SOCIAL ISOLATION AND HEALTH OUTCOMES

IMPACT OF SOCIAL ISOLATION ON MORTALITY AND MORBIDITY

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Lay Abstract

Social isolation (SI) is an emerging socioeconomic factor that could negatively affect health. Prior studies regarding SI were conducted mainly in high income countries. This thesis examines the effect of SI on mortality. This was done first in a systematic review and meta-analysis and, second, by examining the association between SI and health in an international large-scale cohort study (PURE: Prospective Urban Rural Epidemiology) conducted in 21 countries at different country income levels. Our systematic review and meta-analysis showed that SI was associated with 37% increased risk for mortality. The PURE study showed that the association of SI with mortality was seen in diverse populations with different social structures. The impact of SI on mortality would be expected to increase in the future as the number of people with SI is projected to increase with population ageing. This calls for measures to reduce mortality and morbidity in the socially isolated.

Abstract

BACKGROUND: Social isolation (SI) has been seen as an emerging socioeconomic factor that negatively affects health. A considerable body of research has found that SI is associated with increased risk of all-cause mortality. However, the magnitude of the association varies in different studies. Besides that, these studies were conducted mainly in high-income countries. METHODS: We conducted a systematic review and meta-analysis to examine the effect size of SI on mortality. Also, we examined the associated mortality risk using data from the Prospective Urban and Rural Epidemiology (PURE) study of over 140,000 middle-aged adults from 21 countries with different income levels. RESULTS: Our systematic review and meta-analysis showed that the pooled hazard ratio of SI for all-cause mortality was 1.37 (95% confidence interval (CI) 1.28-1.46). The PURE study showed that the hazard ratio of SI for all-cause mortality was 1.26 (95% CI 1.16-1.36). Similar associations of SI with cardiovascular- and non-cardiovascular mortality as well as with incident diseases including stroke, cardiovascular disease, and injury were observed. The associations between SI and health outcomes were observed in diverse populations with different social structures and different country income levels. CLINICAL IMPLICATIONS: The impact of SI on mortality would be expected to be greater in the future as the number of people with SI is projected to increase with population ageing in most societies. Our findings can be used by public health providers and policy makers to develop targeted strategies to reduce the risks associated with SI.

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Thesis Outline

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LIST OF ABBREVIATIONS

AHEI Alternative healthy eating index

CI Confidence interval

COPD Chronic obstructive pulmonary disease

CVD Cardiovascular disease

GRADE The Grading of Recommendations Assessment Development and Evaluation

HIC High-income country

HR Hazard ratio

IPAQ International Physical Activity Questionnaire

LIC Low-income country

MIC Middle-income country

MET Metabolic equivalents

PURE Prospective Urban and Rural Epidemiology

ROBINS-I The Cochrane Risk Of Bias In Non-randomized Studies - of Interventions

RR Relative risk

SD Standard deviation

SNI The Berkman-Syme Social Network Index

WHO World Health Organization

DECLARATION OF ACADEMIC ACHIEVEMENT

The following is a declaration that Ryo Naito has analyzed the data collected in the PURE study and drafted this document. The contributions of Dr. Salim Yusuf, Dr. Darryl Leong, and Dr. Shrikant I. Bangdiwala are also recognized in the completion of the design, research, analyses, and review of this thesis. Ryo Naito contributed to the study design, and was responsible for data analysis, and the writing of the document. Dr. Salim Yusuf established the PURE study and supervised all aspects of the study. Dr. Darryl Leong and Dr. Shrikant I. Bangdiwala contributed to the study design, data analysis, and editing and review of the document. Sumathy Rangarajan provided assistance in study organization.

Chapter 1. Current knowledge of Social Isolation

1.1 DEFINITION OF SOCIAL ISOLATION

Social isolation is characterized as the absence of social relationships (Umberson and Montez, 2010) and is influenced by social contacts, social resources, and participation in social or religious activities (Berkman and Syme, 1979; Seeman, 2000). Many studies have examined social isolation as a risk factor for mortality and morbidity. However, there has been no universal definitions of social isolation. The earliest definition was based on number of social ties, which is an objective measurement and uses a simple counting approach (Berkman, 1983). In 1993, Lien-Gieschen (Lien-Gieschen, 1993) defined social isolation as ‘A state in which an individual experiences a need or desire for contact with others but is unable for some reason to make contact’. This definition is based on feelings of individuals, which are subjective, rather than based on the number of social ties. Several definitions emphasize objective measurements which count number of contacts or relationships with others whereas other definitions weight more subjective aspect of social isolation such as perceived social isolation or loneliness. If social isolation is assessed only subjectively by the presence of a feeling of unsatisfactory relationships, or lack of, a sense of belonging, there would be no clear distinction between social isolation and loneliness which is a subjective emotional feeling. Conversely, if only counting of relationships is used for assessing social isolation, low quality ties with individuals who are unreliable, uncompassionate, or even abusive, might be counted even though those ties are obviously harmful to them. Howat proposed a different definition of social isolation which consists of both subjective and objective measurements (Howat, 2004). The definition includes ‘an objective state involving minimal contact and interaction with others and a generally low level of involvement in community life.’ Previous studies have also examined a concept of social isolation (Nicholson, 2009) comprised of five attributes: number of contacts, feeling of belonging, fulfilling relationships, engagement with others, and quality of network members (Nicholson, 2009). Because of its complexity, it is challenging to define and measure social isolation in a similar way in different countries. Nevertheless, taking into account the general concept of social isolation, it is useful to explore whether a similar definition of social isolation defined using both subjective and objective information is predictive of health outcomes.

1.2 PREVALENCE OF SOCIAL ISOLATION

The prevalence of social isolation varies depending on the populations studied and the definitions used. A study from the National Health and Aging Trends Study in the USA reported that the prevalence of social isolation was 24% among community-dwelling adults aged 65 years and older (Cudjoe et al., 2018). The prevalence ranges from 11 to 17% in other studies (Brummett et al., 2001; Greaves and Farbus, 2006; Iliffe et al., 2007; Kobayashi et al., 2009; Wahrendorf et al., 2008). According to a report from Eurostat in 2006, 7.2% of Europeans were socially isolated, based on a definition in which people who never meet friends or relatives, not even once a year (Eurostat, 2010). The prevalence of social isolation also varies not only across countries but also within each country because environmental factors including residential location, population density, and public transportation system could cause social isolation (Howat, 2004). Epidemiological studies conducted in Japan reported that approximately 19-27% of older adults were socially isolated (Aoki et al., 2018; Ejiri et al., 2018; Fujiwara et al., 2017; Sakurai et al., 2019). Table 1 shows the prevalence of social isolation in studies included in our systematic review, which is fully described in Chapter 2.

Table 1. Prevalence of social isolation among studies included in our systematic review

Author, year published	Country	Number of study population	Age of study subjects at baseline	Assessment of social isolation	Prevalence of social isolation (%)
Alcaraz, 2019	USA	580,182	54.9	Refer to The Berkman-Syme Social Network Index	0.57
Berkman, 1979	USA	4,725	47	The Berkman-Syme Social Network Index	9.2
Berkman, 2004	France	16,699	40-50 (men), 35-50 (women)	Refer to The Berkman-Syme Social Network Index	2.8
Brummett, 2001	USA	430	63.6	The Mannheim Social Support Interview	11.9
Cerhan, 1997	USA	2,575	79.1 (men), 80.3 (women)	Refer to The Berkman-Syme Social Network Index	10.7
Elovainio, 2017	UK	466,901	56.5	Refer to The Berkman-Syme Social Network Index	9.0
Eng, 2002	USA	28,369	55.2	The Berkman-Syme Social Network Index	6.0
Greysen, 2013	USA	1,836	61	Eight original questions	50.0
Jenkinson, 1993	UK, Norway, Sweden, and Denmark	1,376	59	Two original questions	9.9
Kaplan, 1988	Finland	13,301	43.8	Five original questions	Not available
Kawachi, 1996	USA	32,624	60	The Berkman-Syme Social Network Index	5.8
Keller, 2003	USA	1,270	78.4	The Berkman-Syme Social Network Index	16.9
Kreibig, 2014	USA	1,019	66.9	The Berkman-Syme Social Network Index	24.0
Kroenke, 2006	USA	2,835	65.1	The Berkman-Syme Social Network Index	7.0
Kroenke, 2013	USA	2,264	58.2	Refer to The Berkman-Syme Social Network Index	35.2
Kroenke, 2017	USA and China	9,267	56.8	The Berkman-Syme Social Network Index	21.1
Manemann, 2018	USA	1,681	73.3	The Patient-Reported Outcomes Measurement Information System (PROMIS) Social Isolation Short Form 4a v2.0.	6.4
Pantell, 2013	USA	16,849	47.5	The Berkman-Syme Social Network Index	19.1
Saito, 2012	Japan	13,310	72.8	Frequency of contacts with family members and close friends	15.5
Sakurai, 2019	Japan	1,023	72.3	Frequency of contacts with family, relatives, friends, and neighbors	7.6
Sarma, 2018	USA	896	69.8	The Berkman-Syme Social Network Index	10.7
Seeman, 1987	USA	4,174	≥ 38	The Berkman-Syme Social Network Index	Not available
Schoenbach, 1986	USA	2,059	52.5	The Berkman-Syme Social Network Index	Not available
Smith, 2018	UK	7,731	64	Refer to The Berkman-Syme Social Network Index	17.4
Steptoe, 2013	UK	6,500	≥ 52	Refer to The Berkman-Syme Social Network Index	18.9
Tanskanen, 2016	Finland	8,650	45.0	Refer to The Berkman-Syme Social Network Index	Not available
Yang, 2013	USA	6,729	≥ 40	The Berkman-Syme Social Network Index	17.0

1.3 MEASURING SOCIAL ISOLATION

A universal measure of social isolation has not yet been established mainly because of the complex nature of the concept. There are also issues associated with using secondary data sources in terms of question availability and differences in understanding the concept. Berkman and Syme constructed their social network index (The Berkman-Syme Social Network Index; SNI) to assess social relations in 1979 (Berkman and Syme, 1979). The SNI comprises four domains; information on partnership, contact with family members or friends, engagement in religious activities, and membership in organizations or clubs. Subsequent studies have used the SNI or a variation of it, according to available data, as a measure of social isolation.

1.4 SOCIAL ISOLATION AND MORTALITY AND MORBIDITY

1.4.1 Social isolation as a risk of mortality and morbidity

Social isolation has been found to be associated with an increase in all-cause mortality (Elovainio et al., 2017; Holt-Lunstad et al., 2010, p.; Pantell et al., 2013). Social isolation is considered to be as important a risk factor for death as other traditional risk factors including obesity, physical inactivity, smoking, and excessive alcohol consumption. Elovainio et al. reported that the hazard ratio (HR) for the risk of death from over the mean follow-up of 6.5 years among socially isolated people was 1.26 (95% confidence interval (95% CI): 1.20-1.33) compared to non-socially isolated individuals after adjusting for covariates (Elovainio et al., 2017). The results of analyses for cardiovascular- and non-cardiovascular mortality followed a similar pattern to that of all-cause mortality. A previous systematic review and meta-analysis that included 23 papers showed that poor social relationships were associated with increased risk of coronary heart disease by 29% and stroke by 32% (Valtorta et al., 2016).

1.4.2 Mechanisms linking social isolation and mortality and morbidity

Social relationships could inhibit harmful behaviors and promote healthy behaviors (Stokes, 2019). Social isolation is considered to influence health-related behaviors through lack of self-interest and loss of motivation, which originate from lack of social relationships. Some people with social isolation might commit suicide as an extreme manifestation of self-destructive behavior (Poudel-Tandukar et al., 2011). Individuals with social isolation may adopt unhealthy lifestyles because they give less priority to their health due to their feeling of low self-esteem (Stokes, 2019). In a cohort study (Berkman et al., 2004) of middle-aged adults, socially isolated men were more likely to be cigarette smokers, heavy drinkers, to have worse self-rated health, and to report frequent depressive symptoms, whereas socially isolated women tended to report worse self-rated health and mental health (Berkman et al., 2004). Social isolation could lead to increased morbidity and mortality partly through unhealthy lifestyles which include smoking, excessive alcohol intake, poor nutrition, and physical inactivity (Shankar et al., 2011; Yang et al., 2013).

Previous studies reported that fewer social connections were associated with smoking behavior (Christakis and Fowler, 2008; Kobayashi and Steptoe, 2018; Lauder et al., 2006). More social connections could increase the likelihood of engaging in healthy behaviors such as smoking cessation and physical activity, presumably because people with social connections are expected to receive advice regarding their behaviors from other people, receive mutual support or those people may have sense of obligation to stay healthy for family members and friends. The work by Christakis et al. suggested that smoking cessation was less common in socially isolated people compared to people with social connections (Christakis and Fowler, 2008), which suggests the importance of social networks in promoting smoking cessation as people who are socially isolated may lack a sense of self-control, have less motivation to adopt healthy behaviors, and lack appropriate resources and information that is distributed through social ties.

Social isolation is related to excessive alcohol intake and alcohol abuse, and also alcohol-related mortality such as death from liver disease, accidents or poisoning. People who are socially isolated may consume excessive amounts of alcohol to help them deal with the psychological distress of being isolated (Shiovitz-Ezra and Litwin, 2012; Watt et al., 2014) or they may simply lack self-control over drinking. The relationship between social isolation and hazardous alcohol consumption can be bi-directional. People who consume excessive alcohol use at higher risk of being socially isolated as a result of their behaviors related to alcohol that include violence to their kith and kin, alcohol-related crime, or debt due to less workplace productivity, transgression with the law enforcement and related legal expenses, and cost of excessive alcohol, which may segregate them from family, friends, and society.

Social isolation is recognized as a risk factor for malnutrition. Prior research shows that older individuals with social isolation are more likely to have malnutrition due to lack of social supports and connections. This may be more common in rural than urban areas. In rural areas, there are few grocery stores or markets and limited public transportation, which can limit access to food and other community resources (Quandt et al., 1999; Ryan and Bower, 1989). Other research reported people with fewer social contacts or living alone more often consume unhealthy diets with lower nutritional quality and less consumption of fruit and vegetables (Dean et al., 2009). Conversely, those with frequent social contacts consumed more fruit and vegetables (Sahyoun et al., 2005). Interestingly, prior research has suggested a different aspect of social isolation in relation to eating behaviors (Mason and Lewis, 2015; Waller et al., 2002). People with social isolation have a higher frequency of binge eating because they may have inadequate self-regulation or they may seek binge eating to cope with feelings of loneliness (Hawkley and Capitanio, 2015).

Physical inactivity has been recognized as an important risk of all-cause mortality (Kohl et al., 2012; Nocon et al., 2008) and morbidity (Bauman et al., 2012). Previous research has shown that individuals with social isolation are less physically active (Shankar et al., 2011) because they may be less attentive to their health due to feeling of low self-esteem that leads them to lose motivation for healthy lifestyles (Stokes, 2019) or some people might have long-standing illness and mobility limitations which are risk factors of social isolation. Others may also lack social support and networks that could support healthy behaviors. On the other hand, people with greater social networks are less likely to be physically inactive (Hunter et al., 2015). In summary, social isolation is considered to be a socioeconomic factor that is associated with unhealthy behaviors and mortality.

Chapter 2. Systematic review and meta-analysis of social isolation in relation to all-cause mortality

2.1 ABSTRACT

Background: Social isolation is defined as a lack of meaningful social networks. Several epidemiological studies reported that individuals with social isolation had increased risk for mortality compared to those with social supports. However, there is a paucity of studies examining the effect size of social isolation on the incidence of all-cause mortality.

Objective: The objective of this study is to examine the magnitude of effects of social isolation on all-cause mortality.

Data sources: We searched for studies using electronic databases: MEDLINE (1946 to June 29, 2019), EMBASE (1974 to June 29, 2019), and PsycINFO (1806 to June 29, 2019). To complement the electronic database search, we looked at trial registers (World Health Organization International Clinical Trials Registry Platform (June 2019) and ClinicalTrials.gov (June 2019)) and also screened reference lists of past reviews and studies meeting the inclusion criteria. Our systematic review registration number was CRD42020152351.

Selection criteria: We included both prospective and retrospective cohort studies which examine the association between social isolation and all-cause mortality among adults.

Data collection and analysis: Two reviewers screened and extracted data independently. Missing information was acquired from study authors whenever possible. Data were pooled to calculate integrated effect estimates of social isolation on all-cause

mortality.

Main results: The pooled hazard ratio of social isolation on all-cause mortality using a random effect model is 1.37 (95% confidence interval; 1.28-1.46). Overall, the quality of evidence included in this systematic review is judged low. Social isolation is probably associated with increase in all-cause mortality.

Conclusion: This systematic review and meta-analysis finds that social isolation is probably associated with increased risk for all-cause mortality.

2.2 BACKGROUND

Social isolation has increasingly been viewed as negatively affecting people's health (Elovainio et al., 2017; Laugesen et al., 2018; Steptoe et al., 2013; Tanskanen and Anttila, 2016). Epidemiological studies reported that social isolation is associated with increased risk of all-cause mortality. However, the magnitude of the effects of social isolation on mortality risk varied across studies. Thus, it is important to summarize and integrate information on the effect of social isolation on all-cause mortality. In this systematic review and meta-analysis, we examined available evidence on the effect to quantify the association of social isolation with mortality. Such information can enhance the awareness of social isolation as a risk factor for death, and allow clinicians, medical practitioners, stakeholders and policy makers to develop guidelines and recommendations to tackle social isolation with a view to reducing any related excess mortality.

2.3 STUDY ELIGIBLITY CRITERIA

In this systematic review, we included data from prospective or retrospective observational cohort studies that published data on both social isolation and mortality. We included only studies in which social isolation was assessed in study participants at enrollment. Eligible studies must have examined and reported the incidence of death over the follow-up period. We excluded publications that were based on case-reports or case-series designs. We applied no exclusion criteria regarding language of publication, or time or location. We included studies in which adults aged 18 years or older were involved and the effect of social isolation on mortality was evaluated. Mortality was examined as the outcome and the pooled estimates of its association with social isolation were calculated. Since different follow-up periods across studies were expected in particularly observational studies, random-effects models were used in meta-analyses. Additionally, studies with extreme durations of follow-up (longer or shorter than the average follow-up duration ± standard deviation (SD) of the included studies) were excluded in a sensitivity analysis in order to alleviate heterogeneity which could be caused by different follow-up period.

2.4 SEARCH METHODS FOR IDENTIFICATION OF STUDIES

We searched for studies published prior to June 2019 using the electronic databases: MEDLINE (1946 to June 29, 2019), EMBASE (1974 to June 29, 2019), and PsycINFO (1806 to June 29, 2019). Details of the search strategy for each database are provided as Appendix 1. We included thesaurus and free text key terms including social isolation, mortality, death, cohort studies, prospective studies and retrospective studies. We sought expert medical librarian support when needed and ensure that a complex search strategy is used with the respective Boolean operators and relevant search filters in each database. To complement the electronic database search, we screened reference lists of past reviews and studies meeting the inclusion criteria. This is to ensure that potentially relevant studies are considered in our screening process. Two researchers independently screened titles and abstracts before assessing full records. The full text screen phase utilized the same approach. Moreover, the data abstraction and risk of bias stages of this review also utilized duplicate and independent screening and assessment. Disagreements were settled by consensus discussion and 3rd party adjudication was used if needed. To complement the electronic database search, we screened reference lists of past reviews and studies meeting the inclusion criteria.

2.5 DATA COLLECTION AND ANALYSES

2.5.1 Selection of studies

Two individuals (R.N. and L.S.) independently screened titles and abstracts using Rayyan (Ouzzani, 2016), an online systematic review tool, to assess study eligibility for potential inclusion. The two reviewers then screened full texts to determine whether such trials would be included. After each stage, the reviewers met to discuss disagreements. PRISMA Checklist is shown as Appendix 2.

2.5.2 Data extraction and management

Data were extracted from full texts of the studies by one researcher, and checked by a second. We discussed differences after each stage of independent screening. Study authors were contacted to obtain missing data.

2.5.3 Assessment of risk of bias in included studies

The Cochrane Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) (Sterne et al., 2016) tool was used to appraise the quality of included studies. The tool offers a structured and comprehensive approach for the assessment of non-randomized studies. Central features of the ROBINS-I tool include the use of signaling questions to guide risk of bias judgements within seven bias domains. The quality assessment was carried out by one reviewer and then checked by the other. Any disagreements were discussed and resolved. Where necessary, a third reviewer (P.E.A.) was involved to adjudicate unresolved disagreements. Study authors were contacted for additional information to clarify study methods and to gather missing data.

2.5.4 Assessment of the quality of evidence

The Grading of Recommendations Assessment Development and Evaluation (GRADE) tool was used to rate the certainty of evidence from the included studies (Atkins et al., 2004). The certainty of effect is assessed as high, moderate, low or very low if any of the GRADE domains (risk of bias, inconsistency, indirectness and imprecision) are rated as 'not serious,' 'serious' or very serious along with publication bias being rated as 'undetected' or 'strongly suspected'. Evidence from robust non-randomized studies are generally graded as low quality. Nevertheless, if the effect size reported in such studies is large enough and there is no clear evidence of bias to explain those effects, the evidence might be rated as moderate or even high quality. GRADE assessments were applied by one reviewer and then checked by the other.

2.5.5 Quantitative synthesis

We synthesized the data from the included studies and calculated the effect size of social isolation on all-cause mortality. Hazard ratio was chosen as a measure of the synthesized effect size because the majority of the studies reported relative hazards of social isolation and its associated confidence intervals, comparing people with the highest versus the lowest levels of social isolation. Where a group of people with social isolation was used as the reference, results were transformed to allow comparison across studies. Only papers for which an effect estimate and standard error or confidence interval were available or could be calculated, were included in analyses to calculate the pooled estimate. Information on the degree of adjustment for covariates of the estimates in each study are described in the result section (2.6.1). Where a study analyzed multiple models to calculate an effect size, we extracted data from the most complex Cox proportional hazard model to minimize risk of confounding. We used RevMan V.5.3 (Review Manager (RevMan) Version 5.3) to calculate effect estimates, build forest plots and funnel plots, and assess heterogeneity among studies using I^2 statistic.

2.6 RESULTS

2.6.1 Search results

A total of 27 studies was identified for inclusion in the review, after a two-stage screening process. A flow diagram of the study selection process is presented as Figure 1. Summary of the descriptive characteristics of the evidence included in this review are shown in Table 2. Eighteen articles were from North America (one study was conducted in U.S. and China), 7 articles from Europe, and 3 articles from Asia (Japan; 2, China; 1). These studies included data on 1,231,101 participants. Across all studies, the weighted mean age of participants at entry into the study was 54 years. They were followed for an average of 9 years (range from 8 months to 30 years). Due to the wide range of follow-up periods despite the proportional hazard assumption in Cox regression model that a hazard ratio (HR) is constant over time, random-effects meta-analytic models were applied. Besides that, a sensitivity analysis was undertaken in which studies with extremes of follow-up were excluded.

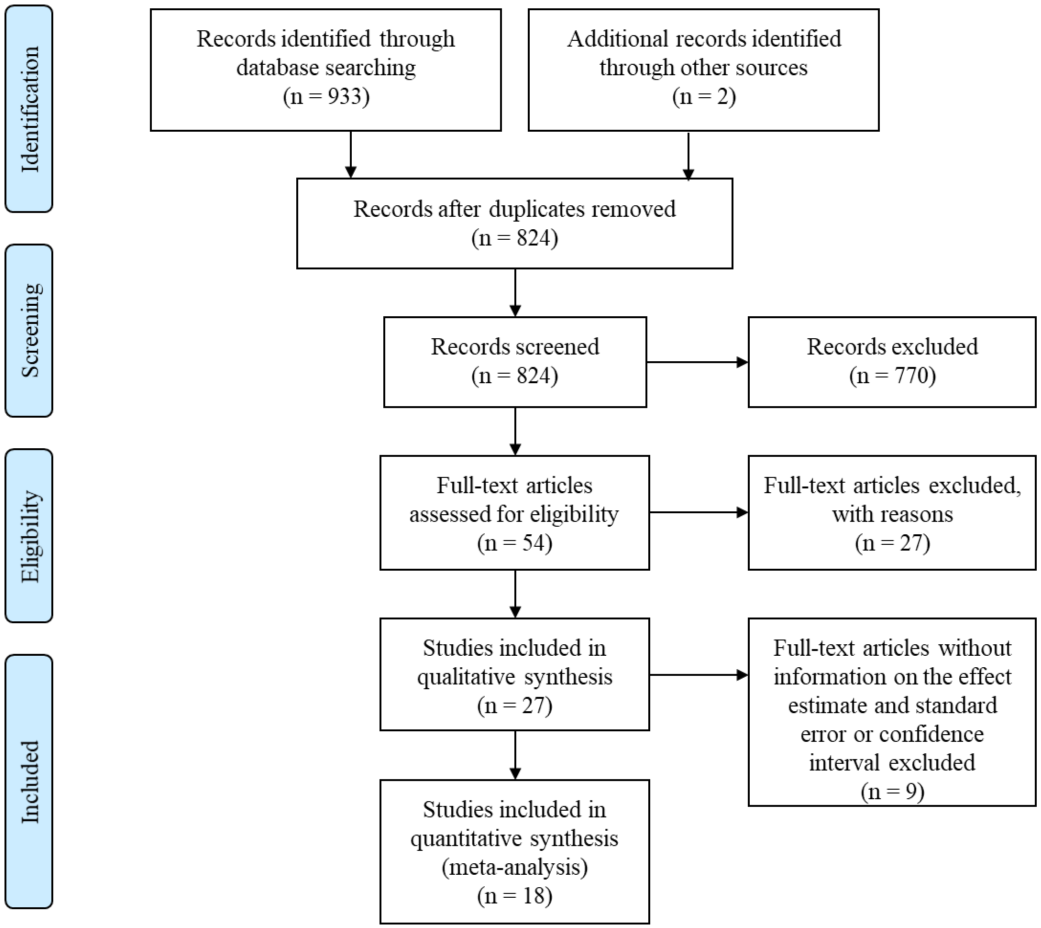

Figure 1. PRISMA Flow diagram

Legend. A total of 27 studies were identified for inclusion in the reviews, after a two-stage screening process. Eighteen studies among them were included in meta-analyses.

Table 2. Characteristics of studies included in this systematic review

Author, year published	Country	Data collection dates	Number of study population	Age of study subjects at baseline	Follow-up period	Outcome measure	Number of events	Covariates adjusted for	Main results for our review
Alcaraz, 2019	USA	1982-1983	580,182	54.9	30 years	All-cause mortality	250,006	Stratified on single-year of age and race, and adjusted for sex, smoking status, education, body mass index, and history of diabetes.	Comparing most isolated to least isolated, HR: 1.43, 95% CI: 1.36-1.50
Berkman, 1979	USA	1965	4,725	47	9 years	All-cause mortality	371	Age	Comparing most socially isolated to most socially connected, Relative risk (RR) 2.3 for men and 2.8 for women
Berkman, 2004	France	1991	16,699	40-50 (men), 35-50 (women)	8 years	All-cause mortality	men; 228 women; 29	Age, occupational grade, cigarette smoking, alcohol consumption, body mass index, depressive symptoms, self-rated health and geographic region of France	Comparing socially isolated to least socially isolated, HR: 2.70, 95% CI: 1.17-6.23 for men. HR: 3.64, 95% CI: 0.72-18.58 for women
Brummett, 2001	USA	1992	430	63.6	47.3 months	All-cause mortality	159	Age, number of diseased vessels, left ventricular ejection fraction, presence or absence of congestive heart failure and comorbidity	Comparing socially isolated to non-isolated, HR: 2.11, 95% CI: 1.39-3.19
Cerhan, 1997	USA	1982-1985	2,575	79.1 (men), 80.3 (women)	8 years	All-cause mortality	1,059	Age, education, smoking status, onset of major illness, change in physical function, change in self-perceived health status, change in depressive symptoms, and memory recall test	Comparing socially isolated to non-socially isolated, HR: 1.5, 95% CI: 1.1-2.1 for men and HR: 1.5, 95% CI: 1.1-2.0 for women
Elovainio, 2017	UK	2007-2010	466,901	56.5	6.5 years	Mortality after AMI or stroke	11,593	Age, sex, ethnicity, body mass index, diastolic blood pressure, systolic blood pressure, grip strength, alcohol consumption, physical activity, smoking, education, household income and Townsend Deprivation Index, depressive symptoms and history of chronic illness.	Comparing socially isolated to non-isolated, HR: 1.26, 95% CI: 1.20-1.33
Eng, 2002	USA	1988	28,369	55.2	10 years	1) all-cause mortality 2) fatal coronary heart disease	1) 1,365 2) 142	Age, occupation, health behaviors, general physical condition, coronary risk factors, and dietary habits	Comparing social network index I to social network index IV, 1) HR:1.20, 95% CI: 0.97-1.48, 2) HR: 1.82, 95% CI: 1.02-3.23
Greysen, 2013	USA	2002-2008	1,836	61	2 years	All-cause mortality	550	Age, race, comorbidities, income, depression and alcohol abuse	Comparing social isolation score ≥ 4 to social isolation score < 4, HR: 1.28, 95% CI: 1.06-1.54
Jenkinson, 1993	UK, Norway, Sweden, and Denmark	1986-1988	1,376	59	3 years	All-cause mortality	247	Age group, previous myocardial infarction, hospital complications, history of diabetes, and history of hypertension	HR: 1.49, 95% CI: 1.01-2.18
Kaplan, 1988	Finland	1972-1977	13,301	43.8	5 years	All-cause mortality	598	Age, province, urban/rural, serum cholesterol, mean weighted blood pressure, cigarettes, body mass index, previous diseases, education and cohort	Compared to the most isolated men to the least isolated men, Odds ratio: 2.12, (95% CI: 1.44-3.12
Kawachi, 1996	USA	1988	32,624	60	4 years	Death from all causes	511	Age, time period, smoking, hypertension, diabetes, high cholesterol, a history of angina pectoris, myocardial infarction, body mass index, alcohol intake and physical activity	Comparing social network index I to social network index IV, RR: 1.38, 95% CI: 0.99-1.93
Keller, 2003	USA	1988-1999	1,270	78.4	4 years	All-cause mortality		Age, income, education, Instrumental Activities of Daily Living, the Cumulative Illness Rating Scale, and informal service use	Comparing social network index I to social isolation index IV, HR: 1.25, 95% CI: 0.97-1.61
Kreibig, 2014	USA	2000-2002	1,019	66.9	6.7 years	All-cause mortality	347	Age, ethnicity, body mass index, income, left ventricular ejection fraction, inducible ischemia, chronic obstructive pulmonary disease, use of statins and diuretics, and biological mediators	Comparing social network index I to social network index IV, HR: 1.53, 95% CI: 1.05-2.25

Author, year published	Country	Data collection dates	Number of study population	Age of study subjects at baseline	Follow-up period	Outcome measure	Number of events	Covariates adjusted for	Main results for our review
Kroenke, 2006	USA	1992-2002	2,835	65.1	6 years	All-cause mortality	224	Age, time between diagnosis and assessment of social networks, cancer stage at diagnosis, chemotherapy, tamoxifen, radiation, estrogen-receptor status, age at menarche, oral contraceptive use, birth index, menopausal status, age at menopause, use of hormone replacement therapy, smoking status, body mass index, physical activity, and protein intake	Comparing socially isolated to socially integrated, HR: 1.66, 95% CI: 1.04-2.65
Kroenke, 2013	USA	1997-2000	2,264	58.2	10.8 years	All-cause mortality	401	Age, time between social assessment and breast cancer diagnosis, disease severity, treatment, education, ethnicity, reproductive variables, body mass index, physical activity, alcohol intake and smoking status	Comparing socially isolated to socially integrated, HR: 1.34, 95% CI: 1.03-1.73
Kroenke, 2017	USA and China	1976-2006	9,267	56.8	10.6 years	All-cause mortality	1,521	Age and time between diagnosis and social network assessment, cohort, education, race, stage, estrogen receptor status, HER2 status, parity, menopausal status, and comorbidity	Comparing socially isolated to socially integrated, HR: 1.69, 95% CI: 1.43-1.99
Manemann, 2018	USA	2013-2015	1,681	73.3	8 months	all-cause mortality	59	Age, sex, education, marital status and Charlson comorbidity index	Comparing high perceived social isolation compared to low, HR: 3.74, 95% CI: 1.82-7.70
Pantell, 2013	USA	1988-1994	16,849	47.5	14.1 years	All-cause mortality		Age, race, education, income level, self-reported health status, clinical risk factor, smoking, obesity, high blood pressure and high cholesterol	Comparing most socially isolated to non-socially isolated, HR: 1.62, 95% CI: 1.29-2.02 for men and HR: 1.75, 95% CI:1.38-2.23 for women
Saito, 2012	Japan	2003	13,310	72.8	4 years	All-cause mortality	1,044	Age, sex, educational attainment, marital status, and history of disease and impairment	Comparing socially isolated to non-isolated, HR: 1.19, 95% CI: 1.02-1.39
Sakurai, 2019	Japan	2008	1,023	72.3	6 years	All-cause mortality	65	Age, sex, number of years of education, comorbidities, depression symptoms, subjective health, and residential areas	Comparing socially isolated over not socially isolated to non-homebound, Hazard ratio (HR): 1.34, 95% confidence interval (CI): 0.64-2.81
Sarma, 2018	USA	1992-2012	896	69.8	9.5 years	All-cause mortality	380	Age at diagnosis, year of diagnosis, race/ethnicity, smoking status, alcohol intake, aspirin use, physical activity, body mass index, cancer stage, cancer grade and cancer site	Comparing social network index I to social network index IV, HR: 1.54, 95% CI: 1.09-2.17
Seeman, 1987	USA	1965	4,174	≥ 38	17 years	All-cause mortality	1,219	Age, race, baseline health status, perceived health , depression and health practices	Comparing social network index I to social network index IV, HR: 1.49, 95% CI: 1.09-2.05
Schoenbach, 1986	USA	1967-1969	2,059	52.5	13 years	All-cause mortality	419	Age, presence of coronary heart disease, stroke, transient ischemic attack, treated diabetes), systolic blood pressure, cholesterol, smoking, Quetelet index, electrocardiogram abnormalities, social status and leisure time physical activity	Comparing social network index I to social isolation index IV, HR: 1.5, 95% CI: 0.8-2.6 for White male, HR: 1.3 95% CI: 0.7-2.3 for White female, HR: 1.3, 95% CI: 0.6-2.7 for Black male and HR: 1.1, 95% CI: 0.5-2.6 for Black female
Smith, 2018	UK	2004/2005	7,731	64	8-9 years	All-cause mortality	1,261	Age, sex, ethnicity, education, occupational class, non-pension wealth, limiting longstanding illness, functional impairment, depressive symptoms, cancer, heart disease, stroke, diabetes, arthritis, chronic lung disease, health behaviors, and cognitive dysfunction	Comparing socially isolated to non-isolated, HR: 1.28, 95% CI: 1.10-1.50
Steptoe, 2013	UK	2004-2005	6,500	≥ 52	7.25 years	All-cause mortality	918	Age, sex, wealth, education, marital status, ethnicity, limiting long-standing illness, mobility impairment, cancer, diabetes, coronary heart disease, chronic lung disease, arthritis, stroke, diagnosed depression and Center for Epidemiologic Studies Depression Scale	Comparing the top quintile of social isolation scale to the bottom quintile, HR: 1.26, 95% CI: 1.08-1.48
Tanskanen, 2016	Finland	1994	8,650	45.0	17 years	All-cause mortality	1,472	Age, gender, self-reported health, body mass index, frequency of heavy alcohol consumption, exercise or sports, educational level, employment or student status, and household income	HR: 1.01, 95% CI: 1.006-1.013 per 1 score increase in social isolation score
Yang, 2013	USA	1988-2006	6,729	≥ 40	18 years	All-cause mortality	2,774	Age, race-ethnicity, education, family income, smoking, drinking, chronic conditions, physical activity, body mass index and self-rated health	Comparing socially isolated to socially connected, HR: 1.53, 95% CI: 1.26-1.87 for men) and HR: 1.45, 95% CI: 1.20-1.75 for women

2.6.2 Assessment of social isolation

The prevalence of social isolation ranges from 0.6% (Alcaraz et al., 2019) to 35.7% (Kroenke et al., 2013). Given that the different population and different assessment for social isolation across the included studies might cause heterogeneity in the effect of social isolation on all-cause mortality, we applied random effects meta-analytic models. Across the 27 studies included in this review, social isolation was assessed using 4 tools; the SNI (Berkman and Syme, 1979) in 12 studies, modified SNI in 8 studies, the Mannheim interview on social support in one study (Brummett et al., 2001), the Patient-Reported Outcomes Measurement Information System Social Isolation Short Form 4a v2.0. (Manemann et al., 2018) in one study, and 5 different tools were used to record the availability and/or frequency of contacts for the other studies.

2.6.3 Effect of social isolation on all-cause mortality

Eighteen out of 27 articles for which the effect size and standard error or confidence interval were available, or could be calculated, were included in meta-analyses to calculate the pooled estimate. All of the studies provided HR adjusted for covariates which included age, health behaviors (i.e. smoking or alcohol) or comorbidities. The random effects weighted average HR of social isolation for mortality is 1.37 (95 % CI; 1.28-1.46) with moderate heterogeneity (heterogeneity: $Chi^2 = 39.71$, $P = 0.001$, $I^2 = 57\%$) (Figure 2). Given the moderate degree of heterogeneity and different type of assessment tools for social isolation used, we conducted subgroup analyses to determine the extent to which the effect estimates were affected by the type of assessment for social isolation. The SNI was used to assess social isolation in seven studies. The random effects weighted average HR among the studies is 1.45 (95% CI; 1.29-1.64) with no significant heterogeneity (heterogeneity: $Chi^2 = 8.11$, $P = 0.23$, $I^2 = 26\%$) whereas among the remainders, the pooled HR was 1.34 (95% CI; 1.24-1.45) with substantial heterogeneity (heterogeneity: $Chi^2 = 28.55$, $P = 0.001$, $I^2 = 65\%$), suggesting that the heterogeneity in the association between social isolation and mortality, may be partly related to the assessment tool for social isolation (Figure 3). We performed further sensitivity analyses in which studies (Alcaraz et al., 2019; Manemann et al., 2018; Seeman et al., 1987) with follow-up periods substantially longer or shorter than the average follow-up duration ± 1 SD of the included studies were excluded (Figure 4). The effect size is attenuated from 1.37 to 1.33 (95 % CI; 1.25-1.42) with less heterogeneity: $Chi^2 = 21.47$, $P = 0.09$, $I^2 = 35\%$) (Figure 5).

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Alcaraz 2019	0.3577	0.0256	14.1%	1.43 [1.36, 1.50]
Brummett 2001	0.7467	0.213	2.2%	2.11 [1.39, 3.20]
Elovainio 2017	0.2311	0.0249	14.1%	1.26 [1.20, 1.32]
Eng 2002	0.1823	0.1086	5.9%	1.20 [0.97, 1.48]
Greysen 2013	0.2469	0.0962	6.8%	1.28 [1.06, 1.55]
Jenkinson 1993	0.3988	0.1984	2.4%	1.49 [1.01, 2.20]
Keller 2003	0.2231	0.1294	4.7%	1.25 [0.97, 1.61]
Kreibig 2014	0.4253	0.1921	2.6%	1.53 [1.05, 2.23]
Kroenke 2006	0.5068	0.2386	1.8%	1.66 [1.04, 2.65]
Kroenke 2013	0.2927	0.1342	4.5%	1.34 [1.03, 1.74]
Kroenke 2017	0.5247	0.0852	7.7%	1.69 [1.43, 2.00]
Manemann 2018	1.3191	0.3675	0.8%	3.74 [1.82, 7.69]
Saito 2012	0.174	0.0786	8.4%	1.19 [1.02, 1.39]
Sakurai 2019	0.2927	0.377	0.8%	1.34 [0.64, 2.81]
Sarma 2018	0.4318	0.1763	3.0%	1.54 [1.09, 2.18]
Seeman 1987	0.3988	0.1595	3.5%	1.49 [1.09, 2.04]
Smith 2018	0.2469	0.0773	8.5%	1.28 [1.10, 1.49]
Steptoe 2013	0.2311	0.0786	8.4%	1.26 [1.08, 1.47]
Total (95% CI)			**100.0%**	**1.37 [1.28, 1.46]**

Heterogeneity: Tau² = 0.01; Chi² = 39.71, df = 17 (P = 0.001); I² = 57%
Test for overall effect: Z = 9.34 (P < 0.00001)

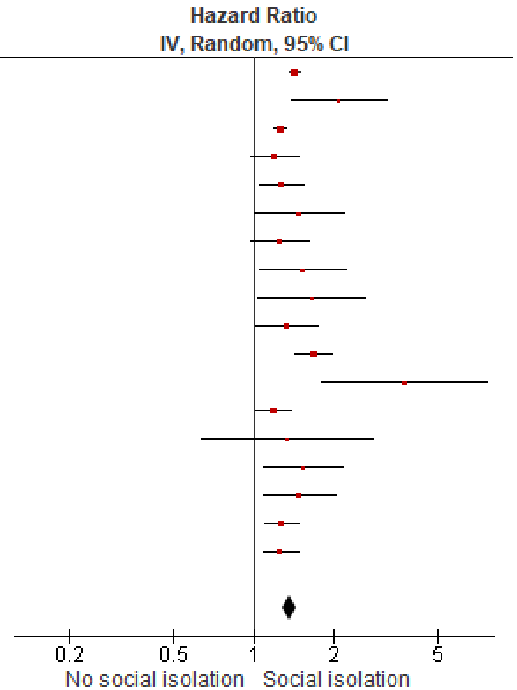

Figure 2. Forest plots and pooled estimates for hazard ratios of social isolation for all-cause mortality

Legend. The random effects weighted average hazard ratios of social isolation for all-cause mortality is 1.37 (95% CI); 1.28-1.46) with moderate heterogeneity (heterogeneity: Chi² = 39.71, P = 0.001, I² = 57%).

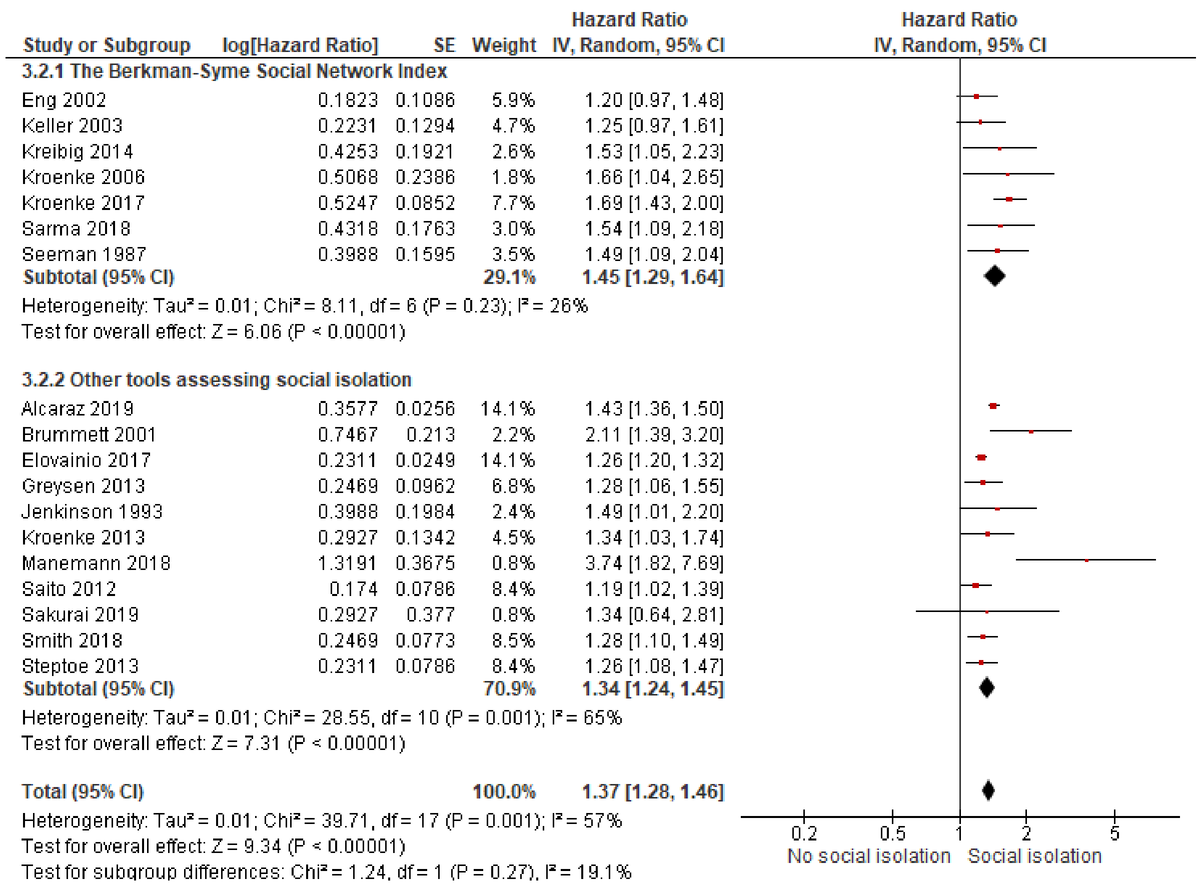

Figure 3. Forest plots and pooled estimates hazard ratios of social isolation for all-cause mortality are shown separately for different social isolation assessment tools

Legend. The hazard ratio among the studies using the Berkman-Syme Social Network Index to assess social isolation is 1.45 (95% CI; 1.29-1.64) with mild heterogeneity (heterogeneity: Chi^2 = 8.11, P = 0.23, I^2 = 26%) whereas that among the remainders is 1.34 (95% CI; 1.24-1.45) with substantial heterogeneity (heterogeneity: Chi^2 = 28.55, P = 0.001, I^2 = 65%).

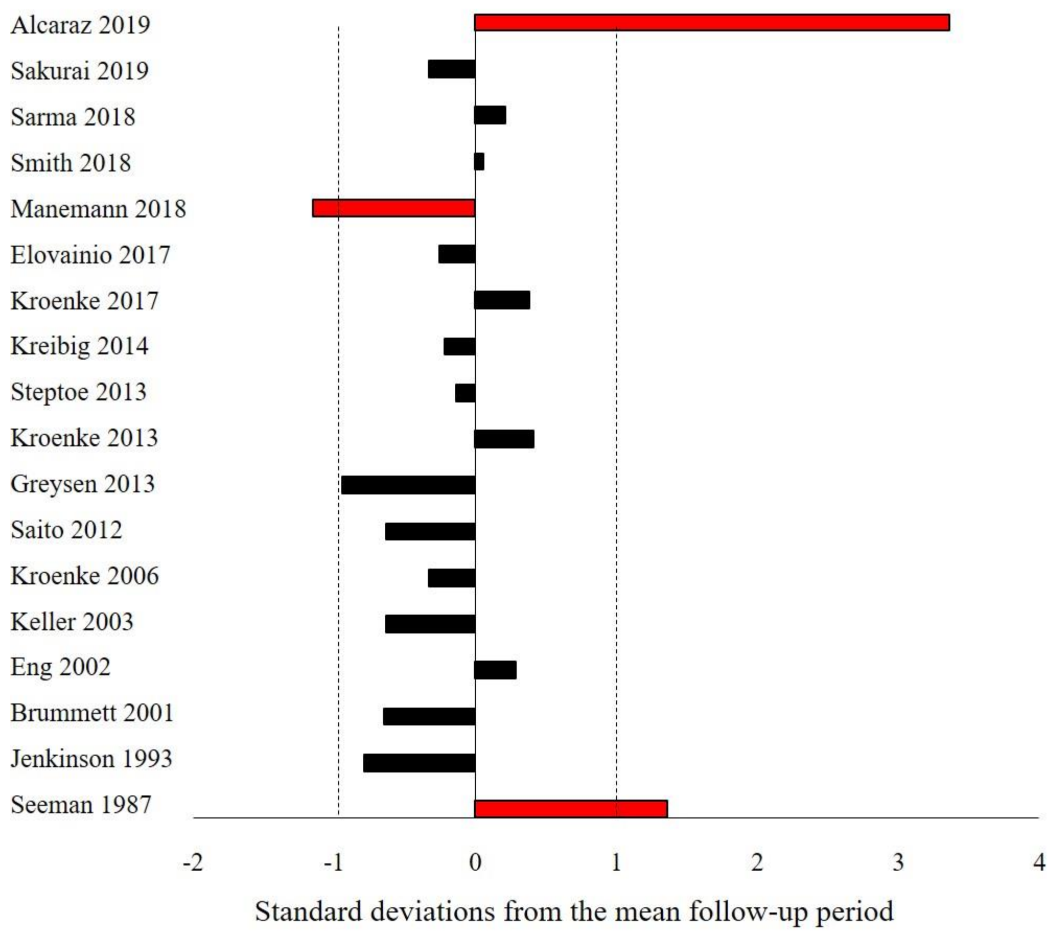

Figure 4. Standardized follow-up period for each study

Legend. Mean follow-up periods among the included studies are standardized. Three studies indicated by red bars are excluded in a sensitivity analysis to deal with heterogeneity through the wide range of follow-up period.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Brummett 2001	0.7467	0.213	2.2%	2.11 [1.39, 3.20]
Elovainio 2017	0.2311	0.0249	21.6%	1.26 [1.20, 1.32]
Eng 2002	0.1823	0.1086	6.8%	1.20 [0.97, 1.48]
Greysen 2013	0.2469	0.0962	8.0%	1.28 [1.06, 1.55]
Jenkinson 1993	0.3988	0.1984	2.5%	1.49 [1.01, 2.20]
Keller 2003	0.2231	0.1294	5.2%	1.25 [0.97, 1.61]
Kreibig 2014	0.4253	0.1921	2.7%	1.53 [1.05, 2.23]
Kroenke 2006	0.5068	0.2386	1.8%	1.66 [1.04, 2.65]
Kroenke 2013	0.2927	0.1342	4.9%	1.34 [1.03, 1.74]
Kroenke 2017	0.5247	0.0852	9.4%	1.69 [1.43, 2.00]
Saito 2012	0.174	0.0786	10.3%	1.19 [1.02, 1.39]
Sakurai 2019	0.2927	0.377	0.8%	1.34 [0.64, 2.81]
Sarma 2018	0.4318	0.1763	3.1%	1.54 [1.09, 2.18]
Smith 2018	0.2469	0.0773	10.5%	1.28 [1.10, 1.49]
Steptoe 2013	0.2311	0.0786	10.3%	1.26 [1.08, 1.47]
Total (95% CI)			**100.0%**	**1.33 [1.25, 1.42]**

Heterogeneity: Tau² = 0.00; Chi² = 21.47, df = 14 (P = 0.09); I² = 35%

Test for overall effect: Z = 8.66 (P < 0.00001)

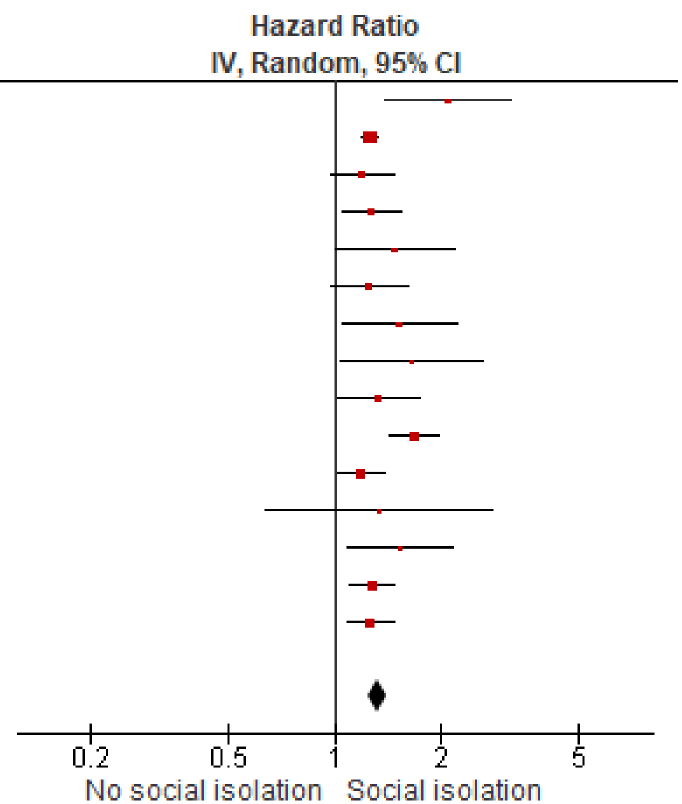

Figure 5. Forest plots and pooled estimates using inverse-variance weighted random effects model for hazard ratios of social isolation for all-cause mortality in which three studies with extreme follow-up periods were excluded.

Legend. The hazard ratios of social isolation for all-cause mortality is 1.33 (95 % CI; 1.25-1.42) with mild heterogeneity

(heterogeneity: Chi² = 21.47, P = 0.09, I² = 35%).

2.6.4 Narrative reviews of remaining studies

Narrative reviews included 9 studies that were excluded from the meta-analyses because information on the effect estimates of social isolation on all-cause mortality, standard error or confidence interval were not available in those studies. Gender-specific effect sizes are provided in 5 studies of which 4 reported statistically significant associations between social isolation and mortality, with HR ranging from 1.50 to 2.70 for men and 1.45 to 3.64 for women (Berkman et al., 2004; Cerhan and Wallace, 1997; Pantell et al., 2013; Yang et al., 2013). The remainder showed no significant association between social isolation and all-cause mortality for both genders (Schoenbach et al., 1986). Two studies reported inconsistent results with regard to relative risks for all-cause mortality among individuals with social isolation (Berkman and Syme, 1979; Kawachi et al., 1996). Kaplan et al. reported a significant association between social connections and all-cause mortality with odds ratio of 1.54 (95% CI; 1.21-1.95) in individuals with low social connections as compared to those with high social connections for men while no significant association was found for women (Kaplan et al., 1988). In the other study that measured social isolation score on a scale from 0 to 100, social isolation score was associated with mortality in a graded fashion (Tanskanen and Anttila, 2016). The risk of bias in the 9 studies was considered moderate. We found inconsistency in the results across the studies and also the magnitude of the effect sizes varied across the studies. Indirectness was rated "not serious" since the results applied to our research question of this systematic review. Publication bias cannot be eliminated despite attempts to search extensively electronic databases and other sources. Overall, this narrative synthesis, with 9 studies, suggests that social isolation is associated with increased risk of all-cause mortality.

2.6.5 Assessment of risk of bias across studies

The Cochrane ROBINS-I was used to appraise the quality of included studies. A summary of the results is shown in Table 3. All studies are judged to be moderate risk of bias for bias due to confounding because potential baseline factors related to both social isolation and mortality were controlled for in estimating the effect of social isolation on all-cause mortality in the studies and serious residual confounding was not expected. Bias in selection of participants is judged to be low in all studies because participants were included when information on social isolation were available and thus, selection bias due to whether or not social isolation was assessed is unlikely in the studies. Besides that, start of follow-up and start of exposure are considered to have coincided given the study design of longitudinal cohorts in all studies. Bias in classification of interventions is judged to be low risk of bias in all studies because social isolation status for study participants were identified in each article with clear definition of social isolation described in the articles. Bias due to deviations from intended intervention is also judged to be low in all studies because it is unlikely that status of social isolation can be affected by the outcome. For bias due to missing data, 20 out of 27 studies are judged to be low risk of bias while the rest of the articles are judged to be moderate because reasons for missing participants in estimating the effect of social isolation on all-cause mortality were not clearly mentioned in those articles. Bias in measurement of outcomes for all studies is judged to be low because the outcome of interest is all-cause mortality for which assessment is unlikely to be influenced by knowledge of social isolation status among study participants. Besides that, error in measuring this outcome is considered unrelated to social isolation status because of objective nature of this outcome. Finally, bias in selection of the reported result is judged to be low among all studies because reported results in each study corresponded to the intended outcome measurement and statistical analyses described in all studies. Based on those judges for all domains, overall risk of bias across studies is rated as moderate since all studies assessed are judged to be at low or moderate risk of bias for all domains.

Table 3. Results of risk of bias across studies

First author & year published	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended intervention	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall
Sakurai, 2019	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Alcaraz, 2019	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Smith, 2018	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Berkman, 2004	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Eng, 2002	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Schoenbach, 1986	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Kroenke, 2006	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Keller, 2003	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Jenkinson, 1993	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Kroenke., 2017	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Saito, 2012	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Elovainio, 2017	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Sarma, 2018	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Seeman, 1987	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kaplan, 1988	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Berkman, 1979	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kawachi, 1996	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Tanskanen , 2016	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kreibig, 2014	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Pantell, 2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Greysen, 2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Yang, 2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Steptoe, 2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kroenke, 2013	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Brummett, 2001	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Cerhan, 1997	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Manemann, 2018	Moderate risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk

2.6.6 Assessment of the quality of evidence

The quality of evidence was assessed using the GRADE system in the following domains; risk of bias, inconsistency, indirectness, imprecision, publication bias and other upgrading factors. A summary of the results is shown in Table 4. Risk of bias is rated serious because the overall risk of bias for the included studies assessed using the Cochrane ROBINS-I tool was moderate and the degree of concern about risk of bias is considered between not serious and very serious. The rating of inconsistency is serious because of variations in the effect size across the studies, with an I-square value of 57% (Figure 2) and a significant chi-square of 39.71 (p=0.001). Indirectness is rated as not serious because the results of the integrated effect size of social isolation on all-cause mortality is applicable to the research question of this systematic review. Imprecision is rated as not serious considering a high number of events (271,159, one article did not provide the number of events) observed among the studies and a relatively narrow confidence interval for the integrated effect size of social isolation on all-cause mortality. Publication bias was assessed by variation for the effect estimates across studies and our search strategy. When funnel plots for the effect estimates of the included studies are plotted, there is a visual suggestion of the bias, while Eggers’s test showed no significant bias (Figure 6) (Egger et al., 1997). One study is observed to have relatively high HR, but it also has a wide confidence interval (Manemann et al., 2018). For our search strategy, we conducted the electronic search for the following databases: MEDLINE (1946 onwards), EMBASE (1974 onwards), and PsycINFO (1806 onwards). We used no language restrictions. In order to identify all possible studies, we examined the reference lists of eligible articles to find other relevant studies. Authors of several studies were contacted when the studies are considered to have unpublished data relevant to our research question, but all of them did not provide the data or respond to our emails. Hence, publication bias was not detected. For other factors applicable to non-randomized studies, magnitude of effect size, a presence of dose response relationship as well as a presence of plausible confounding opposing the effect were checked. The integrated effect size in this systematic review is 1.37 which does not meet a criterion (effect size greater than 2) to rate up the evidence of the effect size (Guyatt et al., 2011). We did not find any reason to recategorize the level of the evidence to a higher level because dose response relationship between social isolation and all-cause mortality cannot be assessed among almost all studies except for a study conducted by Tanskanen (Tanskanen and Anttila, 2016) that reported a positive "dose-response" relationship. Besides that, we did not find any evidence of plausible confounding that could mitigate the effect among the studies. Thus, no factors are identified that can increase the confidence of the observations in this systematic review. Since evidence from non-randomized studies is generally graded as low quality unless the effect yielded by such studies is large (> than 2-fold) and there is a possibility that some biases or confounders may explain any observed effects. Therefore, the confidence in the estimates of the effects of social isolation on mortality based on the evidence of this systematic review is judged to be low.

Table 4. Summary of evidence of the relationship between social isolation and all-cause mortality in this systematic review

Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Certainty of the evidence
Serious	Serious	Not serious	Not serious	Undetected	No factors	Low

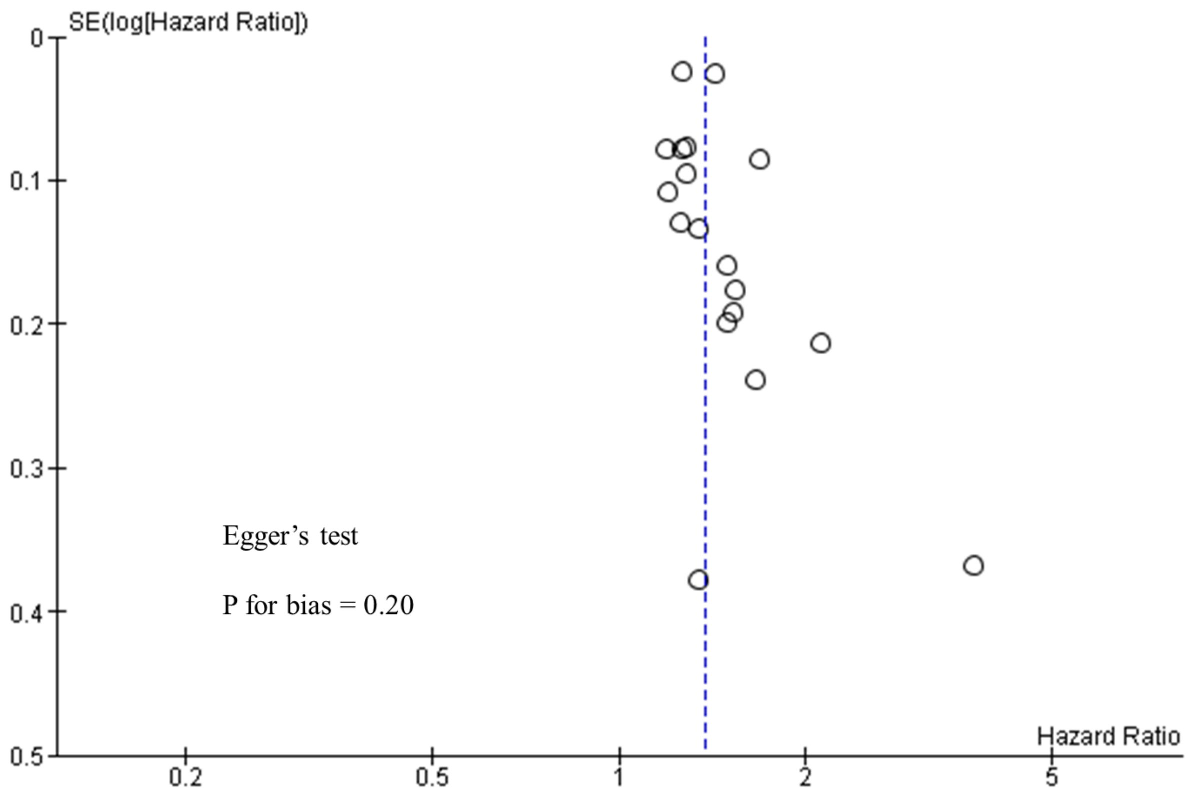

Figure 6. Funnel plots for the hazard ratios of social isolation for all-cause mortality

Legend. No significant asymmetry is found in the plots for the hazard ratios of social isolation for all-cause mortality

2.7 DISCUSSION

2.7.1 Summary of the main results

This systematic review and meta-analysis shows that social isolation is associated with increased risk of all-cause mortality with evidence being low quality. The overall effect size corresponds with a 37% increase (95% CI; 1.28-1.46) in hazards of all-cause mortality in individuals with social isolation as compared to those without. The effect sizes are consistent regardless of type of assessment tools for social isolation. The narrative review of studies excluded from the meta-analysis, also suggests that individuals experiencing social isolation are at higher risk of all-cause mortality. Our review, with its focus on only longitudinal studies could provide evidence indicating the direction of the relationship between social isolation and mortality. Previous reviews reported that people experiencing social isolation are at higher risk of dying (Holt-Lunstad et al., 2015, 2010). A recent systematic review and meta-analysis reported that an increased likelihood of death of 29 % with social isolation after accounting for multiple covariates (Holt-Lunstad et al., 2015). Our finding from the meta-analysis is consistent with prior evidence that demonstrated that the socially isolated are more likely to die compared to individuals with social connections. Our review could reinforce the prior evidence since the included studies were longitudinal studies with social isolation being assessed multi-dimensionally, which is referred to have better predictive validity for assessment of social isolation in relation to mortality.

2.7.2 Applicability of evidence

In this review, the studies from which data were extracted were from mainly the US, Europe and Japan, which limits generalizability. Additionally, measurement of social isolation varied across the included studies with the SNI used in half of the studies and other assessment tools in the rest. However, the results were consistent using both sets of assessments. Ideally, pooled information across studies in which identical assessment tool for social isolation are used, could provide more interpretable evidence even though our subgroup analysis shows that the effect sizes were similar regardless of the type of assessment for social isolation.

2.7.3 Potential biases in the review process

We attempted to reduce bias in the review process to a minimum by extensively searching available databases and not limiting the search by language. We also ensured that study identification and inclusion, data extraction were carried out by two independent review authors. Publication bias was not detected although we cannot completely exclude the possibility of such bias. We could not always obtain missing information from trial authors we contacted.

2.7.4 Limitations

Our review has some limitations. Similar to other systematic reviews of observational studies, proof of a causal association between social isolation and mortality cannot be established from our review. Although the effect estimates were calculated using the effect size of each study, which took into account potential confounding factors, we cannot exclude further confounding by unmeasured potential confounders. Additionally, differences in follow-up duration and the prevalence of social isolation in the populations studied may limit the consistency of the effect sizes reported. However, we tried to mitigate this by using a random-effects meta-analysis model along with a sensitivity analysis in which studies with extremes of follow-up were excluded.

2.7.5 Conclusion

This systematic review and meta-analysis show social isolation is associated with increased risk for all-cause mortality among adults. Given that the effects size shows a 37% increased risk and the data are from observational studies, GRADE criteria would indicate that the evidence is of low quality. However, there are no alternatives to observational data for the question being addressed. Our study suggests that addressing social isolation and providing health care for those with social isolation may reduce the risk for all-cause mortality, but this requires evaluation in large randomized trials. Such trials would need to consider issues related to ethics and feasibility.

2.7.6 Conflict of interest

This review received no funding.

Chapter 3. Social isolation and mortality from The Prospective Urban and Rural Epidemiological (PURE) study: Methods

3.1 RATIONALE OF THE STUDY

With the aging of populations, urbanization and fewer extended families, social isolation is a growing issue. Social isolation has been shown to be associated with negative health outcomes. To date, numerous studies have been conducted to assess the association between social isolation and negative health consequences. A recent systematic review and meta-analysis reported that social isolation was associated with a 29% increase in the risk of death (Holt-Lunstad et al., 2015), which is similar to the estimates we have provided in Chapter 2 based on our own meta-analysis. Other systematic reviews reported that poor social relationships were associated with increased risk of coronary heart disease by 29% and stroke by 32% (Valtorta et al., 2016). The majority of these studies were conducted in high-income countries and the target populations were community-dwelling elderly (Keller et al., 2003; Kreibig et al., 2014; Sarma et al., 2018; Sakurai et al., 2019). Furthermore, none of these studies reported whether the impact of social isolation on health outcomes was related to the presence of comorbidities (people who are sick may interact less with others), whether there are differences in the associations between social isolation and outcomes depending on country income levels (where social networks may be stronger but where conversely social services provided by governments or other organizations may be fewer) or in rural areas. The Prospective Urban and Rural Epidemiology (PURE) study is a cohort study of over 140,000 middle-aged adults from twenty-one high-income, middle-income, and low-income countries. Because of the diversity of the populations included in the PURE study with people from urban and rural settings and living in different economic settings, the PURE study provides a more comprehensive assessment of the association between social isolation and various health outcomes. Moreover, the PURE study collected extensive data on health behaviors, risk factors, and socioeconomic factors and these data enable an exploration as to the reasons why social isolation may be related to health outcomes.

3.2 STUDY OBJECTIVE

The objective was to examine the association between social isolation and mortality and incident diseases in middle-aged adults from high-, middle- and low-income countries in both urban and rural communities.

3.3 HYPOTHESIS

We hypothesized that social isolation is associated with increased risk for mortality and morbidity across diverse population with different socioeconomic status. We also hypothesized that the associations between social isolation and outcomes vary by economic levels of countries and urban vs. rural residence area.

3.4 OVERVIEW OF STUDY DESIGN

We analyzed data from the PURE study, which is a prospective, population-based cohort study that has recruited community-dwelling adults aged 35-70 years old across 21 countries (Yusuf et al., 2014). Countries selected were classified according to the World Bank scheme as high-, middle- and low-income countries at the beginning of the study in 2006. The high-income countries (HIC) include: Canada, Saudi Arabia, Sweden, and the United Arab Emirates. The middle-income countries (MIC) include: Argentina, Brazil, Chile, China, Colombia, Iran, Malaysia, Palestine, Philippines, Poland, South Africa, and Turkey. The low-income countries (LIC) include: Bangladesh, India, Pakistan, Tanzania, and Zimbabwe. Although some of the countries have been subsequently been reclassified with regards to economic status, for simplicity we have retained the countries within their original economic categories assigned at the beginning of the study. Information on lifestyles, health-related risk factors, the presence of chronic disease, and outcomes (including mortality and cause of death) were collected using standardized methods.

3.5 SAMPLING APPROACH

Sampling aimed to achieve a broadly representative sample of adults living in each community. Different sites used varying methods of approaching households. For example, in Canada, invitations to a central clinic were made through mail first, and then by telephone. In rural villages of China and India, community announcements were made through the local community leader, and then by door-to-door visits of each household. At least three attempts of contact were made in all methods of approach. If a household was eligible (at least 1 member was between the ages of 35 and 70 years), then all consent-giving individuals in the household were enrolled. Once recruited, all participants were invited to a study clinic to complete a standardized set of questionnaires and measurements. Information on the participants' vital status was obtained in person or by telephone calls at annual intervals. Information on medically certified death was accessed through administrative registries, where available. Otherwise, event documentation was obtained from household interviews, medical records, death certificates, verbal autopsies (Gajalakshmi et al., 2002), and other sources. Chinese population were excluded from analyses since relevant information on social isolation was not available, as such information was considered to be socially unacceptable.

3.6 DEVELOPMENT OF THE SOCIAL ISOLATION INDEX

In this analysis, we measured social isolation using an adaptation of the SNI (Berkman and Syme, 1979). The SNI is an objective measure of social relations, which combines in a single score information on marital status, interaction with family members or friends, relationship with religious groups, and membership in community organizations. In our study, the social isolation scale was constructed using five items from the PURE baseline questionnaire relevant to the SNI:

(1) marital status (scored as 1 for any of the following: never married, widowed, separated, or divorced; and 0 otherwise),

(2) "Can you count on your family members in a difficult situation?" (possible responses include: none, little, moderate/average, and a great deal) - scored as 1 for "none" or "little" and 0 for "moderate" or "a great deal",

(3) "Can you count on any organization in a difficult situation?" (possible responses include: none, little, moderate/average, and a

great deal - scored as 1 for "none" or "little" and 0 for "moderate" or "a great deal",

(4) "Are you a member of any religious group?" (yes=0, no=1) and

(5) "Are you a member of any social group?" (yes=0, no=1).

Thus, the social isolation scale ranges from 0 to 5. Individuals who score 0 are defined as having the most social support and those who score 5 are defined as having maximum social isolation. In preparatory work we examined whether it was better to use the scale as a continuous or binary variable, but confirmed the relationship with mortality was non-linear so it was more appropriate to treat social isolation as a binary variable. We therefore considered individuals with an index score of 4 or 5 as being socially isolated.

3.7 ETHICS

The PURE protocol was approved by the ethics committees of the participating centres. All participants provided informed consent.

3.8 OUTCOMES

The outcomes were all-cause mortality, cardiovascular mortality, non-cardiovascular mortality, and incident disease (myocardial infarction, stroke, heart failure, cardiovascular disease (CVD), cancer, pneumonia, chronic obstructive pulmonary disease

(COPD), and injury). CVD is defined as myocardial infarction, stroke and heart failure.

3.9 STATISTICAL ANALYSES

The characteristics of participants in each of the two groups (less versus more social isolation) were compared using chi-square tests for categorical variables and student t test or the Mann-Whitney U test for continuous variables. Multivariable logistic regression analyses with social isolation as a dependent variable were done to assess factors associated with social isolation. We used Cox proportional-hazard regression models to evaluate the relationship between social isolation and mortality. To account for the clustered nature of the data, we used shared frailty models in which the community to which each individual belonged, served as the clustering variable. In the models, the less socially isolated with a social isolation score of 0 to 3, served as the reference group. The adjusted model included following baseline variables; age, sex, education attainment (pre-secondary, secondary or post-secondary education), residence area (rural or urban area), country income (LIC, MIC- or HIC), smoking, alcohol use, physical inactivity, diet score, hypertension, diabetes, coronary artery disease, depression, and disabilities. We also performed Cox regression analyses using the adjusted model to evaluate the relationship between social isolation and incident disease (myocardial infarction, stroke, heart failure, CVD, cancer, pneumonia, COPD, and injury).

Physical inactivity was assessed using the long-form International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003) and calculated as a total of occupation, transportation, housework, and recreational activity reported in metabolic equivalents (MET) ×

minutes per week. Physical activity was also reported in minutes per week of moderate intensity physical activity using the equation where minutes reported in each physical activity domain on the IPAQ by the participant are weighted relative to moderate intensity physical activity. Physical inactivity was defined as physical activity level < 600 MET × minutes per week, which corresponds to < 150 minutes of moderate intensity physical activity per week (World Health Organization, 2010). Disability was assessed using the PURE baseline questionnaire asking whether they have trouble grasping/handling with fingers, walking about (or require a walking stick cane/walker), bending down and picking up objects, reading, seeing a person from across the room (with glass worn), speaking, or hearing in a normal conversation. Then, individuals having none of those items were scored as 0, those having one item were scored as 1, and those having two and more were scored as 2, indicating presence of multiple disabilities. Depression was assessed using PURE baseline questionnaire asking whether they have felt sad, blue or depressed for two weeks or longer in the previous year, and if so, whether they experienced loss of interest in pleasurable activities, tiredness, unintentional weight changes, difficulty sleeping or concentrating, feeling of worthless or thoughts about death during the same period. We classified participants with 4 or more of those 7 symptoms as having probable depression, consistent with previous validations studies (Kessler et al., 1998; Patten et al., 2000). A definition of frailty is an abbreviated adaptation of that initially proposed by Fried, et al (Fried et al., 2001). Reflecting data availability in PURE, we operationalized frailty phenotypically as the presence of at least two of: a) low muscle strength (less than the lowest quintile of handgrip strength for sex – 19kg for women and 30kg for men), b) involuntary loss of > 3kg body weight in the past six months, or c) low physical activity (less than the lowest quintile for sex – 679 MET-min/week for women and 510 MET-min/week for men). We defined pre-frailty as the presence of one of the preceding three characteristics. To quantify the contribution of risk factors to mortality, the population attributable fraction were calculated (Eide and Heuch, 2006) from a Cox proportional regression model, in which social isolation, education attainment, smoking, alcohol, physical inactivity, diet quality, hypertension, diabetes, and depression were included. STATA 15.1 (StataCorp, College Station, TX, USA) was used for statistical analyses and graphs.

3.10 CHARACTERISTICS OF PARTICIPANTS WITH AND WITHOUT SOCIAL ISOLATION

A total of 152,592 individuals were enrolled between July 6, 2005, and Jun 2, 2016, of whom 141,311 (92.6%) with the social isolation scale recorded were included in this study. Among them, the proportions of participants from high-, middle-, and low-income countries were 12.8% (N=18,046), 60.2% (N=85,037), and 27.1% (N=38,228), respectively. The prevalence of social isolation (the social isolation score of 4 or 5) was 11.8% (N=16,649). Baseline characteristics showed that the socially isolated were older and more likely to be women. The socially isolated had higher prevalence of comorbid diseases including hypertension, diabetes mellitus, coronary artery disease, stroke, cancer, COPD, depression as well as disabilities (Table 5). Table 6 shows participants' characteristics associated with social isolation. Age, women, and low education level were associated with increased odds of being socially isolated. Employment status was inversely associated with social isolation. The socially isolated were more common in urban areas and low- or middle-income countries. Current smoking, poor diet, and disabilities were associated with social isolation.

Table 5. Characteristics of study participants with and without social isolation

Characteristic	No social isolation (N=124,662)	Social isolation (N=16,649)	p value Univariate analysis
Age, year	50.7 ± 9.7	52.6 ± 10.4	< 0.0001
Women, (%)	72,544 (57.9)	12,548 (74.5)	< 0.0001
Hypertension, (%)	29,524 (23.6)	4,947 (29.4)	< 0.0001
Diabetes Mellitus, (%)	11,346 (9.1)	1,712 (10.2)	< 0.0001
Coronary artery disease, (%)	4,751 (3.8)	848 (5.0)	< 0.0001
Stroke, (%)	1,795 (1.4)	390 (2.3)	< 0.0001
Cancer, (%)	2,201 (1.8)	378 (2.2)	< 0.0001
Chronic obstructive pulmonary disease, (%)	1,174 (1.1)	371 (2.2)	< 0.0001
Depression, (%)	18,377 (14.8)	3,223 (19.2)	< 0.0001

Table 6. Multivariable logistic regression analyses with social isolation as a dependent variable

	Adjusted Odds Ratio (95% CI)
Age, 10-year increase	1.12 (1.09-1.16)
Women (vs. men)	2.37 (2.23-2.51)
Education attainment level Pre-secondary (vs. secondary or post-secondary)	1.42 (1.34-1.51)
Employment (vs. unemployment)	0.93 (0.87-0.98)
Residence area Urban (vs. rural)	1.68 (1.58-1.78)

Country income level (high as reference)	
Middle	1.22 (1.13-1.31)
Low	1.13 (1.03-1.25)
Current smoking (vs. former or never smoking)	1.37 (1.28-1.46)
Current alcohol use (vs. former or never drinking)	1.01 (0.95-1.07)
Physical inactivity (vs. WHO recommended physical activity)	1.05 (0.97-1.14)
Low diet score (lowest tertile of diet score) (vs. the other two tertiles)	1.26 (1.19-1.33)
Number of comorbidities ≥2 (vs. one or no comorbidities)	1.07 (0.98-1.18)
Number of disabilities ≥2 (vs. one or no disabilities)	1.30 (1.22-1.38)
Frailty (vs. pre-frailty or robust)	1.02 (0.91-1.15)

Odds ratios were adjusted for age, sex, education attainment, employment status, residence area, country income level, smoking, alcohol, presence of physical inactivity, diet score, presence of comorbidities, presence of disabilities, and presence of frailty

3.11 SOCIAL ISOLATION BY COUNTRY INCOME

The age-sex adjusted prevalence of social isolation in low-, middle-, and high-income countries were 8.2%, 14.1%, and 11.9%, respectively (Figure 7). Table 7 shows the patients' characteristics associated with social isolation. Women and disabilities were consistently associated with increased odds of being socially isolated regardless of country income levels. The directions of the association between other factors and social isolation were inconsistent in different country groupings. For example, low education and unemployment were strongly associated with social isolation in LICs contrary to MICs or HICs. Age and employment status were not associated with social isolation in HICs as opposed to LICs or MICs.

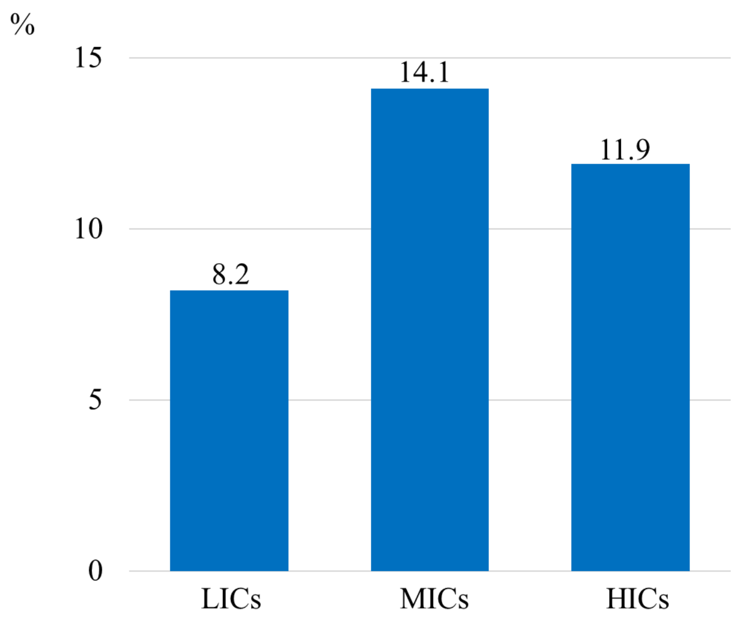

Figure 7. Age-sex adjusted prevalence of social isolation by country income levels

Legend. The prevalence of social isolation is the lowest in the low-income countries. LICs=low-income countries. MICs=middle-income countries. HICs=high-income countries.

Table 7. Multivariable logistic regression analyses with social isolation as a dependent variable by country income levels

Variables	Adjusted Odds Ratio (95% CI)			
	Country income level			
	Low (N=38,048)	Middle (N=85,896)	High (N=18,101)	P for interaction
Age, 10-year increase	1.12 (1.04-1.20)	1.25 (1.20-1.30)	0.98 (0.91-1.05)	<0.0001
Women (vs. men)	2.73 (2.29-3.27)	2.72 (2.53-2.93)	1.36 (1.20-1.53)	<0.0001
Education attainment level Pre-secondary (vs. secondary or post-secondary)	2.52 (2.12-2.99)	1.20 (1.11-1.29)	1.20 (0.99-1.44)	<0.0001
Employment (vs. unemployment)	0.34 (0.29-0.41)	1.12 (1.05-1.21)	1.03 (0.89-1.19)	<0.0001
Residence area Urban (vs. rural)	1.03 (0.88-1.19)	1.70 (1.58-1.83)	1.84 (1.58-2.14)	<0.0001
Current smoking (vs. former or never smoking)	0.87 (0.70-1.07)	1.39 (1.29-1.51)	1.94 (1.68-2.24)	<0.0001
Current alcohol use (vs. former or never drinking)	1.36 (1.08-1.72)	1.31 (1.22-1.40)	0.49 (0.43-0.56)	<0.0001
Physical inactivity (vs. WHO recommended physical activity)	0.85 (0.68-1.06)	0.77 (0.69-0.86)	1.82 (1.56-2.14)	<0.0001
Low diet score (lowest tertile of AHEI) (vs. the other two tertiles)	0.67 (0.56-0.81)	1.36 (1.27-1.46)	1.12 (0.99-1.26)	<0.0001
Number of comorbidities ≥2 (vs. one or no comorbidities)	0.85 (0.61-1.17)	1.03 (0.92-1.16)	1.23 (1.01-1.49)	0.001
Number of disabilities ≥2 (vs. one or no disabilities)	1.18 (1.001-1.40)	1.23 (1.14-1.32)	1.25 (1.05-1.49)	0.007
Frailty (vs. pre-frailty or robust)	1.12 (0.87-1.45)	1.07 (0.92-1.25)	1.44 (1.07-1.93)	<0.0001

Odds ratios were adjusted for age, sex, education attainment, employment status, residence area, smoking, alcohol, presence of physical inactivity, diet score, presence of comorbidities, presence of disabilities, and presence of frailty. AHEI: alternative healthy eating index.

3.12 SOCIAL ISOLATION BY RESIDENCE AREA

The age-sex adjusted prevalence of social isolation in rural and urban areas were 10.0% and 13.3%, respectively (Figure 8). Table 8 shows the patients' characteristics associated with social isolation. The patterns of all variables except for current alcohol use were consistent irrespective of rural or urban area of residence. Age, women, low education, current smoking, poor diet, and disabilities were associated with increased odds of being socially isolated while employment was inversely associated with social isolation. Current alcohol use was associated with social isolation in the rural areas while the inverse association between current alcohol use and social isolation was observed in the urban areas.

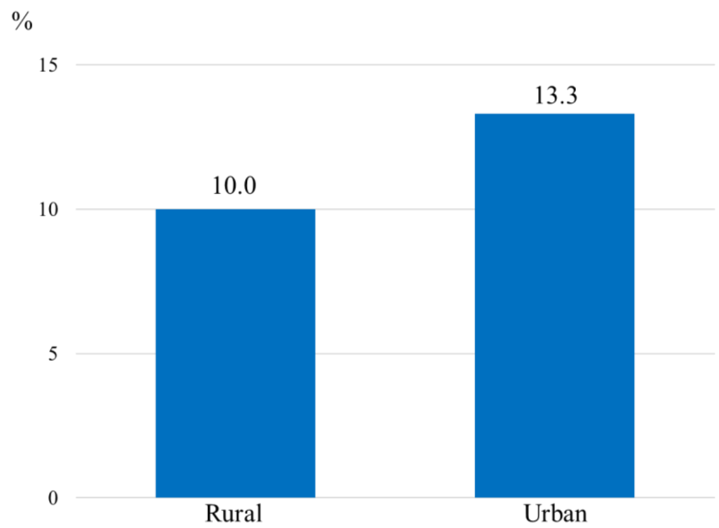

Figure 8. Age-sex adjusted prevalence of social isolation by residence areas

Legend. The prevalence of social isolation is higher in the urban areas.

Table 8. Multivariable logistic regression analyses with social isolation as a dependent variable by residence areas

Variables	Odds ratio (95% CI)		
	Residence area		
	Rural (N=62,318)	Urban (N=79,727)	P for interaction
Age, 10-year increase	1.11 (1.06-1.17)	1.11 (1.07-1.15)	0.4
Women (vs. men)	1.88 (1.70-2.07)	2.71 (2.52-2.91)	<0.0001
Education attainment level Pre-secondary (vs. secondary or post-secondary)	1.78 (1.61-1.97)	1.31 (1.22-1.41)	<0.0001
Employment (vs. unemployment)	0.98 (0.89-1.08)	0.87 (0.81-0.94)	0.02
Current smoking (vs. former or never smoking)	1.25 (1.12-1.40)	1.43 (1.32-1.55)	0.7
Current alcohol use (vs. former or never drinking)	1.13 (1.02-1.25)	0.90 (0.84-0.97)	0.003
Physical inactivity (vs. WHO recommended physical activity)	0.94 (0.81-1.09)	1.12 (1.02-1.24)	0.3
Low diet score (lowest tertile of AHEI) (vs. the other two tertiles)	1.14 (1.04-1.26)	1.36 (1.28-1.46)	0.004
Number of comorbidities ≥2 (vs. one or no comorbidities)	1.07 (0.91-1.27)	1.08 (0.96-1.21)	0.9
Number of disabilities ≥2 (vs. one or no disabilities)	1.48 (1.33-1.64)	1.23 (1.14-1.33)	0.01
Frailty (vs. pre-frailty or robust)	1.17 (0.97-1.41)	0.95 (0.82-1.11)	0.3

3.13 ASSOCIATION BETWEEN SOCIAL ISOLATION AND MORTALITY

Survival analyses were conducted in 115,022 (81.4%) individuals whose vital status were available. During the mean follow-up of 8.8 years, we observed 9,007 (7.8%) deaths (2,605 deaths from cardiovascular disease and 6,402 deaths from non-cardiovascular disease). Kaplan-Meier curves show that all-cause mortality is significantly higher in the socially isolated (Figure 9). Multivariable Cox regression analyses for all-cause, cardiovascular and non-cardiovascular mortality are presented in Figure 10. HRs are adjusted for age, sex, education attainment, residence area, country income, smoking, alcohol use, physical inactivity, diet score, hypertension, diabetes, coronary artery disease, depression, and disabilities with the community as the cluster variable. The adjusted HR for social isolation on all-cause mortality was 1.26 (95% CI, 1.16-1.36). The adjusted HR for social isolation on cardiovascular- and non-cardiovascular mortality were 1.30 (95% CI, 1.12-1.50), and 1.25 (95% CI, 1.14-1.38), respectively. Stratified analyses for the association between social isolation and all-cause mortality were performed since there were significant interaction effects on the association for age group, sex, residence area (rural or urban), and country income level. HR for social isolation on all-cause mortality stratified by age group, sex, residence area and country income level are shown in Table 9. Social isolation was consistently associated with increased risk of all-cause mortality regardless of age group, sex, residence area, and country income level while the magnitude of the association between social isolation and all-cause mortality was more prominent in younger adults, men, and people living in urban areas. Population attributable fractions were examined to quantify the contribution of social isolation to all-cause mortality. The population attributable fraction of social isolation was 2.6% (Figure 11). Regional variations in mortality risks of social isolation are shown in Table 10. Overall, the mortality risk of social isolation was observed across regions with random variation, possibly due to small number of events in Middle East and Southeast Asia.

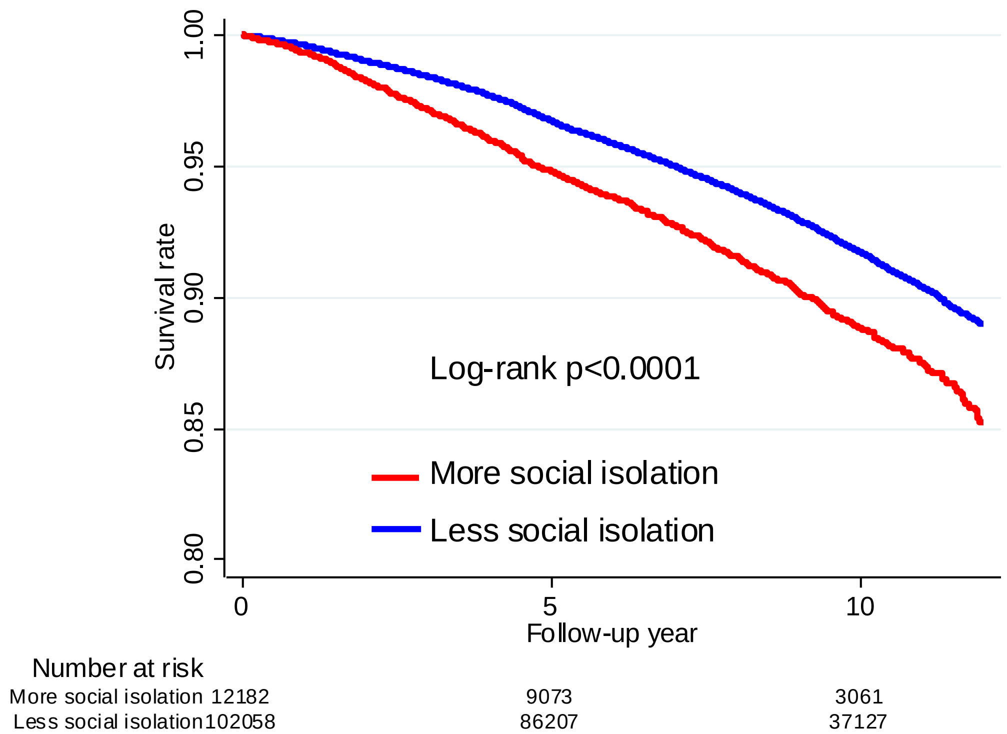

Figure 9. Kaplan-Meier curves for all-cause mortality

Legend: Event-free survival rate for all-cause mortality is significantly lower in the more socially isolated.

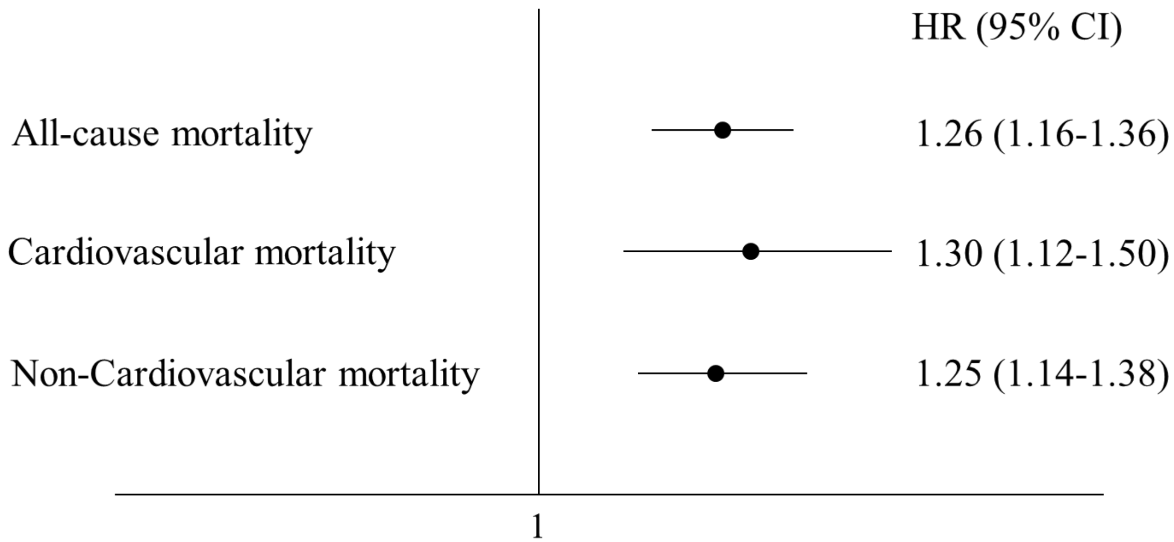

Figure 10. Multivariable Cox regression analyses for the association between social isolation and mortality

Legend: Social isolation is associated with increased risk for mortality. Hazard ratios are adjusted for age, sex, education attainment, residence area, country income, smoking, alcohol use, physical inactivity, diet score, hypertension, diabetes, coronary artery disease, depression, disabilities and community as a shared-frailty variable.

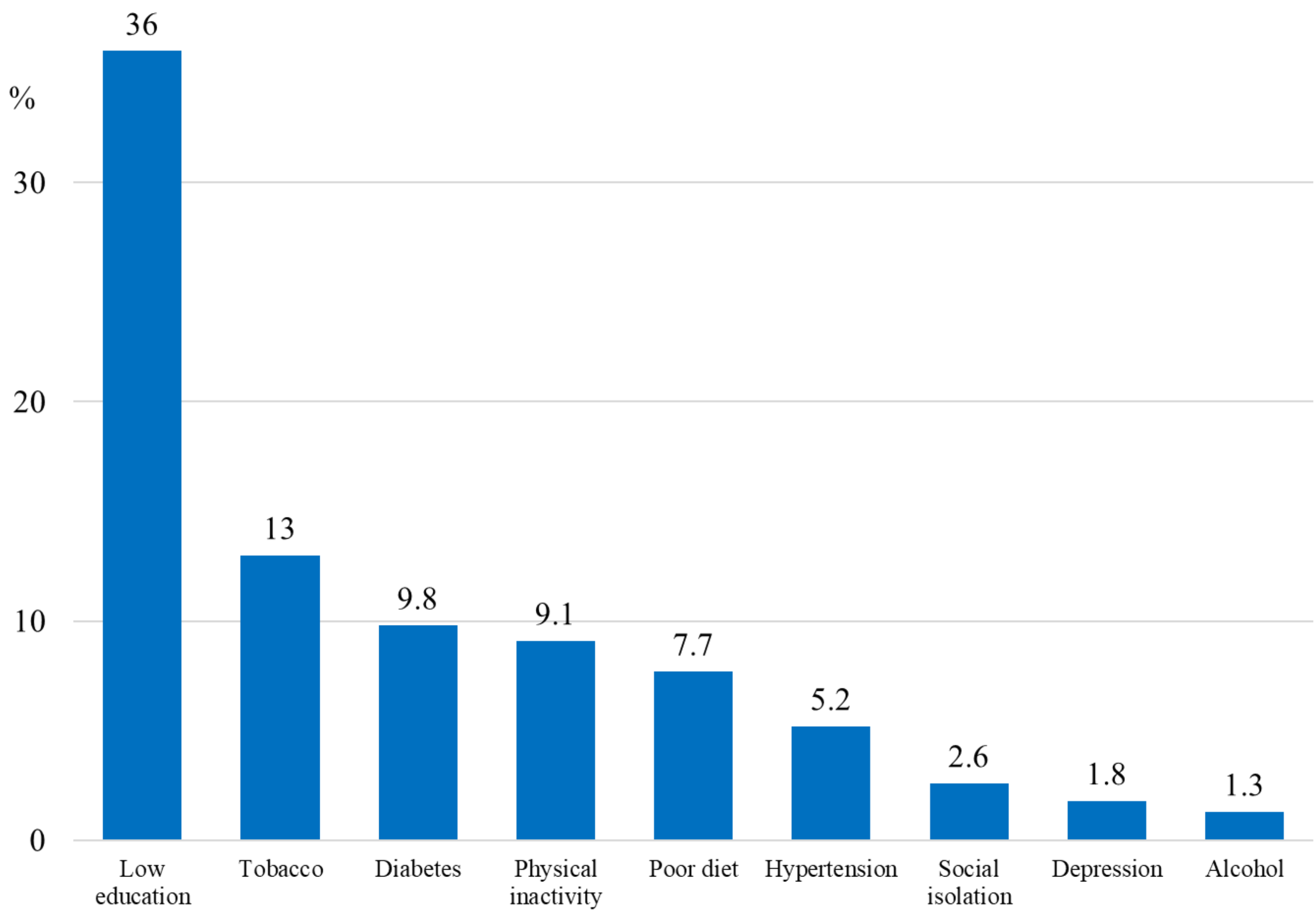

Figure 11. The population attributable fraction of mortality for risk factors in the overall population

Legend: Social isolation is a significant contributor to mortality in the whole study participants. Education and smoking substantially contributed to mortality.

Table 9. Risk of mortality stratified by variables and social isolation

Subgroups	All-cause mortality	p for interaction
Age category		0.001
< 60 years	1.36 (1.20-1.54)	
≥ 60 years	1.20 (1.08-1.33)	
Sex		0.001
Women	1.22 (1.11-1.36)	
Men	1.40 (1.23-1.59)	
Residence area		0.004
Urban	1.34 (1.20-1.50)	
Rural	1.19 (1.07-1.33)	
Country income level		0.005
High	1.40 (1.11-1.78)	
Middle	1.24 (1.13-1.35)	
Low	1.43 (1.26-1.62)	

Table 10. Regional variations in the mortality risk of social isolation

	All-cause mortality					
	Social isolation		No social isolation			
Regions	Number of events	Incidence rate (95% CI) (per 1000 person years)	Number of events	Incidence rate (95% CI) (per 1000 person years)	HR (95% CI) of social isolation	p for interaction
						0.002
North America/Europe	127	7.1 (6.0-8.5)	693	4.0 (3.7-4.3)	1.49 (1.23-1.82)	
South America	273	7.6 (6.7-8.6)	1,220	6.6 (6.2-7.0)	1.12 (0.98-1.29)	
Middle East	45	5.1 (3.8-6.9)	238	3.2 (2.9-3.7)	0.91 (0.61-1.36)	
Southeast Asia	95	13.6 (11.2-16.7)	1,337	11.6 (11.0-12.2)	1.09 (0.87-1.35)	
South Asia	212	21.7 (18.9-24.8)	3,915	12.0 (11.7-12.4)	1.37 (1.18-1.58)	
Africa	297	23.1 (20.6-25.9)	550	16.7 (15.3-18.1)	1.47 (1.27-1.71)	

3.14 ASSOCIATION BETWEEN SOCIAL ISOLATION AND INCIDENT DISEASE

During follow-up, a new myocardial infarction occurred in 3,311 (2.9%), a new stroke in 2,072 (1.8%), new heart failure in 804 (0.7%), a new cancer in 4,197 (3.6%), pneumonia in 2,465 (2.1%), a new diagnosis of COPD in 1,394 (1.2%), and hospitalization for injury in 13,311 (11.6%). Figure 12 shows that social isolation was associated with increased risk of stroke (HR 1.25, 95% CI 1.08-1.46) and CVD (HR 1.11, 95% CI 1.01-1.22). For non-cardiovascular disease, a significant association was observed only for injury (HR 1.09, 95% CI 1.02-1.16). Social isolation was associated with risk of any disease or injury that included all incident disease and injury.

To further examine the mortality risk of social isolation, case fatality rates within 90 days from the occurrence of new illnesses were assessed for myocardial infarction, stroke, heart failure, CVD, cancer, pneumonia, COPD, and injury. Only for stroke was the case fatality rates higher in the socially isolated, indicating socially isolated individuals are less likely to survive within 90 days after they develop stroke (Table 11). The higher case fatality rates from stroke in the socially isolated, despite finding of no association between social isolation and incident stroke, could partly explain their increased risk of cardiovascular mortality. To date, there is no evidence that people with social isolation have higher case fatality rates from both cardiovascular and non-cardiovascular disease compared to those without. Our results suggest that special attention should be paid to the socially isolated patients with stroke since the higher case fatality rates from stroke might have been caused by inadequate access, leading to delayed care in acute phase of stroke and lack of continuity of treatment after discharge for prevention of post-stroke complications and secondary prevention of cardiovascular events.

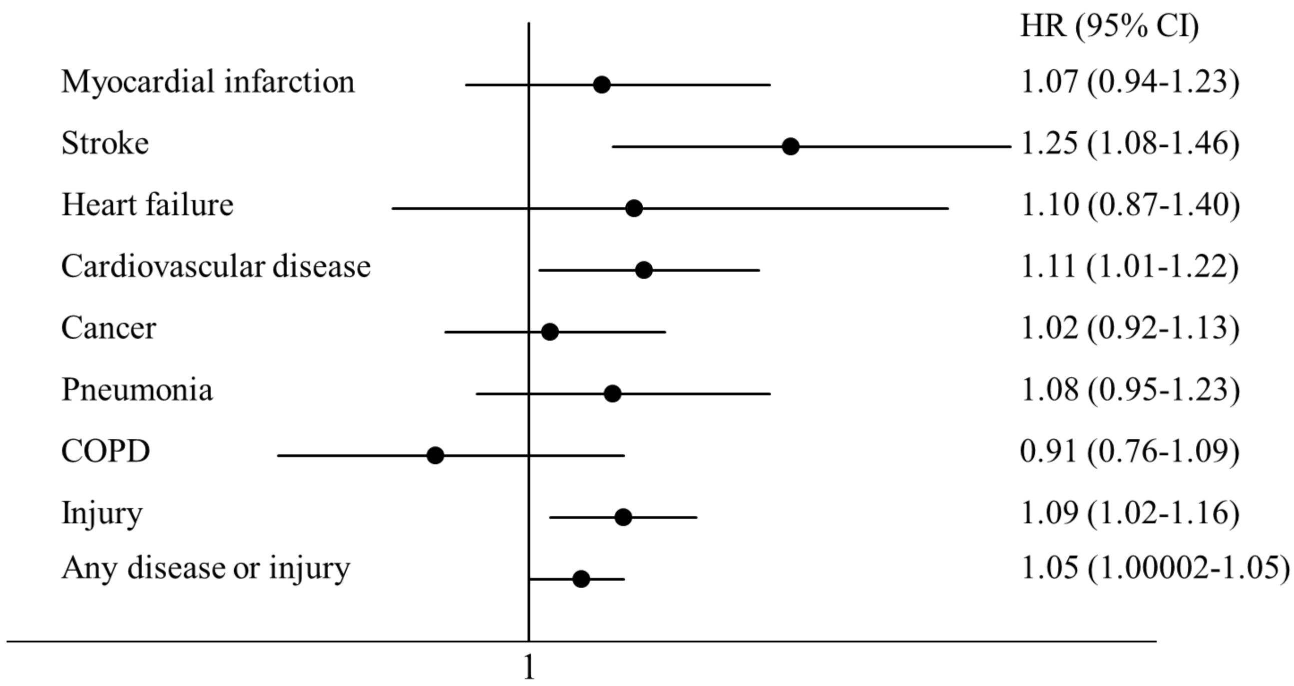

Figure 12. Multivariable Cox regression analyses for the association between social isolation and incident diseases

Legend: Social isolation is significantly associated with increased risk of stroke, cardiovascular disease, injury. Social isolation is also associated with increased risk of any new disease or injury. COPD=chronic obstructive pulmonary disease.

Table 11. Case fatality rates (95% CI) over 90 days from the occurrence of a new illness

	MI	Stroke	Heart failure	CVD	Cancer	Pneumonia	COPD	Injury
No social isolation	36.0% (34.2-37.9)	19.1% (17.3-21.0)	21.8% (18.8-25.1)	28.1% (26.8-29.4)	11.9% (10.9-13.0)	10.0% (8.8-11.4)	3.3% (2.4-4.4)	3.1% (2.8-3.4)
Social isolation	31.4% (25.7-37.5)	29.0% (23.6-35.0)	24.0% (16.4-33.0)	27.9% (24.2-31.8)	14.1% (11.2-17.5)	9.1% (6.4-12.6)	4.5% (2.0-8.7)	2.9% (2.0-3.8)

MI=myocardial infarction. CVD=cardiovascular disease. COPD=chronic obstructive pulmonary disease.

Chapter 4. Social isolation and mortality from The Prospective Urban and Rural Epidemiological (PURE) study: Discussion

4.1 OVERVIEW OF MAIN FINDINGS

The main findings of this study using the PURE dataset are that: 1) factors associated with social isolation differ across low-, middle- and high-income countries; 2) social isolation is significantly associated with increased risk of all-cause, cardiovascular and non-cardiovascular mortality; and 3) social isolation is associated with incident diseases that include stroke, cardiovascular disease and injury.

4.2 CHARACTERISTICS ASSOCIATED WITH SOCIAL ISOLATION

4.2.1 Profiles of social isolation in the whole study population

Our study shows that factors associated with social isolation were age, women, low education, unemployment, urban area of living, and low- or middle-country income. Previous studies have shown that older adults are at risk of being socially isolated due to limited mobility caused by chronic illnesses and disabilities or reduced social ties through life events such as retirement or loss of their spouses, family members or friends (Holt-Lunstad et al., 2015; Iliffe et al., 2007; Pantell et al., 2013). Regarding gender difference in the prevalence of social isolation, mixed results have been reported (Shankar et al., 2011; Steptoe et al., 2013; Vandervoort, 2000) while social isolation was more common among women in the present study. The substantially strong association between women and social isolation in our study population might be explained by limited social contacts among women through less economic opportunities in terms of education and occupation due to gender inequalities which have been observed in some countries, particularly developing countries. In line with prior research (McPherson et al., 2006; Shankar et al., 2011), low educational attainment was associated with social isolation. Education could help people develop skills related to communication and collaboration, which are essential to build interpersonal relationships. Besides that, educated people are more likely to have job opportunities, which could expand their social network.

The associations between current smoking and poor diet, and social isolation observed in our study, are supported by evidence that the socially isolated tend to engage in unhealthy lifestyle behaviors including smoking, excessive alcohol consumption, physical inactivity, and unhealthy diet (Kobayashi and Steptoe, 2018; Shankar et al., 2011; Yang et al., 2013). Social relationships could mitigate harmful behaviors and promote healthy behaviors. Social isolation is considered to lead to adverse health-related behaviors through lack of self-interest and loss of motivation. In a French cohort (Berkman et al., 2004) in which middle-aged men and women were included, socially isolated men were more likely to be current smokers and to have heavy episodic drinking while no similar pattern was observed in socially isolated women. Both men and women with social isolation had poorer self-rated health and more frequent depressive symptoms. Prior research reported that socially isolated people were more likely to smoke. Smokers might be forced to move to periphery of social network under pressures of smoking-related health concerns, which might render them social isolated (Kobayashi and Steptoe, 2018; Lauder et al., 2006). Research also showed socially isolated individuals were less likely to quit smoking as compared to those with social ties (Christakis and Fowler, 2008). Social connection could increase likelihood of engaging in health-promoting behaviors such as smoking cessation and physical activity, presumably because people with social connections may receive advice or support from other people, while social isolation might reduce people's sense of obligation to stay healthy for their family members or friends, which results in engaging in unhealthy behaviors.

Social networks could shrink with both physical barriers such as disabilities and chronic diseases (Havens et al., 2004; Locher et al., 2005), which could support our findings showing the association between social isolation and physical barriers including disabilities, comorbidities, and frailty.

4.2.2 Profiles of social isolation by country income

Our study shows that factors associated with social isolation irrespective of country income levels were women and disabilities. High age is not associated with social isolation in HICs as opposed to LICs or MICs, which could be partly explained by better social networks and community services for the elderly in high-income countries which have fewer extended families than low- or middle-income countries. Current smoking was associated with social isolation in a positive graded manner according to income levels. Smokers might be forced to move to periphery of social network that could render them socially isolated under pressures of smoking-related health concerns, especially in HICs where pressures of smoking cessation are more prominent and public smoking is more strictly restricted. For the other variables assessed at baseline, no definite patterns across different country income levels were observed for the association with social isolation. In LICs as opposed to MICs or HICs, low education and unemployment were strongly associated with social isolation, suggesting that social connectedness could be affected by economic opportunities more substantially in LICs. Urban area of living was the associated factor in MICs and HICs. Urbanized communities might cause weak social connectedness through lack of social contacts or cooperation with others accompanied by individualism especially in highly developed countries. The different characteristics associated with social isolation in our population could be explained by their diverse socioeconomic status including country income level, living area, degree of education attainment, and employment status. To date, there is no evidence as to characteristics of social isolation across different country income levels since many studies have focused on individuals in HICs including U.K., Canada, as well as Japan. One of novel findings in our study is that older adults, low education, and unemployment which have been considered to cause low frequency of social contacts, are the risk of social isolation in LICs while no associations are observed for these factors in HICs. In highly developed societies, various factors affect social relationships because creation and maintenance of social networks have been complicated through substantial development of digital social network using information technologies.

4.2.3 Profiles of social isolation by residence area

The profiles of social isolation in rural areas were considerably similar to those in urban areas with regard to age, women, low education, unemployment, current smoking, poor diet, and disabilities. Rural areas are characterized with poor health behaviors and negative health outcomes. In rural areas, population density is relatively low and people face challenges in reaching resources such as education, occupation, public transportation, as well as access to the Internet, which are related to creation or maintenance of social connectedness. Nevertheless, the prevalence of social isolation was higher in urban areas, suggesting that social connectedness is weaker in the areas compared to the rural areas possibly through lack of interest with other people or lack of interpersonal relationships due to individualistic societies. Despite the similarities in factors associated with social isolation, the magnitude of certain associations was different between rural and urban areas. For example, a stronger association was observed for women in urban areas, indicating women in the areas had smaller social networks than their rural peers possibly due to economic independence or lack of personal relationships with their neighbors which could hinder them from building social relationships. The stronger association between disabilities and social isolation in rural areas as compared to urban areas indicates that access to healthcare have been developed and social supports for those people from local communities or governments have been better implemented in urban areas.

4.3 SOCIAL ISOLATION AND NEGATIVE HEALTH CONSEQUENCES

4.3.1 Social isolation and mortality

In line with previous studies along with our systematic review and meta-analysis presented in the chapter 2, our study shows that social isolation is associated with 26% increased risk for all-cause mortality. The adjusted HR for cardiovascular- and non-cardiovascular mortality in the socially isolated individuals were 1.30 (95% CI; 1.12-1.50) and 1.25 (95% CI; 1.14-1.38), respectively. Social isolation was consistently associated with increased risk for all-cause mortality in stratified analyses for age group, sex, rural or urban area of living and country income level while the magnitude of the mortality risk was greater in young adults, men, and those living in urban areas. One of the novel findings in our study is that social isolation is universally the risk of mortality across the diverse population from urban and rural settings and different socioeconomic settings.

Previous studies have highlighted pathways through which social relationships can influence mortality risk: behavioral (smoking, alcohol, physical inactivity and poor diet); psychological (low self-esteem and self-efficacy); and biological (response to stress (increased cortisol secretion), deterioration in immune function, weight gain, and cardiovascular reactivity). Besides that, the socially isolated tend to have chronic illnesses which include chronic lung disease, arthritis, and impaired mobility (Steptoe et al., 2013), which may render people with social isolation vulnerable to diseases. There has been a paucity of data regarding underlying mechanisms through which social isolation has influence on mortality. A study using data 466,901 residents in the UK with the mean age of 57 years and the mean follow-up of 6.5 years, reported that lifestyle behaviors (i.e. smoking, alcohol) and socioeconomic factors (i.e. education, household income) could explain the mortality risk of social isolation (Elovainio et al., 2017).

Social connection could increase likelihood of engaging in health-promoting behaviors such as smoking cessation and physical activity, presumably because people with social connections may receive advice or support from other people, while social isolation might reduce people’s sense of obligation to stay healthy for their family members or friends, which results in engaging in unhealthy behaviors and eventually leading to morbidities and mortality.

People might develop social isolation through lack of social networks and less frequency of contact with others. Social networks could shrink with both physical barriers such as disabilities and chronic diseases (Havens et al., 2004; Locher et al., 2005), and psychological barriers including altered mental status and cognitive dysfunction (Havens et al., 2004). In this study, the participants with social isolation as compared to those without were more likely to have comorbidities including hypertension, diabetes mellitus, COPD, prior coronary artery disease, prior stroke, prior cancer, frailty, disabilities as well as depression. The socially isolated were considered to carry substantial risk of developing mortality and morbidity related to those comorbidities.

Social supports could provide people with assistance and encouragement which may underlie the reason why they are apt to seek health care and adhere to the therapies. Lack of social support would affect health through inadequate resources that can be used to avoid the risk of disease, minimize their consequences, or influence health-promoting behaviors (Campbell et al., 2000; Seeman, 2000). The influence of social isolation on utilization of healthcare services vary depending on different settings of the studies, different measures of social isolation and healthcare usage, and patients’ backgrounds (Coulton and Frost, 1982; Foreman et al., 1998; Penning, 1995). A recent systematic review and narrative synthesis from 126 articles focusing on older adults in high-income countries, found the association between weak social networks and increased rates of hospital readmissions and long hospital stays while no associations were found between social networks and demands on physician visits or emergency department visit (Valtorta et al., 2018). People with social isolation might be dependent on healthcare providers with increased frequency of visits to clinics or emergency department because they may have low levels of self-rated physical health (Cornwell and Waite, 2009) or they may seek healthcare services as a substitute for social relationships (Coulton and Frost, 1982). Conversely, some might be less likely to access the services due to limited access to social networks and lack of the support provided by the networks, which include transportation, financial aid and health-related advice. Others tend not to care for their health, not to seek help to healthcare system, or dare not to visit heath care facilities even if they find themselves to have some symptoms or health concerns because they may experience feeling of low self-esteem (Stokes, 2019), which place fewer demands on healthcare services and partly explain our results of lack of the association between social isolation and incident disease. As a result, unexpected visits or admissions may increase due to avoidable issues if they had adequate access to healthcare resources. Future research should examine an association between healthcare access and social isolation in relation to health outcomes.

Other novel finding is regional variations that were observed for the mortality risk associated with social isolation. Social isolation was associated with increased risk of all-cause mortality in North America/Europe, South America, South Asia and Africa while no significant associations were found in Middle East and Southeast Asia. To date, substantial improvements for prevention and treatment of non-communicable disease have been made worldwide. However, there remains barriers in implementation of evidence-based medical treatments, particularly in low- and middle-income countries (Joseph et al., 2017). Besides that, diversities in lifestyle, socioeconomic, and cultural factors exist, which result in different disease patterns as well as different patterns in cause of death. In North America and Western Europe where evidence-based medicine has been well implemented, social isolation might be relatively neglected issue that could contribute to higher mortality while in LICs, education, smoking and diet quality would play the main roles that affect health. Also, in Middle East and Southeast regions where collectivism as opposed to individualism has taken rooted, even the vulnerable population such as those with social isolation could be better supported by others or non-governmental organizations, which might neutralize the mortality risk of social isolation.

4.3.2 Social isolation and incident disease

Our study shows that social isolation was associated with increased risk of cardiovascular disease and stroke. Previous studies have shown conflicting results as to the association between social isolation and incident cardiovascular disease (Shankar et al., 2011; Valtorta et al., 2018, 2016). A meta-analysis reported an increased risk of coronary heart disease and stroke in individuals with social isolation (Valtorta et al., 2016) while recent studies reported no association between social isolation and cardiovascular disease (Hakulinen et al., 2018; Valtorta et al., 2018). Inconsistent results across studies could be explained by differences in study populations, methodologies and definitions of social isolation. Individuals with social isolation are considered at high risk of developing atherosclerotic diseases through unhealthy lifestyle behaviors including smoking, excessive alcohol consumption, poor diet, and physical inactivity. Besides that the socially isolated might be less likely to access to healthcare because the socially isolated tend not to care for their health and dare not to visit healthcare facilities even if they have some symptoms or health concerns, indicating that the socially isolated would have morbidities which could be underdiagnosed due to insufficient healthcare access.

Evidence for the association between social isolation and non-cardiovascular disease is scarce as opposed to data for cardiovascular disease. Our finding is that a significant association was observed only for injury among non-cardiovascular diseases despite that non-cardiovascular mortality was higher in people with social isolation than those without social isolation. The increased risk of non-cardiovascular mortality in the socially isolated might be explained by suicide, accident, and drug toxicity that are related to social isolation though detail information on those events were not available. Previous studies showed that socially isolated individuals are at high risk of developing cancer, pulmonary disease as well as infection. In a Japanese prospective study, lack of social support was associated with an increased risk of colorectal cancer among men without prior diagnosis of cancer. The similar association was found among both breast and prostate cancer patients (Kroenke et al., 2017; Zhu et al., 2019). Other studies reported that individuals with less social ties were at higher risk of developing respiratory disease (Cohen et al., 1997; Jordan et al., 2008). The observed association between social isolation and increased risk for injury in our study indicates that the socially isolated are prone to fall possibly due to older age, disabilities, frailty, and comorbidities. Given that social isolation is related to mental health issues (Aylaz et al., 2012; Holt-Lunstad et al., 2010), they could get injured by suicidal attempts, or accidents after drug overuse or overdrinking.

The mechanisms linking social isolation and non-cardiovascular disease could be explained by older age, unhealthy lifestyle behaviors, pre-existing chronic illnesses and so on, even though risk factors vary depending on type of diseases. Unhealthy lifestyle including smoking, excessive alcohol intake, physical inactivity, and unhealthy diet could link social isolation and non-cardiovascular disease as well as cardiovascular disease. The other reason for the association between social isolation and incident disease is that the socially isolated tend to have long-term illnesses which include chronic lung disease, arthritis, and impaired mobility (Steptoe et al., 2013), which may render people with social isolation vulnerable to diseases. Also, prior studies suggested that social networks play a role in resisting infection through regulation of the immune system (Uchino et al., 1996). Our data did not support the association between social isolation and cancer, COPD, and pneumonia. Although inadequate utilization of healthcare services in the socially isolated might be related to underdiagnosis of these conditions, further studies are needed to confirm the association given the lack of evidence in the field. Meanwhile, a pathway between social isolation and health status is considered bidirectional since impaired health status could cause social isolation. Limited mobility due to disabilities as well as chronic diseases such as rheumatoid arthritis may render people socially isolated through social distancing such as less frequent contacts with others and limited access to social resources. People diagnosed with certain infectious disease may develop social isolation. Prior research reported that people diagnosed with HIV had limited social network size (Emlet, 2006). Stigma related to HIV and enacted stigma such as past experiences of discrimination, may lead to self-imposed isolation or exclusion from society, thereby those with HIV could be socially isolated (Emlet, 2006; Turan et al., 2016). In that aspect, people with social isolation might have carried risk of negative health consequences at the time of developing social isolation.

4.4 STRENGTHS OF THE STUDY

The novelty of the study is that the relationships between social isolation and health outcomes were evaluated in many different populations which have different social structures and the results demonstrated that social isolation generally increased mortality risk in most regions of the world regardless of country income level, in men and women and in urban and rural settings. Numerous observational studies have examined the association between social isolation and mortality and morbidity, but the evidence is largely limited to studies from North America and Western Europe, with very little data available from other regions of the world including Asia, South America, Africa, and the Middle East. Presently, it is not known whether the observations from North America and Western Europe can be extrapolated to other regions where socioeconomic factors, lifestyle factors, cultural factors, and disease prevalence differ markedly. Social isolation was associated with increased risk of all-cause mortality in North America/Europe, South America, South Asia and Africa, but not in Middle East and Southeast Asia. The observed difference might be explained by the relatively fewer number of deaths in the latter two regions, potential differences in lifestyle, family structure, socioeconomic, and cultural factors that could exist in different regions.

4.5 LIMITATIONS OF THE STUDY

Our study has certain limitations. First, it is not possible to exclude unmeasured confounding factors in this observational study, although a wide range of potential explanatory factors was evaluated when examining the association between social isolation and clinical outcomes in our study. Another issue is that 7.9% of study participants were excluded due to missing data on social isolation. We could not determine whether the missingness was random or informative. Therefore, sensitivity analyses with multiple imputation for missing value on social isolation scale were conducted. We also conducted other sensitivity analyses to address concerns related to reverse causality. In the analysis, individuals with baseline diseases and those who developed clinical outcomes within the first 2 years of follow-up were excluded. Our results did not change for our main study outcomes. Other limitation is that we did not evaluate the relationship between social isolation and quality-of-life which could affect people's health-related behaviors as well as their health consequences. Future research are needed to examine the relationship and further how the relationship underlies the increased risk of mortality in the socially isolated. Lastly, since this study included individuals with the age between 35 and 70, our findings cannot be generalizable beyond this age range. However, the study participants were recruited from 5 continents and 7 geographic regions (North America and Europe, South America, the Middle East, South Asia, Southeast Asia, and Africa) with a broad range of economic development including different country income status and residence area (urban or rural), which could enhance generalizability of our findings.

4.6 IMPLICATIONS FOR CLINICAL PRACTICE

Social isolation is associated with many risk factors, such as socioeconomic adversity, unhealthy lifestyles, worse mental wellbeing, and insufficient access to healthcare facilities, all of which could contribute to increase mortality and morbidity. Social isolation might alter adherence to medical treatments through lack of social support (Barth et al., 2010; Mason et al., 2016; Udell et al., 2012). Although the extent to which social isolation contributed to population mortality was modest in our study, as measured by the population attributable fraction of social isolation, it would be expected to increase as the number of people experiencing social isolation is projected to increase accompanied by aging society, which results in higher demand on taking measures for those vulnerable population. Our research findings can be applied or used by individuals with social isolation, public health providers including general practitioners, family doctors, nurses, and pharmacologists, public care givers such as social workers, and policy makers. We need to enhance awareness of the impact of social isolation on mortality and morbidity in both general population and health providers by data demonstrating that social isolation could lead health issues. Finally, we have to place emphasis on improvement of healthcare utilization as well as control for modifiable risk factors including smoking, excessive alcohol consumption, physical inactivity and unhealthy diet in order to reduce mortality and morbidity in individuals with social isolation.

4.7 CONCLUSIONS

Our study using the PURE dataset demonstrated increased mortality risk associated with social isolation among the diverse population with different socioeconomic status. This excess risk is consistently seen in high-, middle-, and low-income countries, in urban and rural settings, and also among men and women. The adverse effects of social isolation on mortality (if causal) can be partly mitigated by improving lifestyles, better treatment of comorbidities and better access to health care as a whole for this particularly vulnerable population.

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APPENDICES

Appendix 1. Search strategy for this systematic review

Study eligibility criteria

Type of study

In this systematic review, we will include studies that provide quantitative data regarding individuals' mortality and status of social isolation. We will include only studies that are prospective or retrospective cohorts in which social isolation was assessed in study participants at the study entry. Eligible studies would have examined and reported the incidence of mortality over the follow-up period. We will exclude publications that are a case-report or case-series design. We will apply no exclusion criteria regarding language in publication, or time or location.

Type of participants

We will include studies in which adults aged 18 years or older were involved and the effect of social isolation on all-cause mortality were evaluated among them.

Type of exposure

People with social isolation measured subjectively or objectively using assessment scales, will be compared to those without social isolation.

Outcome measures

All-cause mortality will be examined as the outcome and the pooled estimates of social isolation as a risk of all-cause mortality will be calculated.

Search methods for identification of studies

We will search for studies published up until June 2019 using electronic databases: MEDLINE (1946 to June 2019), EMBASE (1974 to June 2019), and PsycINFO (1806 to June 2019). We will include thesaurus and free text key terms including social isolation, mortality, death, cohort studies, prospective studies and retrospective studies. We will seek expert medical librarian support when needed and ensure that a complex search strategy is used with the respective Boolean operators and relevant search filters in each database. To complement the electronic database search, we will screen reference lists of past reviews and studies meeting the inclusion criteria. This is to ensure that potentially relevant studies are considered in our screening process. Two researchers will independently and in duplicate, screen titles and abstracts before assessing full records. The full text screen phase will utilize the same approach. Moreover, the data abstraction and risk of bias stages of this review will also utilize duplicate and independent screening and assessment. Disagreements will be settled by consensus discussion and 3rd party adjudication were used if needed.

Searching other resources

We will examine the reference lists of eligible articles to find other relevant studies.

Full electronic search strategies

1. MEDLINE search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Searched online 6/29/19 Strategy saved as: social isolation MEDLINE

# ▲	Searches	Results
1	social* isolat*.mp.	17229
2	Social Isolation/	12760
3	social isolation.mp.	16712
4	social isolations.mp.	5
5	or/1-4	17229
6	Mortality/	41703
7	Mortality, Premature/	918
8	mortality.mp.	1068256
9	Death/	17008
10	death.mp.	748118
11	or/6-10	1611879
12	risk:.mp. or exp cohort studies/ or between group:.tw.	3845168
13	exp Prospective Studies/	506358
14	exp Retrospective Studies/	756005
15	or/12-14	3845168
16	5 and 11 and 15	545

2. Embase search strategy

Database: Embase 1974 to Present

Searched online 6/29/19 Strategy saved as: social isolation Embase

# ▲	Searches	Results
1	social* isolat*.mp.	24198
2	social isolation/	20929
3	social isolation.mp.	23553
4	social isolate.mp.	8
5	or/1-4	24198
6	all cause mortality/	18161
7	all cause mortality.mp.	55952
8	mortality/	712120
9	mortality.mp.	1351833
10	death/	268991
11	death.mp.	1159626
12	or/6-11	2218283
13	(cohort or relative risk:).tw.	872409
14	exp prospective study/	529596
15	exp retrospective study/	788952
16	or/13-15	1937216
17	5 and 12 and 16	377

3. PsycINFO search strategy

Database: PsycINFO 1806 to present

Searched online 6/29/19 Strategy saved as: social isolation PsycINFO

# ▲	Searches	Results
1	exp Social Isolation/	7397
2	social isolation.mp.	14650
3	or/1-2	15100
4	exp "Death and Dying"/	37362
5	mortality.mp.	39895
6	death.mp.	92437
7	cardiovascular.mp.	34036
8	or/4-7	145885
9	cohort study.mp.	17574
10	exp PROSPECTIVE STUDIES/	539
11	exp RETROSPECTIVE STUDIES/	420
12	or/9-11	18445
13	3 and 8 and 12	11

Appendix 2. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	9
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	9, 10
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	10
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	10
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	CRD42020152351
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11, 12
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Available in Appendix

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	12, 79-81
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12, 12, 80, 81
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	12, 80
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	13
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	14
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	14

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	15
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	14, 15 and in flow diagram

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19, 20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	26, 27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 3, 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	32
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	34
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	34

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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