nature human behaviour

Article

https://doi.org/10.1038/s41562-023-01617-6

A systematic review and meta-analysis of 90 cohort studies of social isolation, loneliness and mortality

Received: 19 July 2022

Accepted: 27 April 2023

Published online: 19 June 2023

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The associations between social isolation, loneliness and the risk of mortality from all causes, cardiovascular disease (CVD) and cancer are controversial. We systematically reviewed prospective studies on the association between social isolation, loneliness and mortality outcomes in adults aged 18 years or older, as well as studies on these relationships in individuals with CVD or cancer, and conducted a meta-analysis. The study protocol was registered with PROSPERO (reg. no. CRD42022299959). A total of 90 prospective cohort studies including 2,205,199 individuals were included. Here we show that, in the general population, both social isolation and loneliness were significantly associated with an increased risk of all-cause mortality (pooled effect size for social isolation, 1.32; 95% confidence interval (CI), 1.26 to 1.39; $P < 0.001$; pooled effect size for loneliness, 1.14; 95% CI, 1.08 to 1.20; $P < 0.001$) and cancer mortality (pooled effect size for social isolation, 1.24; 95% CI, 1.19 to 1.28; $P < 0.001$; pooled effect size for loneliness, 1.09; 95% CI, 1.01 to 1.17; $P = 0.030$). Social isolation also increased the risk of CVD mortality (1.34; 95% CI, 1.25 to 1.44; $P < 0.001$). There was an increased risk of all-cause mortality in socially isolated individuals with CVD (1.28; 95% CI, 1.10 to 1.48; $P = 0.001$) or breast cancer (1.51; 95% CI, 1.34 to 1.70; $P < 0.001$), and individuals with breast cancer had a higher cancer-specific mortality owing to social isolation (1.33; 95% CI, 1.02 to 1.75; $P = 0.038$). Greater focus on social isolation and loneliness may help improve people's well-being and mortality risk.

Social relationships are essential to human well-being and play a vital role in the maintenance of health[1]. Social isolation (SI) and loneliness are reflections of the objective and subjective characteristics of impoverished social relationships, respectively[2]. Considerable research attention has been devoted to investigating SI, loneliness and the potential risk of death.

SI is a state that refers to an objective lack of (or limited) social contact with other people and is characterized by a person having a limited

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social network, having infrequent social contacts or possibly living alone[3]. By contrast, loneliness is a subjective feeling of distress, arising when there is a discrepancy between desired and actual social relationships[4]. Several possible pathways have been proposed to explain the adverse effects of SI and loneliness on health and mortality[5–7]. SI may promote unhealthy behaviours, such as malnutrition and physical inactivity[6], which may increase the risk of death. SI has also been associated with health-related biological processes, such as higher C-reactive protein and lipid levels and poorer immune function[5,8]. In terms of loneliness, mechanisms including deleterious health behaviours, sleep disorders, and neuroendocrine and immune dysfunction have been identified as contributing to the negative association of loneliness and health[7,9]. The findings of epidemiologic studies on the associations between SI, loneliness and mortality are controversial. Some studies have found a higher risk of mortality from all causes, cardiovascular disease (CVD) and cancer associated with SI and loneliness[10–13], whereas others have reported non-significant results[14–17]. The only meta-analysis[18] up to 2015 found that SI and loneliness were factors contributing to all-cause mortality, with SI increasing all-cause mortality by 29% (95% CI, 1.06 to 1.56) and loneliness increasing all-cause mortality by 26% (95% CI, 1.04 to 1.53). Many subsequent studies have been carried out on the relationship between SI or loneliness and mortality, but the results are inconsistent[12,14,19–21]. Additionally, studies have shown that the link between social support and health is bidirectional, which could lead to a vicious cycle where poor health causes patients to lose social support (for example, SI) over time, but patients tend to need social support more than the general population. However, no systematic review of an association of SI or loneliness with the risk of mortality in patient populations (for example, individuals with CVD or cancer) has been conducted.

We therefore conducted an updated and more comprehensive systematic review and meta-analysis to summarize the associations between SI, loneliness and risk of mortality from all causes, CVD and cancer in the general population, as well as in a subset of individuals with CVDs or breast/colorectal malignancies. Our findings can provide vital clarification to help in promoting population health management and improving primary health services.

Results

Literature search

We identified 14,358 records (9,328 for SI and 5,030 for loneliness) through electronic database searches of PubMed, Web of Science and Embase. After we excluded 14,176 articles that did not meet the selection criteria, 182 records remained (118 for SI and 64 for loneliness). Following a full-text review, 81 articles were further excluded for the following reasons: 28 studies did not consider SI or loneliness as an independent variable, 17 studies did not analyse mortality as an outcome variable, 20 studies had duplicated data, 13 studies had insufficient data, 2 studies enrolled individuals with HIV and HIV-infected/uninfected older veterans, and 1 study was conducted among older patients in the intensive care unit. Additionally, 18 articles analysing both SI and loneliness were retrieved repeatedly and later removed, and 7 studies were added after a manual search and review of the reference lists. The independent retrieval processes are shown in Fig. 1.

After the above steps, 90 prospective studies with 2,205,199 individuals were included in this systematic review and meta-analysis[10–17,19–100], among which 67 investigated the risk of all-cause mortality (38 for SI and 45 for loneliness; 16 were cross-repeats)[10–17,19–22,24,25,28,30–38,40,42–45,47,50,52,53,55,56,65–96], 17 investigated the risk of mortality owing to CVD or circulatory system diseases (12 for SI and 8 for loneliness; 3 were cross-repeats)[11,15–17,22,30,32,37,39,40,47,52,66,77,81,97,98] and 11 investigated the risk of cancer mortality (11 for SI and 3 for loneliness; 3 were cross-repeats)[15,16,22,26,29,30,32,37,52,60,66] in the general population. Moreover, in individuals with cancer, 6 studies investigated SI and all-cause mortality[41,48,59,61,62,64], and 7 studies analysed SI and cancer-specific mortality[41,46,48,59,61,62,64]. Among individuals with CVD, 10 studies analysed associations between SI (8 studies) or loneliness (4 studies; 2 were cross-repeats) and all-cause mortality[23,27,49,51,54,57,58,63,99,100].

Characteristics of the included studies

Supplementary Tables 5–9 present the characteristics of all included studies. Of the 90 included studies, 29 were conducted in the USA, and 61 were performed in other countries, such as the UK, Japan, Korea and Finland, with most (90%) conducted in developed countries. Publication dates ranged from 1986 to 2022, and the follow-up duration ranged from 2 to 24.4 years in general populations and from 6 months to 20.44 years in patient populations. Sample sizes ranged from 119 to 580,182 for SI and from 227 to 466,901 for loneliness. In total, 2,205,199 participants (1,485,469 for SI and 1,209,407 for loneliness) were included in this systematic review. All participants were aged 18 years or older, and most (70%) were aged 50 years or more. In most studies, controlling for confounders of conventional risk factors was carried out, including age, sex, body mass index, smoking and alcohol consumption. Other variables such as physical activity, education level, depression, cognitive function, diabetes and hypertension were also adjusted in some specific studies.

On the basis of the Newcastle–Ottawa scale, all studies had a low risk of bias in all components. A total of 43 studies had a rating of 7; 30 studies had a rating of 8, which was considered high quality; and 17 studies with a rating of 6 were considered medium quality. Supplementary Table 10 presents the details of the risk-of-bias assessment.

SI or loneliness and all-cause mortality

In total, 38 and 45 papers, including 1,485,469 and 1,209,407 participants, investigated the association of SI and loneliness, respectively, with all-cause mortality in the general population. The total pooled effect estimate was 1.32 (95% CI, 1.26 to 1.39; $P < 0.001$) for SI and 1.14 (95% CI, 1.08 to 1.20; $P < 0.001$) for loneliness (Fig. 2). Substantial heterogeneity was observed among the included studies ($I^2 = 77.8\%$, $P < 0.001$ for SI; $I^2 = 91.1\%$, $P < 0.001$ for loneliness). Significant publication bias was detected using funnel plots (Supplementary Fig. 1a) in the SI analysis, as well as in Egger's ($P = 0.006$) and Begg's ($P = 0.019$) tests. However, the pooled effect size was not substantially changed after adjustment using the trim-and-fill method (Supplementary Table 11). Little evidence of publication bias was observed in the loneliness analysis ($P = 0.465$ in Egger's test; $P = 0.021$ in Begg's test; Supplementary Fig. 1b). Additionally, five papers including 54,561 participants reported the combined effects of SI and loneliness on all-cause mortality when co-existing in the general population. The pooled effect estimate was 1.18 (95% CI, 1.05 to 1.32; $P < 0.001$) with significant heterogeneity ($I^2 = 79.2\%$, $P = 0.001$) (Supplementary Fig. 2a). No evidence of publication bias was detected (Egger's test, $P = 0.849$; Begg's test, $P = 0.806$) (Supplementary Table 11).

A total of 21 and 18 papers reported associations between SI and all-cause mortality among men and women, respectively, in the general population. The pooled effect estimate was 1.39 (95% CI, 1.27 to 1.51; $P < 0.001$; $I^2 = 78.6\%$; $P < 0.001$; Egger's test, $P = 0.003$; Begg's test, $P = 0.053$) in men and 1.44 (95% CI, 1.28 to 1.61; $P < 0.001$; $I^2 = 79.4\%$; $P < 0.001$; Egger's test, $P = 0.306$; Begg's test, $P = 0.612$) in women (Supplementary Figs. 2b,c and 3a,b and Supplementary Table 11). Additionally, 11 and 9 papers reported associations between loneliness and all-cause mortality in men and women, respectively. However, our meta-analysis found no evidence for these associations in men (1.09; 95% CI, 0.99 to 1.20; $P = 0.080$; $I^2 = 69.8\%$; $P < 0.001$; Egger's test, $P = 0.506$; Begg's test, $P = 0.755$) or in women (1.01; 95% CI, 0.98 to 1.05; $P = 0.488$; $I^2 = 15.4\%$; $P = 0.306$; Egger's test, $P = 0.031$; Begg's test, $P = 0.348$) (Supplementary Figs. 2d,e and 3c,d and Supplementary Table 11).

In subgroup analyses according to country, follow-up time, education, depression, smoking, drinking, body mass index, ethnicity, chronic disease and the assessment methods of SI and loneliness,

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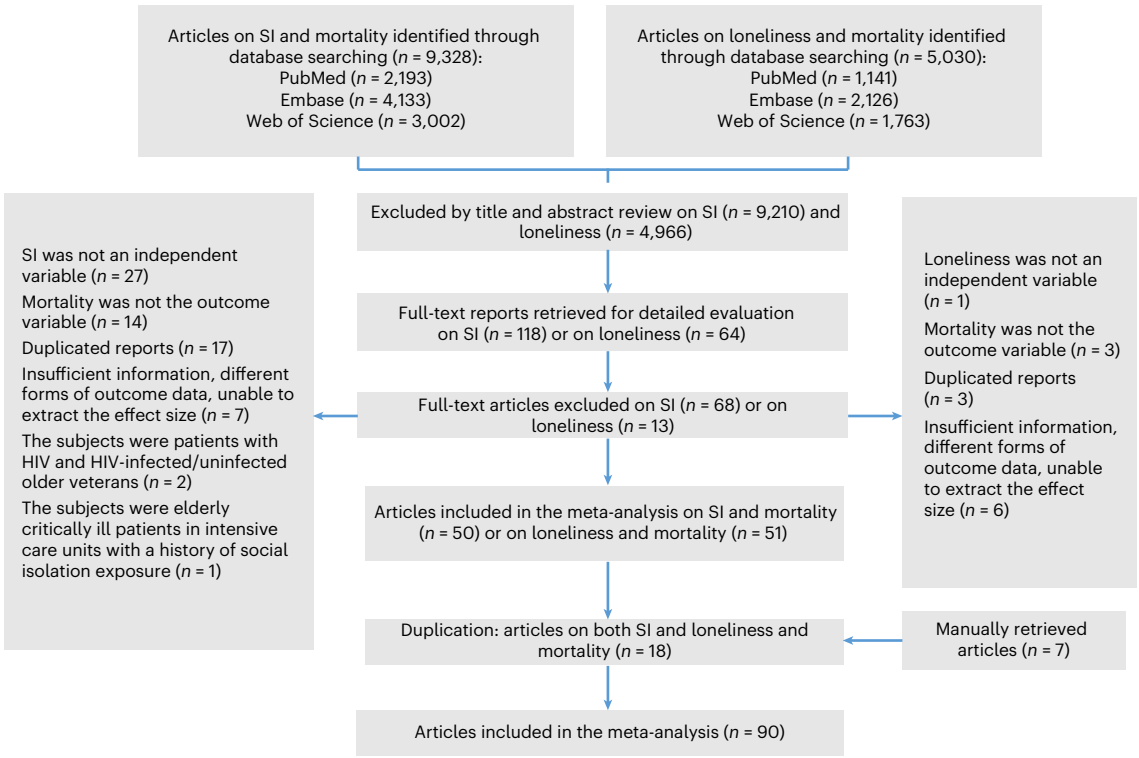

Fig. 1 | Studies included in the present review. The retrieval processes shown found 90 studies that met the selection criteria and were relevant to this meta-analysis.

a significant difference was observed only for country, between the US and non-US countries ($P = 0.039$, Supplementary Table 12). There were no significant differences in subgroup (Supplementary Table 13) and sensitivity analyses for loneliness and all-cause mortality (Supplementary Fig. 4). Six studies[10,15,24,37,42,55] reported serial hazard ratios (HRs) and 95% CIs of all-cause mortality for SI according to different social network index grades (Supplementary Table 14). The trend test result showed that social network index grade was correlated with the risk of all-cause mortality ($P = 0.001$); that is, the risk of mortality increased significantly with increased degree of SI.

SI or loneliness and CVD mortality

Fifteen and eight papers, including 1,265,108 and 487,982 participants, examined the association of SI and loneliness, respectively, with the risk of mortality from CVD or circulatory disease in the general population. The pooled effect estimate was 1.34 (95% CI, 1.25 to 1.44; $P < 0.001$; $I^2 = 63.3\%$; $P < 0.001$) for SI and CVD or circulatory disease mortality, with non-significant publication bias in Egger's ($P = 0.160$) and Begg's tests ($P = 0.363$) (Fig. 3a, Supplementary Fig. 5a and Supplementary Table 11). But the pooled effect estimate was non-significant for loneliness (1.14; 95% CI, 0.97 to 1.35; $P = 0.118$; $I^2 = 77.3\%$; $P < 0.001$; Egger's test, $P = 0.012$; Begg's test, $P = 0.371$) (Fig. 3b, Supplementary Fig. 5b and Supplementary Table 11). There was no significant heterogeneity observed for sex, country, follow-up duration or adjustment for confounding, except for education level ($P = 0.024$; Supplementary Table 15) in the subgroup analysis of SI and CVD mortality.

SI or loneliness and cancer mortality

Thirteen and three papers examined the association of SI and loneliness, respectively, with the risk of mortality from cancer in the general population. A total of 1,171,644 and 476,404 participants were analysed, and positive associations with cancer mortality were observed for SI (1.22; 95% CI, 1.18 to 1.27; $P < 0.001$; $I^2 = 42.8\%$; $P = 0.040$; Egger's test, $P = 0.042$; Begg's test, $P = 0.488$) and for loneliness (1.09; 95% CI, 1.01 to 1.17; $P = 0.030$; $I^2 = 0.0\%$; $P = 0.952$; Egger's test, $P = 0.147$; Begg's test, $P = 0.296$) (Fig. 4, Supplementary Fig. 6 and Supplementary Table 11). The subgroup analysis of SI and cancer mortality did not reveal sources of heterogeneity (Supplementary Table 16).

SI or loneliness and all-cause mortality in individuals with CVD

The association of SI and loneliness with all-cause mortality in individuals with CVD was examined in eight and four papers, including 487,722 and 50,936 participants, respectively. The pooled effect estimate was 1.28 for SI (95% CI, 1.10 to 1.48; $P = 0.001$; $I^2 = 64.9\%$; $P = 0.004$; Egger's test, $P = 0.113$; Begg's test, $P = 0.076$) and 1.26 for loneliness (95% CI, 0.94 to 1.68; $P = 0.120$; $I^2 = 83.7\%$; $P < 0.001$; Egger's test, $P = 0.003$; Begg's test, $P = 0.072$) (Supplementary Fig. 7 and Supplementary Table 11).

SI and mortality in individuals with cancer

Among individuals with cancer, only those with breast or colorectal cancer were analysed for the relationship between SI and mortality in original studies. On the basis of 7 papers including 21,913 individuals with cancer, there were significant associations with pooled effects for all-cause mortality (1.47; 95% CI, 1.33 to 1.63; $P < 0.001$) and for cancer-specific mortality (1.26; 95% CI, 1.04 to 1.52; $P = 0.016$) (Supplementary Fig. 8a,b). No significant heterogeneity or publication bias was found (Supplementary Table 11).

Among the total, 4 papers including 18,955 individuals with breast cancer showed pooled effect estimates of 1.51 for all-cause mortality (95% CI, 1.34 to 1.70; $P < 0.001$; $I^2 = 34.6\%$; $P = 0.190$; Egger's test, $P = 0.540$; Begg's test, $P = 1.000$) and 1.33 for cancer-specific mortality (95% CI, 1.02 to 1.75; $P = 0.038$; $I^2 = 59.5\%$; $P = 0.042$; Egger's test, $P = 0.836$; Begg's test, $P = 0.806$) (Supplementary Fig. 8c,d and Supplementary Table 11). Two studies including patients with colorectal cancer found conflicting results for all-cause mortality, with one study reporting a significant positive association (HR, 1.54; 95% CI, 1.09 to 2.17; $P = 0.03$)[62] and the other study reporting no association (HR, 1.27; 95% CI, 0.97 to 1.66)[64]. Three papers including 2,976 patients with colorectal cancer indicated no evidence of increased risk of cancer-specific

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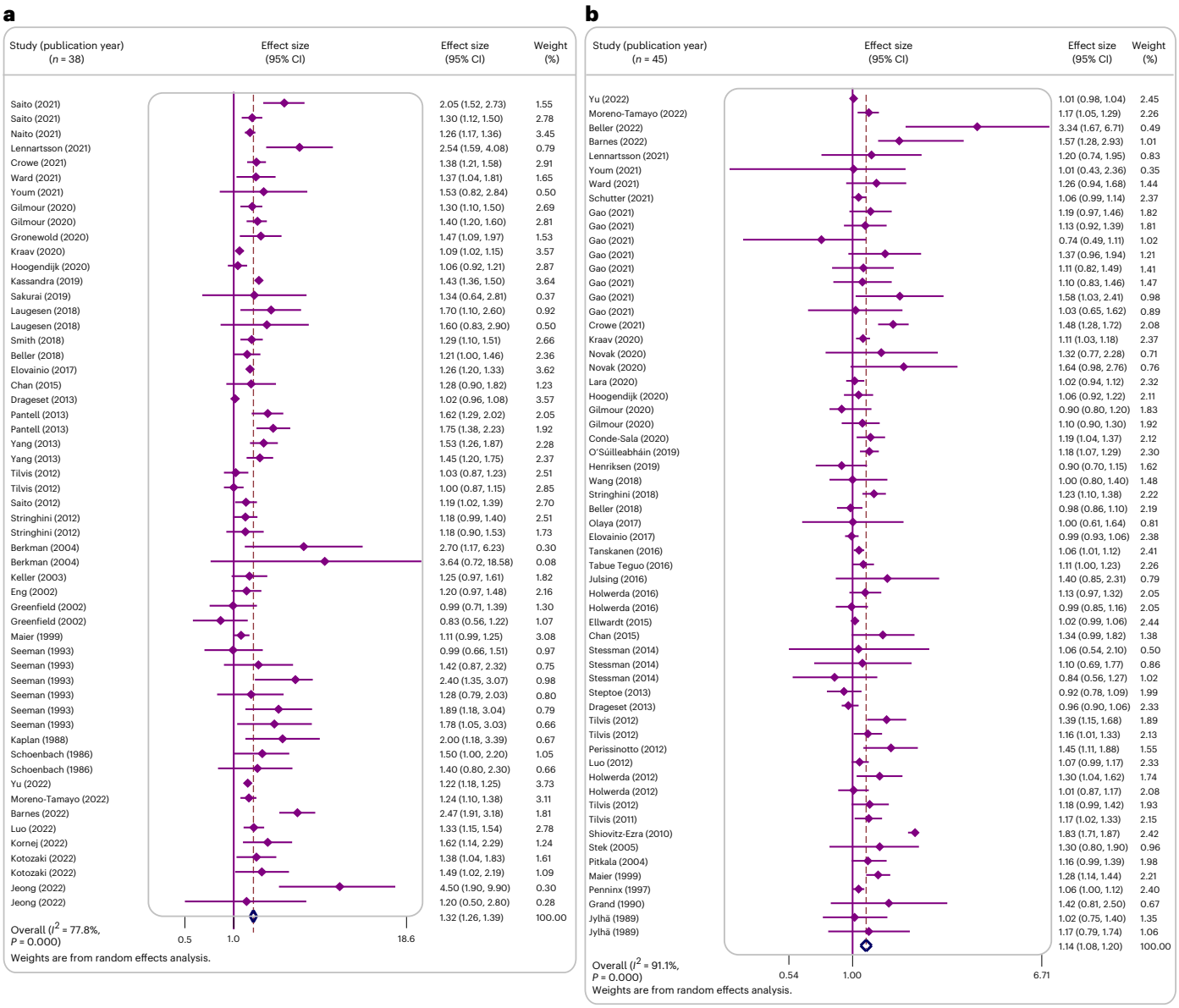

Fig. 2 | Association of SI or loneliness and risk of all-cause mortality. **a**, Association of SI and risk of all-cause mortality. **b**, Association of loneliness and risk of all-cause mortality. The pooled effect estimates were generated using a random-effects model. The statistical tests were two-sided. *n* indicates the number of studies included. Only the first author of each study is listed. Each solid diamond represents the effect size of each study. The horizontal bars represent the 95% CIs for each study effect size. The hollow diamond represents the overall estimated effect and its 95% CI. The data are presented as HRs (95% CI).

mortality, with a pooled effect estimate of 1.07 (95% CI, 0.96 to 1.20; $P = 0.205$) (Supplementary Fig. 8e and Supplementary Table 11).

GRADE assessment

Supplementary Table 11 shows the GRADE assessments of the overall certainty of the evidence for the associations between SI, loneliness and risk of mortality from all causes, CVD and cancer in the general population and in individuals with CVD or cancer. Owing to the observational study design, most evidence for these pooled effect estimates was graded as low ($n = 4$) or very low ($n = 14$), all downgraded because of inconsistency or publication bias.

Discussion

With a sample size of more than two million, this systematic review and meta-analysis provides a large set of evidence on the associations between SI and loneliness and mortality from all causes, CVD and cancer. We found that in the general population, both SI and loneliness were significantly associated with an increased risk of all-cause and cancer mortality. SI also increased the risk of CVD mortality. No positive combined effect of SI and loneliness on all-cause mortality was observed. The findings also highlight that socially isolated individuals with CVD or breast cancer had increased all-cause mortality, and individuals with breast cancer had higher cancer-specific mortality due to SI.

A recent representative study in 20 high-, middle- and low-income countries on five continents showed that SI increased the risk of all-cause mortality by 26% (95% CI, 1.17 to 1.36)[11]. Those researchers held the view that SI is correlated with increased mortality on a par with or greater than traditional risk factors such as alcohol use, smoking and obesity[42,101]. By contrast, in a study by Hoogendijk et al.[53], SI was not found to be significant ($P = 0.41$; HR = 1.06; 95% CI, 0.92 to 1.21)

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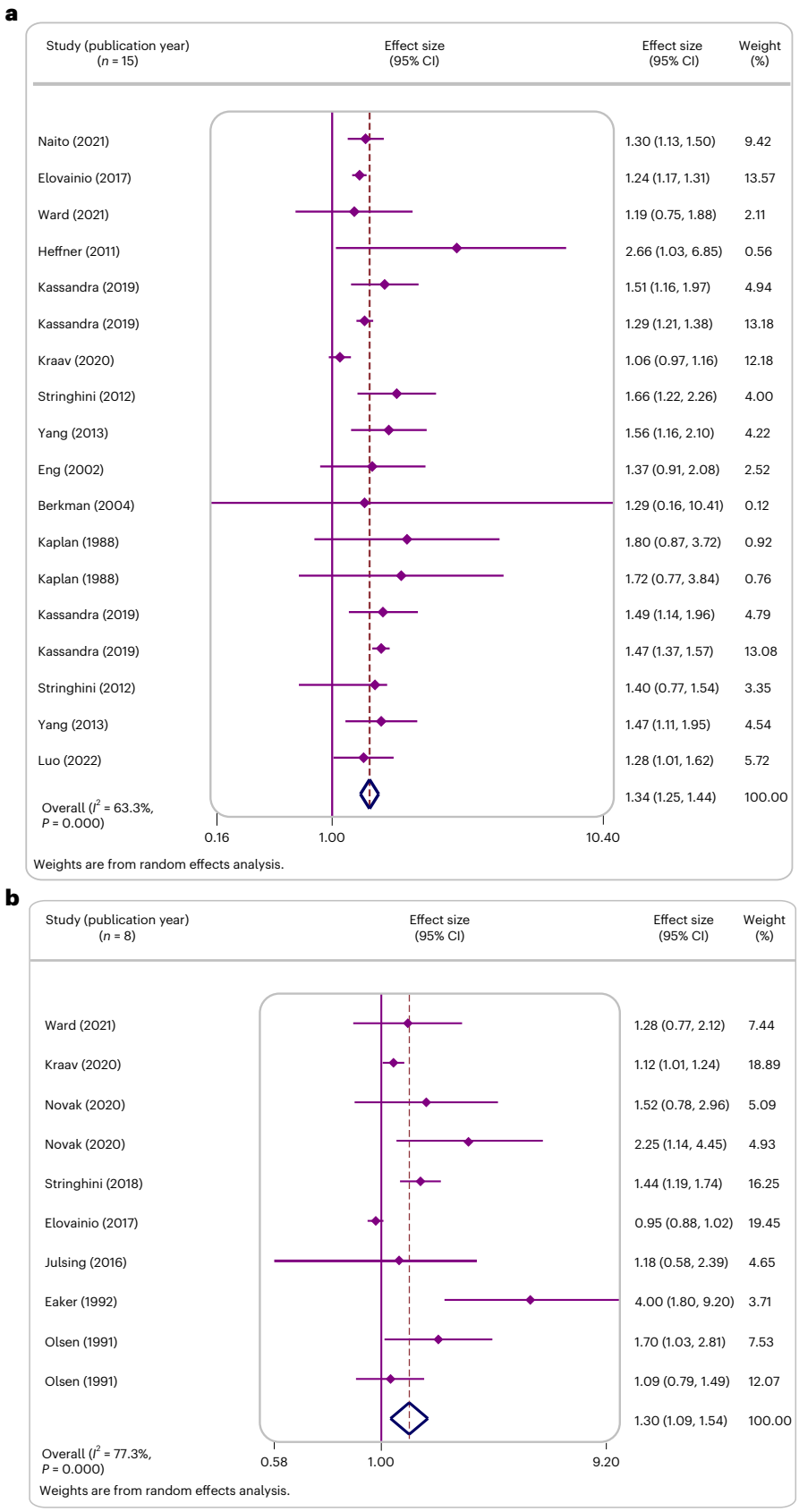

Fig. 3 | Association of SI or loneliness and risk of cardiovascular or circulatory system disease mortality. a, Association of SI and risk of cardiovascular or circulatory system disease mortality. **b**, Association of loneliness and risk of cardiovascular or circulatory system disease mortality. The pooled effect estimates were generated using a random-effects model. The statistical tests were two-sided. *n* indicates the number of studies included. Only the first author of each study is listed. Each solid diamond represents the effect size of each study. The horizontal bars represent the 95% CIs for each study effect size. The hollow diamond represents the overall estimated effect and its 95% CI. The data are presented as HRs (95% CI).

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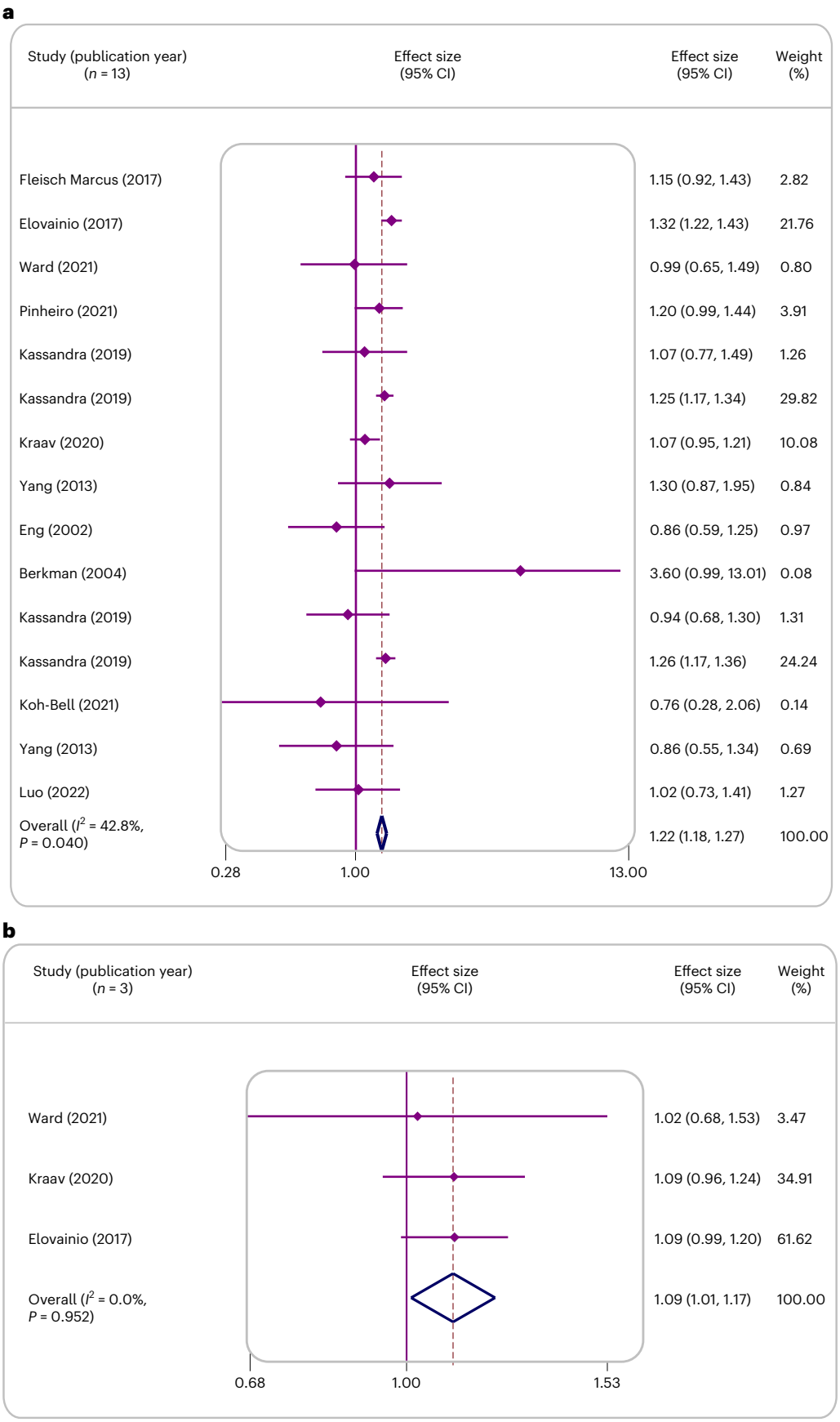

Fig. 4 | Association of SI or loneliness and risk of cancer mortality. **a**, Association of SI and risk of cancer mortality. **b**, Association of loneliness and risk of cancer mortality. The pooled effect estimates were generated using a fixed-effects model. The statistical tests were two-sided. *n* indicates the number of studies included. Only the first author of each study is listed. Each solid diamond represents the effect size of each study. The horizontal bars represent the 95% CIs for each study effect size. The hollow diamond represents the overall estimated effect and its 95% CI. The data are presented as HRs (95% CI).

among older adults who were not frail. Sakurai et al.[14] also revealed a non-significant result ($P = 0.446$; HR = 1.34; 95% CI, 0.64 to 2.81) for SI in a non-homebound population. Given that frailty[102] and homebound status[103] are considered independent risk factors affecting mortality, potential confounding may explain these negative results. The results have been similarly controversial in studies linking loneliness and all-cause mortality. For example, both Moreno-Tamayo et al.[13] and Barnes et al.[65] showed that loneliness is a risk factor for all-cause mortality, with $P < 0.01$, HR = 1.17 (95% CI, 1.05 to 1.29) and $P < 0.001$, HR = 1.57 (95% CI, 1.28 to 2.93), respectively. However, loneliness was reported as non-significantly associated with mortality in a study by Yu et al.[20] ($P = 0.69$; HR = 1.01; 95% CI, 0.98 to 1.04), as well as in other studies in Western countries[27,85]. A putative reason for these inconsistent conclusions can be attributed to discrepancies in adjusting confounding among previous individual studies. Compared with the abovementioned studies and the meta-analysis from 2015[18], our meta-analysis included the most complete set of prospective studies to date and generated pooled effect estimates based on the fully adjusted effect sizes from the original studies. We confirmed that SI and loneliness were positively correlated with all-cause mortality in the general population.

Identifying and understanding gender differences in the relationship between SI or loneliness and all-cause mortality may help in improving gender equity and promoting population health status. Ward et al.[16] observed that SI increased the risk of all-cause mortality in women (HR = 1.66; 95% CI, 1.08 to 2.54) but not in men (1.18; 95% CI, 0.79 to 1.75). Gronewold et al.[28] found the opposite result, with SI positively increasing all-cause mortality in men (HR = 2.45; 95% CI, 1.54 to 3.87) but not in women (1.11; 95% CI, 0.77 to 1.62). Similarly, Holwerda et al.[88] found that loneliness was associated with increased mortality only in men ($P < 0.05$; HR = 1.3; 95% CI, 1.04 to 1.62). Generally, the prevalence of SI or loneliness varies by gender[22]. Owing to differences in occupation, social position and physiological specificity, women are more susceptible to feelings of loneliness than men[104], but women have larger social networks than men, even later in life[105]. Living alone and having a lack of interpersonal connections seem particularly predominant and detrimental in men[106]. Additionally, considerable differences in other exposures closely related to SI and loneliness (such as smoking, unhealthy diet, physical inactivity and health care utilization by gender subgroups) are objectively common, especially in some countries with a low sociodemographic index. Studies may be hindered by limited statistical power, and discrepant results produced in a single study may be attributed to adjustment for different confounding factors. For example, Henriksen et al.[75] did not adjust for physical activity, depression or alcohol consumption in their research, and Novak et al.[17] did not adjust for a history of diabetes or hypertension. We found a significantly increased risk for all-cause mortality with SI in both sexes in the meta-analysis. Although marginal non-significance within groups was observed, loneliness was associated with an obvious increase in all-cause mortality when combining 45 cohorts, which provides reliable evidence regarding this complex relationship.

Because a small number of respondents experienced high levels of both loneliness and SI, the included literature lacked studies analysing the combined effect or interaction of SI and loneliness. Loneliness has been shown to predict mental health[32,107] (for example, depression), and SI has been shown to predict cognitive and physical health[107]. Beller and Wagner[50] found a synergistic effect on mortality; however, the combined effect (1.18; 95% CI, 1.05 to 1.32) of SI and loneliness was not larger than the separate effects (1.32 for SI and 1.14 for loneliness) according to our meta-analysis, and SI alone most strongly influenced premature mortality. A similar inference has been put forth by Thoits[108], who stated that people who are lonely but not socially isolated have mental health stress but might be resilient to it because of their social networks. Ward et al.[16] also suggested that study participants reporting low loneliness and high SI showed a higher mortality risk than the group with high loneliness and low SI. Socially isolated individuals should therefore be given higher priority than individuals experiencing loneliness in terms of social attention.

SI and loneliness have been reported to have a critical role in the mechanisms of CVD incidence, progression and mortality[109], including hypothalamic–pituitary–adrenocortical (HPA) activation[110], sympathetic nervous system hyperactivity[111], parasympathetic dysfunction[112] and pro-inflammatory immune response[113]. Smith et al.[114] indicated that the risk of death without hospital admission was substantially higher in the most socially isolated individuals than in the least isolated individuals for coronary heart disease and stroke. A meta-analysis in 2016 reported an increased risk of coronary heart disease and stroke in individuals reporting SI[115]. However, most included studies reported effect sizes on a small scale, and the meta-analysis evidence was limited by publication bias. It remains unclear whether these associations are independent of biological, behavioural, psychological, health and socio-economic factors. On the basis of the fully adjusted effect sizes from the original studies, our results confirmed that SI can significantly increase CVD mortality by 34% in the general population. However, because SI and loneliness have been associated with many of the conventional factors, such as low education, obesity, smoking and pre-existing chronic illness, the lack of these adjustments may lead to an underestimation of the true effect size. For example, the present meta-analysis of the effect of SI on CVD mortality was influenced by education ($P = 0.024$), possibly because SI is more common among less-educated and unemployed individuals[11]. Additionally, Hakulinen et al.[27] identified a 1.5-fold risk associated with SI for all-cause mortality in individuals after acute myocardial infarction or stroke. Similar results were found for SI in our meta-analysis, but not for loneliness after adjustment for publication bias. It thus seems that the deleterious effect of SI on mortality after cardiovascular events is stronger than that of loneliness. Further prospective studies and cumulative meta-analyses are needed to confirm this association.

By analysing data from the UK Biobank cohort study, Elovainio et al.[32] revealed a significant association (HR, 1.32; 95% CI, 1.22 to 1.43) between SI and cancer mortality. However, Alcaraz et al.[22] observed a positive correlation only in female and white participants in the USA; no significant association was observed in some other studies[16,37]. According to the summarized data from 11 studies conducted in five countries, our results showed a significant positive association (1.22; 95% CI, 1.18 to 1.27). The only three studies[16,30,32] on loneliness all showed meaningless results, but the pooled results revealed a weak positive correlation (1.09; 95% CI, 1.01 to 1.17). Hence, the risk of SI and loneliness for cancer-related mortality should not be ignored.

In the Nurses' Health Study among 2,835 postmenopausal women with breast cancer, Kroenke et al.[41] found that socially isolated women were twice as likely to die of breast cancer than socially integrated women. However, in the Women's Health Initiative Study[116], Kroenke et al. found that associations between social networks and mortality outcomes depended on levels of social support and the burden in relationships. Accordingly, the difference may be explained by the degree of acceptance women experience in their social roles or self-perceived stress (such as loneliness or overburden)[17]. We summarized four studies including 18,955 individuals with breast cancer; the results showed that SI increased the risk of all-cause (1.51; 95% CI, 1.34 to 1.70) and cancer-specific mortality (1.33; 95% CI, 1.02 to 1.75). However, similar results were not found in patients with colorectal cancer. From the perspective of risk factors, breast cancer is more closely related to women's psychological factors, SI and social stress[117,118], but colorectal cancer is more closely related to dietary and physical activity factors[119,120]. It is therefore essential to improve the social relationship status of individuals with cancer, especially those with breast cancer, to prolong survival time.

The mechanism related to SI, loneliness and mortality may be as follows. First, the HPA axis is the main producer of glucocorticoids[121].

There is clear evidence that SI and loneliness can lead to activation of the HPA axis in animals and humans[110,111,122], which results in the release of cortisol, a physiological state of glucocorticoids. For example, the separation of pair-bonded prairie voles from their partners leads to an elevation of circulating corticosterone concentrations, indicating an activation of the entire HPA axis[110]. In human studies, socially isolated individuals among healthy middle-aged men and women in the Whitehall II cohort were found to show a greater cortisol arousal response and a greater total cortisol output over the course of the day[123]. In addition, lonely individuals have greater morning cortisol increases[124], elevated circulating cortisol concentrations and impaired glucocorticoid receptor sensitivity, suggesting that loneliness also causes overaction of the HPA axis[125]. Continuous activation of the HPA axis and glucocorticoids affects a wide range of physiological functions, including glucose regulation, metabolism and inflammatory control; it also has cardiovascular, reproductive and neuronal effects[126] and increases the risk of CVD, cancer and mortality[122]. Second, both SI and loneliness are independently associated with negative mental health outcomes later in life, including higher rates of depression and cognitive decline[127,128]. Third, harmful behaviours associated with increased mortality are more common among people who are lonely or isolated, such as smoking, alcohol drinking, unhealthy dietary choices, and lower likelihoods of exercising[129] and adhering to prescription medications[85]. Finally, socially isolated individuals are less likely to receive emergency and routine medical care owing to their smaller social network[85]. Poor care provided by health care professionals who perceive this group as difficult to treat or time consuming further exacerbates adverse health outcomes[130].

This study systematically evaluated the association of SI, loneliness and mortality from all causes, CVD and cancer. This study possesses the following strengths. First, owing to the prospective design of the included studies, recall bias and selection bias were effectively avoided. Second, the summarized analyses included the largest number of participants to date. Third, potential confounding was controlled to the greatest extent because only effect sizes from fully adjusted models in the original studies were included. Fourth, most included studies were of high quality, with a low risk of bias. Our meta-analysis also has some limitations. First, the source of heterogeneity is difficult to identify owing to a large number of internal adjustment factors in different original studies and the inconsistency of adjustment factors among studies. Potential unknown confounders may still exist in present analysis. Second, the measurement tools of SI and loneliness in the original studies are not completely consistent, which may affect the accuracy of our assessment. Third, most included studies were from high-income countries; additional results from other regions are required to comprehensively understand this topic. Fourth, SI was noted to be associated with an increased risk of suicide, which is also associated with premature death. Some of the original studies[23,25] controlled for this effect by excluding people who died prematurely if their outcome occurred within a year, but not all studies took this approach. It was therefore inevitable that our findings would be influenced by premature deaths from suicide, self-harm or other causes.

SI and loneliness are critical factors associated with an increased risk of all-cause, cardiovascular and cancer mortality. SI and loneliness may be exacerbated by post-cancer or CVD stress and less social contact as well as limited access to care, especially informal care from friends and family. Strategies are urgently needed to address this public health concern, such as raising awareness about the adverse health effects of SI and loneliness among health care professionals and the general public. It is also critical to develop interventions based on innovative technologies that mobilize resources from family members and community networks to address SI and loneliness. The health care system should also develop methods to identify SI and loneliness in health care settings so that health care professionals can provide appropriate clinical and public health interventions.

Methods

The findings of this systematic review and meta-analysis are reported in accordance with the Reporting Checklist for Meta-analyses of Observational Studies (MOOSE)[131] (Supplementary Table 1) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[132] (Supplementary Table 2). The protocol of this study was registered with PROSPERO on 5 February 2022 (reg. no. CRD42022299959) at https://www.crd.york.ac.uk/PROSPERO/.

Data sources and database search

We searched PubMed, Web of Science and Embase for studies published in English between database inception and October 2022. Supplementary Table 3 provides the details of the search terms used. Manual retrieval and a review of the reference lists of retrieved studies were also performed to avoid missing eligible studies.

Inclusion and exclusion criteria

All article titles and abstracts were reviewed independently by two authors (Y.G. and Z.H.). The study inclusion criteria were as follows: (1) studies with a prospective observational design including adults aged more than 18 years; (2) studies reporting effect sizes using HRs and relative risk with the corresponding 95% CIs, for the association of SI or loneliness as the exposure of interest and mortality from all causes, CVD or specific cancers as the outcome (diagnoses were classified according to the World Health Organization International Classification of Diseases[133,134]); and (3) if multiple studies reported data from the same population, only the study with the largest sample size was included. The following studies were excluded: (1) commentaries, editorials, letters, reviews, unpublished studies or meta-analyses; (2) studies in which SI or loneliness was not considered as an independent variable; (3) studies performed on individuals with HIV; and (4) studies reporting effect sizes of mixed risk factors for disease and mortality.

Because there was no standardized assessment method, all original studies using differing measures to assess SI or loneliness were included, for greater statistical power. The details are shown in the Supplementary Information (Supplementary Table 4). Subgroup analysis and sensitivity analysis were used to assess the impact of the differential measures in the meta-analysis.

Data extraction

The data were extracted independently by two researchers (Y.G. and Z.H.). Any disagreement was resolved in discussion or by a project supervisor. The following data were extracted from each publication: name of the first author, publication year, study design, location of the study, age range, sex, cohort size, duration of follow-up, methods used for the assessment of SI or loneliness, and effect sizes of comparison results (for categorical variables (SI versus non-SI and loneliness versus non-loneliness) or graded analyses with the lowest level as the reference) together with 95% CIs and confounding variables adjusted in the statistical analyses. In cases where the study population consisted of only male (or female) participants, or when the results of a mixed population were analysed separately by sex, we considered each analysis as a distinct study. If the included studies reported both crude and multivariable-adjusted effect estimates, we extracted the most fully adjusted outcomes. The extracted data were sorted in Excel 2016 (ref. 135).

Statistical methods

We summarized HRs and relative risks (along with 95% CIs) for comparisons of SI with non-SI and loneliness with non-loneliness or graded variables in the original studies to calculate pooled effect estimates for the association of SI or loneliness and mortality outcomes (significant at an α level of 0.05). Heterogeneity was determined using Cochran's Q test (significant at $P < 0.10$) and quantified with the I^2 statistic (range, 0–100%). We took $I^2 \geq 50\%$ to indicate high heterogeneity and used a random-effects model (DerSimonian and Laird); we considered $I^2 < 50\%$

to indicate low heterogeneity and used a fixed-effects model. We examined the possibility of publication bias by using funnel plots and conducting Egger's and Begg's tests (each significant at $P < 0.05$). When there was publication bias, we used the trim-and-fill method[136] to adjust the influence of bias. Subgroup and meta-regression analyses were conducted using predefined criteria, including study country, duration of follow-up, and SI or loneliness assessment tools, and statistically controlling for confounders (such as education, depression, smoking, drinking, body mass index and chronic diseases). A polynomial contrast procedure was used to analyse the changing trends in social network index grade and risk of mortality. Additionally, we conducted a sensitivity analysis, in which each prospective cohort study was excluded in turn, to examine the influence of that study on the overall estimates. All statistical analyses were performed using Stata statistical software version 14.2 (StataCorp). All statistical tests were two-sided.

Risk-of-bias assessment and GRADE assessment

Because all eligible studies were designed with a cohort study, the Newcastle–Ottawa quality assessment scale for cohort studies was used to evaluate the methodological quality[137,138] of the included studies. The GRADE[139] method was used to assess the quality of evidence and generate a profile that ranks the evidence as high, moderate, low and very low certainty (the details are in the Supplementary Methods). Two authors (Y.G. and Z.H.) independently conducted a risk assessment of bias for each study and a GRADE evaluation of the results of the meta-analyses, and any inconsistencies between them were resolved by regular group discussion or adjudicated by a project supervisor. The ratings were conducted in GRADEprofiler[140].

Patient and public involvement

There was no patient or public involvement in setting the research question or the outcome measures, in developing the study plans or in interpreting or writing up the results. There are no plans to involve patients in the dissemination of the research results. Our findings will be accessible to the general public as an open-access published article.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All included literature is available in PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com) and Embase (https://www.embase.com). The data that support the findings of this study are available from the corresponding author upon request.

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Acknowledgements

This work was supported by the Dr. Wu Lien teh Science Foundation of Harbin Medical University (WLD-QN1106, F.W.). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Author contributions

F.W. and M.W. conceived the idea for the review. M.W. and F.W. designed, supervised and coordinated the study. Y.Z. gave crucial intellectual input. Y.G., Z.H. and Y.Y. searched the literature, extracted the data and assessed the risk of bias. Z.L., B.P., Y.C., Y.W., J.Y. and Y.G. coded the statistical analysis, figures and supplementary information in collaboration with X.J. Y.G., F.W. and M.W. interpreted the data. Y.G. and F.W. drafted the manuscript. F.W. obtained the funding. All authors have read and approved the final manuscript. The corresponding authors attest that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted. F.W. and M.W. are the guarantors of this manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41562-023-01617-6.

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Peer review information *Nature Human Behaviour* thanks Chen Mao, Bin Yu and Natalia Martín-María for their contribution to the peer review of this work. Peer reviewer reports are available.