

**FACTORS ASSOCIATED WITH LONELINESS:
AN UMBRELLA REVIEW OF OBSERVATIONAL STUDIES**

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ABSTRACT

Background: Evidence provides inconsistent findings on risk factors and health outcomes associated with loneliness, and no umbrella review has attempted to summarize evidence from meta-analyses and systematic reviews. The aim of this work was to grade the evidence on risk factors and health outcomes associated with loneliness, using an umbrella review approach.

Methods: For each meta-analytic association, random-effects summary effect size, 95% confidence intervals (CIs), heterogeneity, evidence for small-study effect, excess significance bias and 95% prediction intervals were calculated, and used to grade significant evidence ($p < 0.05$) from convincing to weak. For narrative systematic reviews, findings were reported descriptively.

Results: From 210 studies initially evaluated, 14 publications were included, reporting on 18 outcomes, 795 studies, and 746,706 participants. Highly suggestive evidence (class II) supported the association between loneliness and incident dementia (relative risk, $RR=1.26$; 95%CI: 1.14-1.40, I^2 23.6%), prevalent paranoia (odds ratio, $OR=3.36$; 95%CI: 2.51-4.49, I^2 92.8%) and prevalent psychotic symptoms ($OR=2.33$; 95%CI: 1.68-3.22, I^2 56.5%). Pooled data supported the longitudinal association between loneliness and suicide attempts and depressive symptoms. In narrative systematic reviews, factors cross-sectionally associated with loneliness were age (in an U-shape way), female sex, quality of social contacts, low competence, socio-economic status and medical chronic conditions.

Conclusions: This work is the first meta-evidence synthesis showing that highly suggestive and significant evidence supports the association between loneliness and adverse mental and physical health outcomes. More cohort studies are needed to disentangle the direction of the association between risk factors for loneliness and its related health outcomes.

Key words: loneliness; meta-analysis; risk factor; health outcome; umbrella review.

Introduction

Loneliness is a perceived deficit between actual and desired quality or quantity of relationships, which is different from objective social isolation.¹⁻³

Several social and clinical factors have been proposed as putative risk factors for loneliness. For instance, coping strategies⁴, socio-economic status⁵, psychotic illness⁶, depressive disorder⁷, among others have been proposed as putative risk factors of loneliness.

Also, a number of mental and physical health outcome have been associated with loneliness, and an increased mortality has also been shown in older subjects experiencing loneliness.⁸ Among neuro-psychiatric disorders, anxiety disorders⁹, depressive disorders^{10,11}, schizophrenia spectrum disorders¹², even in its early phases¹², Alzheimer's disease¹³ and ultimately suicide¹⁴ have been associated with loneliness. Also, among subjects with mental illness, loneliness has been associated with more severe symptoms, less recovery and poorer social functioning.¹⁵

However, most studies investigating associations between loneliness and mental or physical health outcomes were cross-sectional, hence precluding any causal inference between loneliness and putative risk factors or health outcomes.¹⁶ For instance, several biases may be affecting literature on aforementioned associations, including publication bias, small sample sizes, excess of significance, or high heterogeneity.

Finally no umbrella review has graded the available evidence on risk factors and health outcomes of loneliness based on objective criteria, nor encompassing both meta-analyses and narrative systematic reviews to the best of our knowledge.

The aim of the present work is to provide an overview of risk factors and health outcomes nominally associated with loneliness according to systematic reviews and meta-analyses, and where feasible to grade the evidence according to strict objective and widely accepted criteria, in the context of an umbrella review.

Methods

A protocol for this study was registered on PROSPERO 2019: CRD xxx. We performed a systematic review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations¹⁷ and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.¹⁸

Search strategy and selection criteria

We searched PubMed and PsycInfo databases, last search performed October 16th, 2019, to identify systematic reviews or meta-analyses pooling observational (cross-sectional, case-control, cohort) studies examining any association between putative risk factors or mental/physical health outcomes, and loneliness. The following search key was used: “(loneliness) AND (Meta-Analysis[ptyp] OR metaanaly*[tiab] OR metaanaly*[tiab] OR Systematic review [ptyp] OR “systematic review” [tiab]))mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, an, sy, tc, id, tm, mh]”. Two reviewers (DG, NV) independently searched titles/abstracts for eligibility, and assessed the full text of those articles surviving title/abstract phase. A third reviewer resolved any conflict (MS).

When more than one meta-analysis assessed the same risk factor or the same outcome, we only include the one with the larger number of studies, as previously described.¹⁹⁻²¹

Exclusion criteria were: 1) meta-analyses of randomized controlled trials (RCTs) 2) published in languages other than English, 3) meta-analyses assessing the association between risk factor or health outcomes and construct similar but different from loneliness, such as social isolation.

Data extraction

The same two investigators that performed the screening independently extracted data in a pre-defined excel spreadsheet. For each meta-analysis, we extracted PMID/DOI, first author, publication year, population included in the study, factor associated with loneliness, study design, age of participants, number of included studies and the total sample size.

For each primary study, we recorded information on first author, year of publication, study design (i.e., cohort or case-control), number of cases (subjects having loneliness in studies assessing risk factors and number of developing the health outcomes in studies assessing the outcome of loneliness), adjusted (or unadjusted) effect sizes (ESs), with their 95% confidence intervals (CIs), and study location.

For meta-analyses only providing pooled estimates, we also extracted at meta-analytical level the effect size with their 95%CI, and the I^2 as a measure of heterogeneity.

For narrative reviews, we also extracted the narrative synthesis of main results of included studies.

The methodological quality of each included meta-analysis was assessed with the Assessment of multiple systematic reviews (AMSTAR) 2 tool (available at <https://amstar.ca/Amstar-2.php>), which is a recent update of AMSTAR,²² by same two investigators (DG, NV).

Data analysis

For each association of meta-analyses providing individual studies data, we extracted effect sizes of individual studies and re-performed the meta-analysis calculating the pooled ES and the 95% confidence intervals, with random-effects models to compare homogeneously analyzed results.²³ Heterogeneity was assessed with the I^2 statistic.²⁴ Additionally, we calculated the 95% prediction intervals for the summary random ESs providing the possible range in which the ESs of future studies is expected to fall.²⁵

We also tested the presence of small-study effect bias,^{19,26-28} which is deemed present in case of both pooled estimate larger than the individual largest study, and publication bias (Egger's regression asymmetry test ($p \leq 0.10$)). We finally assessed the existence of excess significance bias by evaluating whether the observed number (O) of studies with nominally statistically significant results ("positive" studies, $p \leq 0.05$) were different from the expected number (E) of studies with statistically significant results (significance threshold set at $p \leq 0.10$)^{28,29}, a test designed to assess whether the published meta-analyses comprise an over-representation of false positive findings.²⁸

No additional analysis was performed for meta-analyses providing pooled estimates and for narrative systematic reviews.

Assessment of the credibility of the evidence

Credibility of meta-analyses providing individual studies data was assessed according to stringent criteria based on previously published umbrella reviews.^{21,26,27,30-32} In brief, associations that presented nominally significant random-effects summary ESs (i.e., $p < 0.05$) were ranked as convincing, highly suggestive, suggestive, and weak evidence based on number of events, strength of the association, and the presence of several biases (criteria available in **Supplementary Table 1**).

Quality of included meta-analyses and narrative systematic reviews were assessed by means of AMSTAR2.

Results

Search

The flow-diagram of search, selection and inclusion process is fully reported in **Figure 1**. Out of 269 hits initially identified, after duplicate removal 206 were assessed at title/abstract level. Fifteen papers were excluded with specific reasons, namely they did not follow a systematic approach to the literature ($k=7$), they did not focus on loneliness ($k=5$), or on any health-outcome ($k=2$) or risk factor, or only included one single study ($k=1$). Finally, 14 systematic reviews were included in this umbrella review.^{15,33-45} The list of references of excluded studies, with reason, is available as **Supplementary Table 2**.

Supplementary Table 3 shows the quality assessment using the AMSTAR 2. Of 14 papers included, one was rated as high quality, nine as moderate, four as critically low.

Meta-analyses providing individual studies data

Grading and results of meta-analyses providing individual studies data are reported in **Table 1**. Median number of included studies was 13 (range 3 to 31), median sample size was 21,221, three meta-analyses included only cohort studies⁴³⁻⁴⁵, while two meta-analyses included cross-sectional designs.^{41,42} All included meta-analyses reported a significant association of investigated factors with loneliness, but heterogeneity was high in four, small study effect was present in three, prediction intervals included null value in three, and excess of significance bias was present in one. Three associations were supported by highly suggestive evidence (class II), namely prevalent paranoia ($k=18$, $n=33,355$, OR 3.36, 95%CI 2.51-4.49, I^2 92.8%) and prevalent psychotic symptoms ($k=13$, $n=2,668$, OR 2.33, 95%CI 1.68-3.22, I^2 56.5%), which were based on cross-sectional studies, and incident dementia ($k=8$, $n=3,345$, RR 1.26, 95%CI 1.14-1.4, I^2 23.6%), based on cohort studies. A significant association also emerged for the association between mortality and incident coronary heart disease, based on cohort studies, but such associations were only supported by suggestive and weak credibility, respectively.

Meta-analyses providing pooled estimates

Results of the umbrella review of narrative systematic reviews are reported in **Table 2**. Three papers³⁸⁻⁴⁰, including seven different outcomes and providing pooled estimates, reported a significant association between loneliness and investigated factors. All meta-analyses included cross-sectional studies. Loneliness was associated with increased suicide attempts, depressive symptoms, with age following a U-shaped curve (i.e. younger and older individuals experienced more frequently loneliness), female gender, poor quality of social network, low competence, and low socio-economic status.

Narrative systematic reviews

Results of the umbrella review of narrative reviews are reported in **Table 3**. Six narrative systematic reviews^{15,33-37} were included in the present umbrella review. Four of them included cross-sectional studies. One included only cohort studies, and one include both cross-sectional and cohort studies. Authors concluded that loneliness was associated with autism, emotion-focused coping strategies, acute stress reactivity, poorer cognitive function in cross-sectional studies, that loneliness increased the risk of depression in longitudinal studies, and with presence of chronic disease according to mixed cross-sectional and cohort studies.

Discussion

Our work includes 14 systematic reviews and 18 outcomes, 795 studies, and 746,706 participants. The present umbrella review shows that several risk factors and both mental and physical health outcomes are nominally significantly associated with loneliness. Mental illness such as autism and female gender are plausible risk factors for loneliness, while depression, suicide attempts, and dementia are plausible health outcomes associated with loneliness. Mainly cross-sectional evidence focused on the association between loneliness and psychotic symptoms, cognitive functioning, coping strategies, and a number of medical conditions which could either be a risk factor or a consequence of loneliness itself.

We believe that our findings are important for several reasons. First, and most important, loneliness is a highly prevalent condition in adult and older people. It is estimated that loneliness, in North America, may range from 17% to 57% in the general population, being higher in some vulnerable populations such as people suffering from heart disease, depression, anxiety, or dementia.⁴⁶ Similar data and characteristics are similar in Europe.⁴⁷ Given that this condition is a highly prevalent and often associated with negative health outcomes, as also our umbrella review confirms, recently the United Kingdom Government proposed a specific ministry for loneliness.⁴⁸ At the end of 2017, in fact, an UK government commission helped by more than a dozen non-profit organizations observed that 9 million Britons suffer from loneliness, equal to 14% of the population.⁴⁸ This “provocative” political action was well-received in all the world as confirmed by a seminal article in the New York Times defining loneliness as a health epidemic.⁴⁹ Second, our umbrella review confirms the important role of loneliness as potential risk factor for some medical conditions, particularly neurological and psychiatric ones. The re-analysis of already published data shown in our work suggested that a highly suggestive evidence (i.e. an evidence poorly biased) supported the association between loneliness and incident dementia and with prevalent paranoia/psychotic symptoms, and pooled data indicated a significant association between loneliness and suicide attempts and depressive symptoms in longitudinal studies. The lack of social contacts which is associated with loneliness

Finally, our work also evidenced the importance of some (risk) factors for loneliness, namely age (in a U-shaped mode), female sex, quality of social contacts, low competence and socio-economic status. Taken together, after excluding not modifiable factors, our umbrella review supports the importance of social factors in indicating people that can suffer from loneliness, even if this evidence is limited by the cross-sectional nature of these studies.

As previously observed in a previous overview of systematic reviews without a quantitative assessment of the evidence, some authors proposed some biological explanations that can associate loneliness to the higher presence and incidence of health outcomes.⁵⁰ Some authors have in fact indicated that loneliness is associated with reduced levels of protective hormones leading to adverse effects on heart rate, blood pressure and the repair of blood vessel walls⁵¹ and to a downregulation of the immune system and to a neuroendocrine dysregulation⁵¹, potentially justifying the epidemiological evidence that we found in our work. Moreover, people experiencing loneliness may be more likely to initiate harmful health behaviors such as smoking, excess alcohol consumption, overeating or food restriction as a psychological relief mechanism

and all of them are well-known risk factors and correlates for psychiatric conditions.^{52,53} Moreover, loneliness has been shown to be associated with poor physical activity,⁵⁴ which in turn is cross-sectionally and longitudinally associated with depression and psychosis among other mental health outcomes.⁵⁵⁻⁵⁷ Hence low physical activity might have mediated or moderated the association between loneliness and health outcomes. Loneliness has been shown to be associated with psychosis throughout the whole course of psychosis, since the very beginning of psychotic symptoms, namely from at risk mental state⁵⁸ to multi-episode schizophrenia.⁵⁹ Subjects with psychosis predominantly show negative symptoms in the long term, which are responsible for the poor functioning together with cognitive function.⁶⁰⁻⁶² Hence, given the relevance of poor social interactions with a potential involvement of loneliness in maintaining negative symptoms, a pilot study has also started to target loneliness in subjects at risk for psychosis, confirming that loneliness is clinically relevant construct not only in the elderly population, but also in young subjects at risk or with early phases of mental illness.⁶³ However, these hypotheses, mainly based on observational data, must be confirmed by large collaborative long-term cohort studies adjusting for confounders,⁵⁰ and any role of loneliness in the treatment of negative symptoms of young subjects at risk for psychosis, or with psychosis should be tested in well-designed and adequately powered randomized controlled trials.

The strength of the present work is it being the first umbrella review providing a qualitative evidence synthesis on the risk factors and health outcomes associated with loneliness, including both meta-analyses and narrative systematic reviews. Second, it applies stringent quantitative criteria to grade the evidence. Third, it indicates future research directions in order to accumulate evidence to eventually reach convincing evidence threshold for risk factors or health outcomes related with loneliness. The main limitations of the present work are related and due to the included studies. Specifically, two out of three among the associations reaching highly suggestive evidence, as well as evidence from narrative systematic reviews yield from cross-sectional studies. Hence any direction cannot be inferred from such study designs, and both prevalent paranoia and psychotic symptoms could either be risk factors or health outcomes associated with loneliness.

In conclusion, there is highly suggestive evidence from meta-analyses that loneliness increases the risk of dementia, and that paranoia and other psychotic symptoms could either be a risk factors or an health outcome associated with loneliness. Moreover, meta-analyses providing only pooled data show that loneliness is associated with depressive symptoms and suicide attempts. Narrative systematic reviews suggests that loneliness increases the risk of depression, and that cognitive function, coping strategies, and medical conditions are associated with loneliness. More longitudinal cohort studies matching subjects for a multi-dimensional propensity score should assess risk factors and health outcomes associated with loneliness.

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Table 1. Grading of evidence from meta-analyses of observational studies on factors associated with loneliness

Population	Factor associated with loneliness	Design	Number of studies	Type of metric	Effect size (95%CI)	P	I ²	Small study effects	Excess significance bias	Largest study significant	Cases	Sample size	PI	Level of evidence
General population	Incident Dementia	Cohort	8	RR	1.26 (1.14-1.40)	8.97E-06	23.6	yes	no	yes	3345	33355	1.03-1.55	II
Psychosis	Prevalent Paranoia	Cross sectional	18	R to OR	3.36 (2.51-4.49)	3.56E-16	92.8	yes	NA	yes	NA	21221	1.18-9.58	II
Psychosis	Prevalent Psychotic symptoms	Cross sectional	13	R to OR	2.33 (1.68-3.22)	3.64E-07	56.5	yes	NA	yes	NA	2668	0.93-5.81	II
General population	Incident Mortality	Cohort	31	RR	1.22 (1.10-1.36)	0.0003	94.5	no	NA	yes	NA	51053	0.71-2.10	III
General population	Incident Coronary Heart Disease	Cohort	3	RR	1.80 (1.02-3.17)	0.04	65.3	no	yes	no	430	2722	0-999	IV

Abbreviations: PI, Prediction Interval

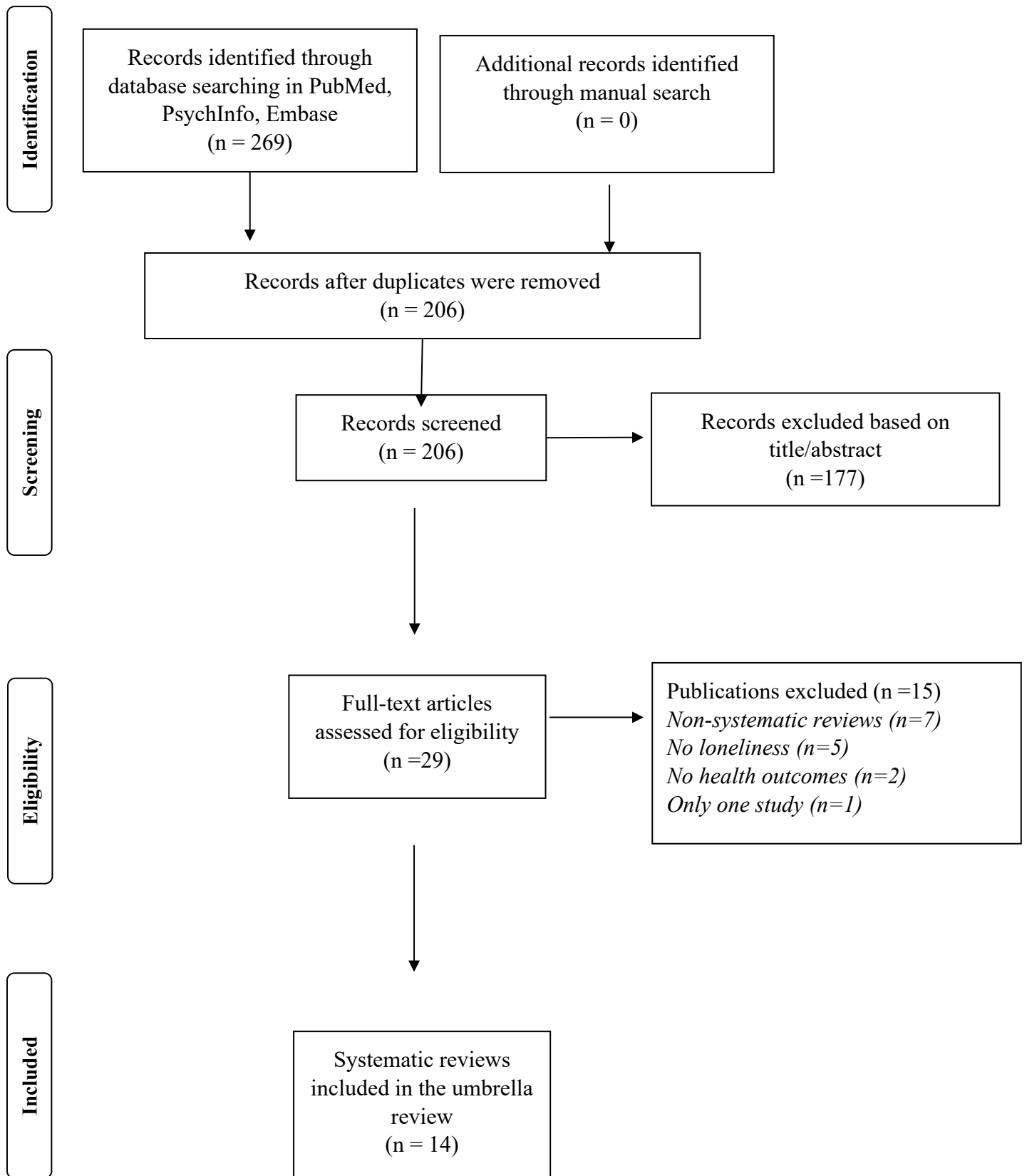
Table 2. Evidence from the meta-analyses reporting pooled data of the observational studies included

population	outcome	study design	type of effect	n of studies	sample size	ES	p-value	Heterogeneity	Publication bias	Main findings
Older people	Suicide attempts	cross-sectional	OR	3	NR	2.24 (1.73-2.90)	NR	no	NR	Loneliness is associated with a higher rate of suicidal attempts in older people
Subjects with depression	Depressive symptoms	cross-sectional	Pearson's R	88	40068	0.50 (0.44-0.55)	NR	NR	NR	Loneliness had a moderately significant effect on depression
General population	Age (as risk factor for loneliness)	cross-sectional	Pearson's R	106	62363	-0.01 (-0.02 to -0.0001)	NR	yes	NR	U-shaped association between age and loneliness is identified
General population	Gender (as risk factor for loneliness)	cross-sectional	Pearson's R	91	73213	-0.08 (-0.09 to -0.07)	NR	yes	NR	Female sex is associated with higher loneliness perception
General population	Social contacts (as risk factor for loneliness)	cross-sectional	Pearson's R	235	93934	-0.18 (-0.19 to -0.17)	NR	yes	NR	Quality of social network correlated more strongly with loneliness, compared to quantity
General population	Competence and Activity (as risk factor for loneliness)	cross-sectional	Pearson's R	67	38796	-0.12 (-0.13 to -0.11)	NR	yes	NR	Low competence is associated with higher loneliness feeling
General population	Socio economic status (as risk factor for loneliness)	cross-sectional	Pearson's R	62	39319	-0.13 (-0.14 to -0.12)	NR	yes	NR	Low socioeconomic status is associated with higher loneliness presence

Table 3. Evidence from the systematic reviews of the observational studies included

Studies design	Outcome	Number of studies	Sample size	Main findings
Cross sectional	Social participation in autism	2	53	Compared to controls, people with autism had a greater loneliness perception
Cross sectional	Coping strategies	12	3124	Significant association between loneliness and coping consistently showed that problem-focused coping styles were associated with lower levels of loneliness, and emotion-focused coping styles with higher levels of loneliness.
Cross sectional	Acute stress reactivity	11	1585	The majority of studies reported positive associations between loneliness and acute stress responses, such that higher levels of loneliness were associated with exaggerated physiological reactions. Unclear effect on blood pressure, heart frequency
Cross sectional	Cognitive function	10	260079	Loneliness is significantly and negatively correlated with cognitive function, specifically in domains of global cognitive function or general cognitive ability, intelligence quotient, processing speed, immediate recall, and delayed recall.
Longitudinal	Depression	2	NA	Greater loneliness predicts poorer depression outcome in terms of severity and remission of depression
Longitudinal, cross-sectional	Presence of chronic disease	33	23153	Loneliness is a significant biopsychosocial stressor that is prevalent in adults with heart disease, hypertension, stroke, and lung disease. The relationships among loneliness, obesity, and metabolic disorders are understudied.

Figure 1. PRISMA flow-chart



Supplementary table 1. Credibility assessment criteria for meta-analyses of observational studies

Evidence classification	Criteria
Convincing (class I)	<p>Associations with $p < 0.000001$; $>1,000$ cases (or $>20\,000$ participants for continuous outcomes) having the event of interest; the largest component study reporting a nominal statistically significant result ($p < 0.05$); a 95% PI that excluded the null; no large heterogeneity ($I^2 < 50\%$); no evidence of small-study effect ($p > 0.10$); no excess significance bias ($p > 0.10$).</p>
Highly suggestive (class II)	<p>Associations with $P < 0.000001$; >1000 cases (or $>20\,000$ participants for continuous outcomes) having the event of interest; the largest component study reporting a statistically significant result ($p < 0.05$).</p>
Suggestive (class III)	<p>Associations with $P < 0.001$; >1000 cases (or $>20\,000$ participants for continuous outcomes) having the event of interest</p>
Weak (class IV)	<p>Remaining statistically significant associations with $P < 0.05$.</p>

Abbreviations: PI = prediction interval; RCT = randomized controlled trial.

Supplementary Table 2. List of excluded references, with reasons.

<i>Non-systematic reviews (n=7)</i>
Abdellaoui A, Sanchez-Roige S, Sealock J, et al. Phenome-wide investigation of health outcomes associated with genetic predisposition to loneliness. <i>bioRxiv</i> . 2018:468835.
Bessa B, Ribeiro O, Coelho T. Assessing the social dimension of frailty in old age: A systematic review. <i>Arch Gerontol Geriatr</i> . 2018;78:101-113.
Kitzmuller G, Clancy A, Vaismoradi M, Wegener C, Bondas T. "Trapped in an Empty Waiting Room"-The Existential Human Core of Loneliness in Old Age: A Meta-Synthesis. <i>Qualitative health research</i> . 2018;28(2):213-230.
Mund M, Freuding MM, Mobius K, Horn N, Neyer FJ. The Stability and Change of Loneliness Across the Life Span: A Meta-Analysis of Longitudinal Studies. <i>Personality and social psychology review : an official journal of the Society for Personality and Social Psychology, Inc.</i> 2019:1088868319850738.
Leigh-Hunt N, Baggeley D, Bash K, et al. An overview of systematic reviews on the public health consequences of social isolation and loneliness. <i>Public Health</i> . 2017;152:157-171.
Hagan R, Manktelow R, Taylor BJ, Mallett J. Reducing loneliness amongst older people: a systematic search and narrative review. <i>Aging Ment Health</i> . 2014;18(6):683-693.
Levine MP. Loneliness and eating disorders. <i>The Journal of psychology</i> . 2012;146(1-2):243-257.
<i>No health outcomes (n=2)</i>
Lindsay Smith G, Banting L, Eime R, O'Sullivan G, van Uffelen JGZ. The association between social support and physical activity in older adults: a systematic review. <i>The international journal of behavioral nutrition and physical activity</i> . 2017;14(1):56.
Dyal SR, Valente TW. A Systematic Review of Loneliness and Smoking: Small Effects, Big Implications. <i>Substance use & misuse</i> . 2015;50(13):1697-1716.
<i>No loneliness (n=5)</i>
Heidari Gorji MA, Fatahian A, Farsavian A. The impact of perceived and objective social isolation on hospital readmission in patients with heart failure: A systematic review and meta-analysis of observational studies. <i>Gen Hosp Psychiatry</i> . 2019;60:27-36.
Teo AR, Lerrigo R, Rogers MA. The role of social isolation in social anxiety disorder: a systematic review and meta-analysis. <i>Journal of anxiety disorders</i> . 2013;27(4):353-364.
Seabrook EM, Kern ML, Rickard NS. Social Networking Sites, Depression, and Anxiety: A Systematic Review. <i>JMIR mental health</i> . 2016;3(4):e50.
Hashem MD, Nallagangula A, Nalamalapu S, et al. Patient outcomes after critical illness: a systematic review of qualitative studies following hospital discharge. <i>Critical care</i> . 2016;20(1):345.
Mezuk B, Rock A, Lohman MC, Choi M. Suicide risk in long-term care facilities: a systematic review. <i>Int J Geriatr Psychiatry</i> . 2014;29(12):1198-1211.
<i>Only one study (n=1)</i>
Smagula SF, Stone KL, Fabio A, Cauley JA. Risk factors for sleep disturbances in older adults: Evidence

from prospective studies. Sleep medicine reviews. 2016;25:

Supplementary Table 3: AMSTAR 2 quality assessment of included papers.

	AMSTAR 2 items ^{a, c}																
Author, Year [Reference]	1	2 ^b	3	4 ^b	5	6	7 ^b	8	9 ^b	10	11 ^b	12	13 ^b	14	15 ^b	16	Overall rating (based on critical domains)
Boss, 2015	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate
Brown, 2017	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Moderate
Chang, 2017	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Moderate
Chau, 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Partial Yes	High
da Rocha, 2018	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes	Moderate
Deckx, 2018	Yes	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	No	Yes	Critically Low
Erzen, 2018	Yes	Yes	Yes	Partial Yes	No	No	Yes	Yes	Yes	Partial Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Lara, 2019	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Moderate
Petitte, 2015	Yes	Yes	No	No	Yes	No	Yes	Yes	Partial Yes	Partial Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Pinquart, 2001	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	No	Critically Low
Rico-Urbe, 2018	Yes	Yes	Yes	Partial Yes	No	No	Yes	Partial Yes	Partial Yes	Yes	Yes	Yes	Yes	No	No	Yes	Moderate
Tobin, 2013	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Moderate
Valtorta, 2015	Yes	Yes	No	No	Yes	No	No	No	No	Yes	Yes	Yes	No	No	Yes	No	Critically Low
Wang, 2018	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	Yes	Yes	Critically Low

^a Yes, No, Other

^b Critical Domains

^c AMSTAR 2 items:

1. **Did the research questions and inclusion criteria for the review include the components of PICO (Population, Intervention, Comparator group, Outcome)?**
YES/NO. For yes, must have all four.
2. **Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?** YES, PARTIAL YES, NO. For Partial YES: the authors state that they had a written protocol or guide that included ALL the following (review question(s), a search strategy, inclusion/exclusion criteria, a risk of bias assessment). For YES: as for partial yes, plus the protocol should be registered and should also have specified: a meta-analysis/synthesis plan, if appropriate, and a plan for investigating causes of heterogeneity, justification for any deviations from the protocol.

3. **Did the review authors explain their selection of the study designs for inclusion in the review?** YES/NO. For YES, the review should satisfy one of the following: explanation for including only RCTs, or explanation for including only NRSI, or explanation for including both RCTs and NRSI.
4. **Did the review authors use a comprehensive literature search strategy?** YES, PARTIAL YES, NO. for PARTIAL YES must have all of the following: searched at least 2 databases (relevant to research question), provided key word and/or search strategy, justified publication restrictions (eg. Language). For YES should also have all of the following: searched the reference lists/biographies of included studies, searched trial/study registries, included/consulted content experts in the field, searched for grey literature where relevant, conducted search within 24 months of completion of the review.
5. **Did the review authors perform study selection in duplicate?** YES/NO. for YES, either ONE of the following: at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder selected by one reviewer.
6. **Did the review authors perform data extraction in duplicate?** YES/NO. For YES, either one of the following: at least two reviewers achieved consensus on which data to extract from included studies OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent) with the remainder extracted by one reviewer.
7. **Did the review authors provide a list of excluded studies to justify the exclusions?** YES, PARTIAL YES, NO. FOR partial yes must provide a list of all potentially relevant studies that were read in full text form but excluded from the review. For YES must also have justified the exclusion from the review of each potentially relevant study.
8. **Did the review authors describe the included studies in adequate detail?** YES, PARTIAL YES, NO. For PARTIAL YES, must describe all of the following: populations, interventions, comparators, outcomes, research designs. For YES should also have all of the following: described populations in detail, described intervention and comparator in detail (including doses where relevant), described study setting, timeframe or follow-up.
9. **Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?** For RCTs: YES, PARTIAL YES, NO, INCLUDES ONLY NRSI. For PARTIAL YES must have assessed RoB from unconcealed allocation and lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality); for YES must also have assessed RoB from allocation sequence that was not truly random and selection of the reported result from among multiple measurements or analyses of a specified outcome. For NRSI (Non Randomized Studies of Intervention): YES, PARTIAL YES, NO, INCLUDES ONLY RCTs. For PARTIAL YES must have assessed RoB from confounding and from selection bias. For YES, must also have assessed methods used to ascertain exposures and outcomes, and selection of the reported results from among multiple measurements or analyses of a specified outcome.
10. **Did the review authors report on the sources of funding for the studies included in the review?** YES/NO. For YES: must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies
11. **If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?** For RCTs: YES, NO, NO META-ANALYSIS. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present and investigated the causes of heterogeneity. For NRSI: YES, NO, NO META-ANALYSIS CONDUCTED. For YES: the authors justified combining the data in a meta-analysis and they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present, and they statistically combined effects estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available, and they reported separate summary estimates for RCTs and NRSI separately when both were included in the review.
12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?** YES, NO, NO META-ANALYSIS INCLUDED. For YES: included only low risk of bias RCTs or, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analysis to investigate possible impact of RoB on summary estimates of effect.
13. **Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?** YES/NO. for YES: included only low risk of bias RCTs or, if RCTs with moderate or high RoB, or NRSI were included, the review provided a discussion of the key impact of RoB on the results
14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** YES/NO. For Yes: there was no significant heterogeneity in the results OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

- 15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** YES, NO, NO META-ANALYSIS CONDUCTED. For YES: performed graphical statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias
- 16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** YES/NO. For Yes: the authors reported no competing interests OR the authors described their funding sources and how they managed potential conflicts of interest.

^d Rating overall confidence in the results of the review:

HIGH: *no on one non-critical weakness*: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

MODERATE: *more than one non critical weakness* (multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence): the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

LOW: *one critical flaw with or without non-critical weaknesses*: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

CRITICALLY LOW: *more than one critical flaw with or without non-critical weaknesses*: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.