ate eggs

36. About how many TIMES A WEEK do you usually eat:

- the following vegetables? *(0 if none usually)*

broccoli ☐☐ cooked tomatoes ☐☐

cauliflower ☐☐ bean curd foods (eg soya, tofu) ☐☐

cabbages or sprouts ☐☐ baked beans or pulses (eg lentils, chickpeas) ☐☐

- the following fruits? *(number of times a week; 0 if none usually)*

an apple ☐☐ an orange, satsuma, etc ☐☐

a banana ☐☐ a stone fruit (eg plum, apricot, peach) ☐☐

a pear ☐☐ grapes, berries ☐☐

prunes ☐☐ tinned fruit (except prunes) ☐☐

stewed fruit (except prunes) ☐☐ dried fruit (except prunes) ☐☐

37. In total how many PIECES OF FRESH FRUIT A WEEK?

☐☐ number of pieces a week *(count one apple, one banana, 10 grapes, 10 berries etc as one piece; 0 if none usually)*

38. How many tablespoons of SALAD/VEGETABLE A WEEK?
(number of tablespoons a week; 0 if none usually)

raw tomatoes ☐☐ raw vegetables (except tomato and green salad) ☐☐

green salad ☐☐ cooked vegetables (except potatoes) ☐☐

39. How much WHOLEMEAL BREAD A WEEK do you eat?
(0 if none usually)

Slices, rolls etc of wholemeal bread a week (not white or brown bread) ☐☐

40. How many bowls of CEREAL A WEEK do you eat?

All-Bran ☐☐ wholewheat (eg Weetabix, Shredded wheat) ☐☐

branflakes or muesli ☐☐ other cereal (eg oats, rice crispies, cornflakes) ☐☐

41. How much YOGURT A WEEK do you eat?

dairy yogurt or desserts ☐☐ number of small pots

soya yogurt or desserts ☐☐ number of small pots

42. About how many TIMES A WEEK do you usually eat:

any fish (fresh or tinned) ☐☐ any meat or poultry (fresh or processed) ☐☐

tuna ☐☐ any poultry (chicken, turkey, etc) ☐☐

oily fish (salmon, sardines, trout, mackerel, etc) ☐☐ any processed meat (bacon, ham, sausages, etc) ☐☐

TEA, COFFEE, MILK, DIGESTION

43. How much TEA do you usually drink? ☐☐ cups a day

- do you have your tea:

☐ very hot ☐ hot ☐ warm ☐ cool

- do you usually add:

☐ milk ☐ sugar ☐ artificial sweetener

44. How much COFFEE do you usually drink? ☐☐ cups a day

- do you have your coffee:

☐ very hot ☐ hot ☐ warm ☐ cool

- do you usually add:

☐ milk ☐ sugar ☐ artificial sweetener

45. On average, how much MILK A WEEK do you drink?
include milk in cereal, cocoa, tea, coffee, cooking etc

☐☐ pints **OR** ☐☐ litres *(0 if less than one)*

46. Which type of milk do you use most often?

☐ cow's milk ☐ soya milk ☐ other/none

47. How frequently are you troubled by:

	rarely/ never	less than weekly	about weekly	more often
bleeding gums?	☐	☐	☐	☐
difficulty swallowing?	☐	☐	☐	☐
reflux/heartburn?	☐	☐	☐	☐
constipation?	☐	☐	☐	☐
intestinal gas (flatulence)?	☐	☐	☐	☐
diarrhoea?	☐	☐	☐	☐

48. About how many bowel movements (motions) do you have each week? ☐☐ times a week

WEIGHT AND HEIGHT

49. About how much do you weigh now?

☐☐ stone ☐☐ lbs **OR** ☐☐☐ kgs

50. Compared to about 5 years ago, have you lost weight?

☐ No ☐ Yes

If Yes, how did you lose it? *(you can cross more than one box)*

☐ dieting ☐ exercise ☐ illness ☐ other

51. What is your:

waist measurement? ☐☐ inches **OR** ☐☐☐ cms

hip measurement? ☐☐ inches **OR** ☐☐☐ cms

52. What size clothes do you wear now?
(you can cross more than one box if the size varies)

☐ 10 or less ☐ 12 ☐ 14 ☐ 16 ☐ 18 ☐ 20+

53. Are you shorter now than when you were in your 20s/30s?

☐ no ☐ a little shorter ☐ noticeably shorter

54. About how tall are you now?

☐ feet ☐☐ inches **OR** ☐☐☐ cms

ALCOHOL AND TOBACCO

55. Have you EVER had an alcoholic drink?

♦ ☐ No, I am a lifelong non-drinker (go to **58**) ☐ Yes

56. Did you have an alcoholic drink in the past year?

☐ No ☐ Yes

- If No, age when you last drank alcohol ☐☐ years old

57. About how many "units" a week, now and in the past?
a unit = glass of wine, half pint of beer or cider, or 25ml tot of spirits

in past year	☐☐	units of alcohol a week, in total *(0 if less than one)*
in your 40s	☐☐	units of alcohol a week, in total
in your 20s	☐☐	units of alcohol a week, in total

58. Have you EVER smoked tobacco?

☐ Never (go to **64**) ☐ Current smoker ☐ Ex-smoker

59. Current smokers: might you quit in the next 5 years?

☐ No ☐ Yes ☐ not sure

60. Ex-smokers: might you restart in the next 5 years?

☐ No ☐ Yes ☐ not sure

61. Give your ages at starting/stopping, as best you can:
(or cross box if not applicable)

- first smoked any tobacco	☐☐ years old	
- began smoking regularly (daily, or on most days)	☐☐ years old, or	☐ N/A
- first seriously quit	☐☐ years old, or	☐ N/A
- last smoked regularly	☐☐ years old, or	☐ N/A
- last smoked any tobacco	☐☐ years old, or	☐ N/A

62. How much do/did you generally inhale?

☐ slightly ☐ moderately ☐ deeply

63. How many cigarettes a day, now and in the past?

in past year	☐☐	typical number of cigarettes a day *(0 if less than one cigarette a day)*
in your 40s	☐☐	typical number of cigarettes a day
in your 20s	☐☐	typical number of cigarettes a day

MEDICAL HISTORY: YOU AND YOUR FAMILY

64. Have YOU (even if already reported) or any of your BLOOD RELATIVES ever had, to your knowledge:

	you	mother	father	sister	brother		you	mother	father	sister	brother
heart attack	☐	☐	☐	☐	☐	glaucoma	☐	☐	☐	☐	☐
other heart disease	☐	☐	☐	☐	☐	Parkinson's disease	☐	☐	☐	☐	☐
stroke	☐	☐	☐	☐	☐	Alzheimer's disease	☐	☐	☐	☐	☐
high blood pressure	☐	☐	☐	☐	☐	other dementia	☐	☐	☐	☐	☐
diabetes	☐	☐	☐	☐	☐	severe depression	☐	☐	☐	☐	☐
severe arthritis	☐	☐	☐	☐	☐	breast cancer	☐	☐	☐	☐	☐
hip fracture	☐	☐	☐	☐	☐	bowel cancer	☐	☐	☐	☐	☐
osteoporosis	☐	☐	☐	☐	☐	lung cancer	☐	☐	☐	☐	☐
asthma	☐	☐	☐	☐	☐	skin cancer	☐	☐	☐	☐	☐
emphysema or chronic ♦ bronchitis	☐	☐	☐	☐	☐	prostate cancer			☐		☐

MWS-PF/301/0910

FINALLY...

65. Are you now in paid work?

☐ No ☐ Yes - full time ☐ Yes - part time

66. Have you worked for a total of 10 years or more as a:
(you can cross more than one box)

☐ secretary/clerk?	☐ hairdresser?	☐ cook?
☐ shop worker?	☐ gardener?	☐ nurse?
☐ factory worker?	☐ farm worker?	☐ teacher?
☐ flight attendant?	☐ waitress?	☐ cleaner?
☐ bus conductor?	☐ bar worker?	☐ telephonist?

67. How much do you talk on a mobile phone? ☐☐☐ minutes per week *(0 if none)*

- How long have you used a mobile phone? ☐☐ total years *(0 if less than one)*

68. Have you ever regularly used:

	No	Yes	If Yes, for about how long?
mouthwash?	☐	☐	☐☐ total years *(0 if less than one)*
underarm deodorant?	☐	☐	☐☐ total years
talcum powder for feminine hygiene?	☐	☐	☐☐ total years
a sunbed?	☐	☐	☐☐ total years

69. What is your eye colour?

☐ blue ☐ grey ☐ brown/black
☐ green ☐ hazel ☐ other/not sure

♦

70. Compared to other women, do you have:

☐ fewer freckles? ☐ more freckles? ☐ about average?
☐ fewer moles? ☐ more moles? ☐ about average?

71. If you go out in the summer sun do you:
(you can cross more than one)

☐ burn easily? ☐ tan easily? ☐ rarely tan?

72. In the last 5 years about how many holidays did you take in sunny places? ☐☐ number of holidays

73. In which country were you born? *eg* W A L E S

☐☐☐☐☐☐☐☐☐☐☐☐☐☐

74. Optional: print your email address below if you might consider answering similar questions online in the future

75. Optional: write your phone number (with area code)

76. If your name/address has CHANGED or is incorrect please give the correct details below

For office use only

Thank you for your help! Professor Valerie Beral, University of Oxford, FREEPOST OX3 7DG. Please post the completed form back to me.