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Review

Does loneliness contribute to mild cognitive impairment and dementia? A systematic review and meta-analysis of longitudinal studies

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ABSTRACT

There is growing evidence that loneliness is associated with mild cognitive impairment (MCI) and dementia. However, the extent of this association remains unclear. A systematic review and meta-analysis of longitudinal studies examining this association was conducted. Six electronic databases were searched from inception to November 15th 2018. A random-effects meta-analysis was performed to obtain pooled estimates and 95% CIs. Studies were also assessed for heterogeneity, methodological quality and publication bias. A total of 4270 hits were retrieved based on the initial search strategy and ten studies met the eligibility criteria involving 37339 individuals (mean age from 64.9 to 83.1 years). Variation between studies was present for the measurement of loneliness as well as for the case ascertainment of MCI and dementia. Loneliness was positively associated with increased risk of dementia (overall RR = 1.26; 95% CI = 1.14, 1.40; n = 8). Due to lack of sufficient data, we could not explore the association between loneliness and risk of MCI through a meta-analysis, but limited evidence suggests a potential effect of loneliness on MCI. A further understanding of the deleterious effects of loneliness on MCI and dementia may assist the design of environmental and psychological interventions to prevent or delay the onset of these neuropsychiatric conditions.

1. Introduction

Population ageing is the main driver of the dementia epidemic (Prince et al., 2013). According to estimates from the World Alzheimer Report (Prince et al., 2015), the number of individuals living with dementia are expected to dramatically increase in the coming decades, from 47 million in 2015 to 131.5 million by 2050, with a particularly steep increase in low- and middle-income countries. Primary prevention and early detection of dementia should be a public health priority not only for the increasing incidence, but also for the accompanying serious functional limitations, long-term care needs and substantial financial and societal costs (Prince et al., 2015; Wimo et al., 2017). The World Health Organization (WHO) has recently identified priorities to address dementia within the Global action plan on the public health response to dementia 2017–2025, which highlights the importance of investing in health and social systems, and increasing research on dementia to improve knowledge about prevention and risk reduction (World Health Organization, 2017). This is especially relevant given that treatment options for dementia are limited. Consequently, major efforts are being directed towards the identification of potentially modifiable risk factors that could prevent or delay the onset of dementia and mild cognitive impairment (MCI) (Soto-Gordoa et al., 2015). This latter construct represents a transitional state between normal ageing and dementia, for which targeted early preventive interventions may be feasible (Petersen et al., 2009).

A vast amount of research has established associations between some modifiable risk factors (e.g. diabetes, physical inactivity and depression) and subsequent MCI or dementia (Baumgart et al., 2015; Xu et al., 2015). Furthermore, longitudinal studies have documented that community engagement, perceived social support and larger social

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networks may reduce the risk of developing dementia (Crooks et al., 2008; Fratiglioni et al., 2004; Khondoker et al., 2017; Saczynski et al., 2006; Zhou et al., 2018b). Yet, the understanding regarding the association between loneliness and the risk for MCI and dementia remains unclear. Loneliness refers to an individual´s subjective and distressing experience about the discrepancy between one´s social needs and one´s actual interactions with others (Heinrich and Gullone, 2006). Feelings of loneliness are common among older individuals (Nyqvist et al., 2017; Sundstrom et al., 2009) and have a major influence on adverse health outcomes such as functional decline, depression and mortality (Cohen-Mansfield et al., 2016; Rico-Uribe et al., 2018). Such is its impact in the older population that the British government has recently appointed a Minister for loneliness, while in Japan, excessive loneliness among the oldest old became an alarming social concern.

Several pathways through which loneliness may affect MCI and dementia have been proposed. First, loneliness may trigger neural responses that may directly influence the development of neurodegenerative conditions (Boss et al., 2015). Perceived social isolation induces augmented stress reactivity, which is associated with prolonged activation of the hypothalamic-pituitary-adrenal axis (HPA) and the sympathoadrenal system. This disrupted brain response further leads to sleep deprivation, dysregulation of the immune system, increased levels of oxidative stress and over-expression of proinflammatory genes (Cacioppo et al., 2015; Cacioppo and Hawkley, 2009; Darweesh et al., 2018; Hawkley and Cacioppo, 2010; Jaremka et al., 2013; Nersesian et al., 2018; Xia and Li, 2018). Recent publications have provided further evidence on the genetic mechanisms linking loneliness and dementia (Donovan et al., 2016; Hsiao et al., 2018; Salinas et al., 2017). For instance, Donovan et al. (2016) showed that loneliness was associated with amyloid burden in healthy older adults, and this relationship was stronger in APOEe4 carriers, which in turn alter amyloid-related mechanisms involved in dementia pathogenesis (Ge et al., 2018). In the same line, evidence from DNA studies supports the hypothesis that both loneliness and dementia are associated with accelerations in leukocyte telomeres shortening later in life (Forero et al., 2016; Wilson et al., 2018). Second, it is possible that lonely individuals engage in health-damaging behaviours (Hawkley and Cacioppo, 2010), such as physical inactivity, substance abuse or poor dietary choices, all of which may affect cognition either directly via biophysiological mechanisms or via increased risk for cardiometabolic diseases (Steptoe et al., 2004). Third, loneliness is known to be closely associated with depression (Cacioppo et al., 2010) and the contribution of depression to cognitive decline and dementia is well established (Diniz et al., 2013; Duan et al., 2017). Loneliness may lead to depressive symptomatology by deconstructing social expectations and motivations derived from the absence of perceived positive social stimuli (Cacioppo and Hawkley, 2009). Conversely, behavioural alterations that lead to maladjustment to the social environment may compound feelings of loneliness among individuals with depression. Nevertheless, there is sufficient evidence showing that loneliness constitutes an independent risk factor for cognitive decline and dementia even after controlling for the effect of depression (O'Luanaigh et al., 2012; Shankar et al., 2013; Tilvis et al., 2004). Finally, the influence of social involvement may also be related to the critical pathway through which social factors increase dementia risk or cognitive decline (Berkman, 2000), since individuals who feel lonely are less likely to experience cognitive and sensory stimulation derived from social participation, leading to lower cognitive reserve (CR) and consequent poorer cognitive function (Scarmeas and Stern, 2003).

Boss and colleagues (2015) conducted a systematic review on loneliness and cognitive function in the ageing population and concluded that greater loneliness was associated with poorer global cognition and declines in specific cognitive domains including processing speed, immediate recall, and delayed recall. Moreover, a meta-analysis of longitudinal cohort studies on social relationships and the risk of dementia (Kuiper et al., 2015) showed that individuals reporting feelings of loneliness were at a 1.58 (95% confidence interval (CI) = 1.19, 2.09) times higher risk for dementia than in those without feelings of loneliness. This review, though valuable, did not specifically focus on loneliness, only covered three studies on loneliness published in English until 2012 (Chen et al., 2011; He et al., 2000; Wilson et al., 2007), and did not include the most recent population-based studies exploring the specific association between loneliness and subsequent MCI and dementia (Holwerda et al., 2014; Rafnsson et al., 2017; Sutin et al., 2018; Zhou et al., 2018a). Considering these new studies is important, as conflicting results have been found. For example, while Holwerda et al. (2014) found that participants reporting higher levels of loneliness had an increased risk of dementia in a cohort study among 2173 community-living older individuals, Chen and colleagues (2011) showed that loneliness was not associated with incident dementia in a population-based sample of 1526 elderly individuals aged 65+ years. Additionally, no study has summarised the potential association between loneliness and incident MCI to date. Therefore, the aim of this systematic review and meta-analysis is to investigate the longitudinal association between loneliness and risk of MCI and dementia among the middle-aged and older adults from the general community-dwelling population.

2. Methods

This study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA-P) guidelines (Moher et al., 2015). The protocol of this study has been previously registered at the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42018102623).

2.1. Search strategy

Six electronic databases were searched from inception to November 15th 2018: CINAHL, Cochrane Library, PsycINFO, PubMed, Scopus and Web of Science. The search strategy included combined terms on: a) loneliness (e.g. lonely, feeling isolated, social withdrawal); b) MCI and dementia; and c) study design (longitudinal, cohort, follow-up). The specific search strategy for each database is displayed in Appendix A in the supplementary material. Additionally, a manual search of all the included studies and previous related systematic reviews and meta-analyses (Boss et al., 2015; Evans et al., 2018b; Kuiper et al., 2015, 2016; Pillai and Verghese, 2009; Wilson and Bennett, 2017) was performed to identify further eligible articles.

2.2. Study selection

Records were selected if they fulfilled the following inclusion criteria: i) included middle- and older-aged individuals (50+ years) from the general community-based population (Singh-Manoux et al., 2012); ii) explored loneliness (i.e. perceived social isolation or subjective loneliness) as the exposure variable; iii) included at least one of the outcomes for this review (incident MCI or dementia); iv) included cognitively healthy individuals at baseline; v) followed a longitudinal design, lasting at least one year (longitudinal observational studies, prospective cohort studies); vi) reported quantitative data; and vii) were peer reviewed articles. No time or language restrictions were imposed in either the computerised or the manual searches.

Records were excluded if they: i) were conducted in animals, clinical or younger populations; ii) assessed other related constructs of social networks different from loneliness or measured loneliness during the follow-up assessment rather than at baseline or prior to the final follow-up; iii) considered MCI or dementia as covariates; iv) included individuals cognitively impaired at baseline (e.g. prevalent cases of MCI or dementia); v) were case-series studies,case studies, ecological studies, cross-sectional studies, case control studies, retrospective cohort studies, qualitative studies, and experimental or quasi experimental

studies; vi) were books, comments, conference papers, editorials, letters, theses or related.

2.2.1. MCI and dementia diagnosis

The presence of MCI and dementia could be determined by a combination of clinical evaluation, self-reported or proxy-reported physician diagnosis, medical history, laboratory tests, and/or underlying cause of death, provided they were clearly stated.

2.3. Data extraction

Several steps were performed in order to select the studies and extract the information. In a first step, duplicate records identified through the electronic search were removed using a reference manager software package. After that, E.L. screened the title and abstract of all records using the abovementioned criteria to select potentially relevant studies. A second reviewer (N.M.-M.) independently double-checked a random sample of 20% of retrieved articles. Discrepancies on articles' eligibility were reviewed and discussed until a consensus was reached. The degree of agreement between the researchers was 99.4% (kappa = 0.82; 95% CI = 0.62, 1.00), which indicates a high level of inter-rater agreement (Peat, 2001). Subsequently, full-texts of all potentially eligible publications were assessed for final selection and coded as either included or excluded (with reasons for exclusion). Finally, the following data were extracted: first author´s name, year of publication, study design (location, sample size, follow-up period), participants' information (mean age, age range, percentage of females), loneliness measurement, definition of MCI and dementia (separately), adjustment for covariates and estimates of associations (effect size with its 95% CI). When necessary, corresponding authors of the original articles were contacted to obtain unreported data required for this study.

2.4. Quality assessment

Quality of study assessment was conducted using an adapted version of the Newcastle-Ottawa Scale (NOS) for assessing risk of bias (Wells et al., 2000). The NOS is an eight-item instrument designed to rate methodological aspects of case-control and cohort studies. It includes three domains: study selection (representativeness of the exposed cohort, selection of the unexposed cohort, ascertainment of exposure and demonstration of absence of outcome at start of study), comparability of cohorts on the basis of the design or analysis (i.e. statistical models appropriately adjusted for confounders), and outcome (outcome assessment, follow-up period and adequacy of follow-up). Detailed information is provided in Appendix C. A study was given a maximum of one point for each numbered item within the study selection and outcome domains, while a maximum of two points can be allocated for the comparability domain. The overall score ranges from 0 to 9. Scores < 5 were considered as low-quality studies (i.e. high risk of bias), scores 5–6 as moderate-quality studies and scores ≥ 7 indicated high-quality studies (Stang, 2010).

2.5. Statistical analysis

Meta-analysis for each outcome was planned separately (i.e. MCI risk, dementia risk and articles reporting both MCI and dementia risk as a single outcome). Given the difficulties associated with the case ascertainment of dementia and dementia subtypes, especially in the context of epidemiological research (Brayne and Davis, 2012), we combined studies reporting incident dementia and specific types of dementia (e.g. Alzheimer´s Disease). When a study provided data on both dementia and type of dementia separately, only dementia was included in the present meta-analysis. The same procedure was followed for all-cause MCI and its subtypes.

Relative risk (RR) was used as the effect size measure. Other estimates (e.g. odds ratio (OR), betas (B) or hazard ratio (HR)) were converted and interpreted as RR given that the outcome incidence among study participants was uncommon (i.e. $< 20\%$) in all studies (Higgins and Green, 2008). In all cases, effect estimates were transformed to their natural logarithm. A random-effects meta-analysis was performed as heterogeneity was expected due to the variability among study settings and outcomes being derived from different procedures (Jackson et al., 2010). The inverse-variance method was used to obtain pooled estimates and 95% CI. This approach minimises the uncertainty of the pooled effect estimate, as larger studies, which have smaller standard errors, are given more weight than smaller studies (Higgins and Green, 2008). Adjusted estimates over crude estimates were prioritised. In case of several studies reported findings on a same cohort, we retained data with higher sample size, longer follow-up or the most complete confounder adjustment.

Heterogeneity between studies was assessed by means of the Cochran Q test and the point I^2 statistic with its 95% CI (von Hippel, 2015). I^2 values higher than 50% represent substantial heterogeneity (Higgins and Green, 2008).

Visual inspection of potential publication bias was conducted via the contour-enhanced funnel plot (Peters et al., 2008). The natural logarithm of the effect estimates was plotted against the inverse of its standard error. This technique allows distinguishing asymmetry due to publication bias from other factors by including areas of statistical significance on the funnel plot. Missing studies in areas of non-statistical significance would possibly suggest asymmetry caused by publication bias. On the contrary, in areas of high statistical significance where studies appear to be missing, the observed asymmetry is more likely to be due to factors other than publication bias (Higgins and Green, 2008). We also intended to use statistical tests as objective measures of asymmetry (Begg and Mazumdar, 1994; Egger et al., 1997).

A series of sensitivity analyses was conducted to explore the robustness of the main findings. Firstly, the effect of loneliness on dementia was assessed through a meta-analysis excluding studies that assessed dementia subtypes rather than all-cause dementia. A similar procedure was planned for all-cause MCI and its subtypes but not conducted as there were insufficient studies. Secondly, we excluded articles that assessed loneliness though a single question. Thirdly, a meta-analysis focusing exclusively on studies with moderate or high risk of bias due to weak methodological controls was performed. Fourthly, studies with follow-up periods shorter than 5 years were omitted to explore whether loneliness may account as a causal risk factor rather than a prodrome of dementia. Finally, in order to assess the extent to with the association between loneliness and dementia may be influenced by depression, which is known to be related with both loneliness and dementia (Cacioppo et al., 2010; Diniz et al., 2013), we tested whether the main results remained unchanged exclusively in studies that adjusted for depression. All these analyses were conducted using random-effects models. Data analyses were performed using Stata 14 (Stata Corp LP, College Station, TC, USA) by means of the metan, heterogi and confunnel commands.

3. Results

3.1. Literature search

A total of 4272 hits were retrieved based on the initial search strategy (Fig. 1). After excluding duplicates, 2572 titles and abstracts were screened. Of these, 61 potentially relevant records were selected for full-text revision. Fifty-two citations did not meet the eligibility criteria and were excluded, resulting in nine selected articles. Complementarily, the manual search yielded one additional article (Chen et al., 2011). Articles that reported effect sizes for different outcomes were considered as separated studies (Lobo et al., 2008). Thus, eleven studies derived from ten articles were included in the qualitative

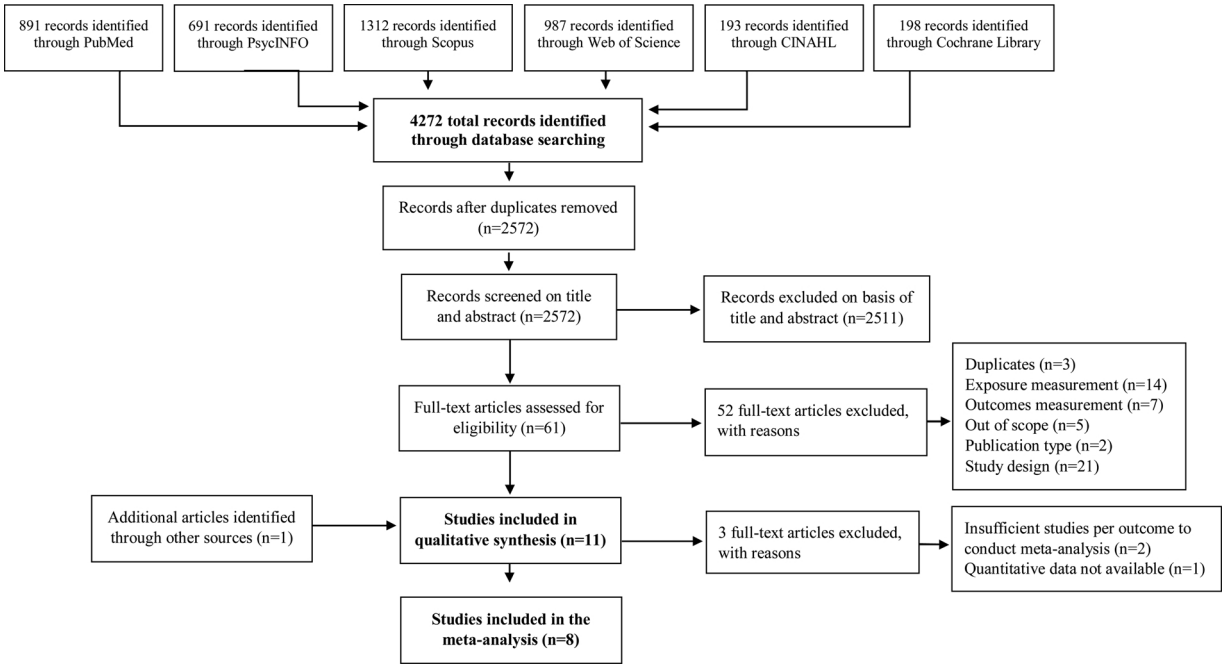

Fig. 1. Flowchart of the study selection.
Note = Articles refer to papers while studies allude to analysis and effect sizes for specific outcomes (e.g. one article may provide data for MCI and dementia separately).

synthesis (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017; Rawtaer et al., 2017; Sutin et al., 2018; Wilson et al., 2015, 2007; Zhou et al., 2018a). Of them, eight studies were included in the meta-analyses (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017; Sutin et al., 2018; Wilson et al., 2007; Zhou et al., 2018a).

3.2. Qualitative synthesis

3.2.1. Study and participants' characteristics

Table 1 lists the main characteristics of all included studies. Four studies concerned Asian populations (Chen et al., 2011; He et al., 2000; Rawtaer et al., 2017; Zhou et al., 2018a), three were conducted in the United States (Sutin et al., 2018; Wilson et al., 2015, 2007), and four involved individuals from European countries (Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017). All studies enrolled community-dwelling populations, and participants were randomly selected in nine studies (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017; Rawtaer et al., 2017; Sutin et al., 2018; Zhou et al., 2018a), while three studies included representative non-institutionalised samples from England (Rafnsson et al., 2017), United States (Sutin et al., 2018) and China (Zhou et al., 2018a). In total, 37,339 individuals were included (range 529–12030), and the mean age ranged from 64.9 to 83.1 years and samples mostly consisted of female participants in all but one of the studies (43.5%–78.9% female individuals) (Chen et al., 2011). Seven studies had follow-up periods longer than 5 years (Chen et al., 2011; He et al., 2000; Rafnsson et al., 2017; Rawtaer et al., 2017; Sutin et al., 2018; Wilson et al., 2015, 2007). Loneliness was assessed using a single Likert-scale or yes-no format question in six studies (Chen et al., 2011; Holwerda et al., 2014; Lobo et al., 2008; Rawtaer et al., 2017; Zhou et al., 2018a), while four studies used a validated rating scale (Rafnsson et al., 2017; Sutin et al., 2018; Wilson et al., 2015, 2007) and one study did not provide information on the measurement of loneliness (He et al., 2000). MCI occurred in 406 of 2183 individuals during follow-up (Lobo et al., 2008; Wilson et al., 2015); dementia, either Alzheimer´s disease or all-cause dementia, was diagnosed in 2237 of 33,555 participants (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017; Wilson et al., 2007; Zhou et al., 2018a); and 163 of 1601 subjects were diagnosed with MCI/dementia (Rawtaer et al., 2017). Diagnoses were based on several procedures: reported physician diagnosis, brief or comprehensive clinical evaluations, laboratory tests and death certificates. All studies but one (Zhou et al., 2018a) included clinical examinations for case ascertainment. Four studies (He et al., 2000; Lobo et al., 2008; Rawtaer et al., 2017; Wilson et al., 2007) followed Petersen´s criteria (Petersen et al., 1999), the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984) and/or criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 1980, 1994) to define MCI, AD and dementia respectively (Appendix B).

3.2.2. Quality assessment

Table 2 provides the methodological quality assessment of each included study according to the NOS tool and Appendix C presents scoring criteria. Studies that were retrieved from the same article were assessed together (Lobo et al., 2008). Major methodological flaws were found for the exposure assessment (4/10), the length of follow-up for the outcome to occur (7/10) and attrition (i.e. follow-up rate or description of individuals that were lost to follow-up) (4/10). Overall, scores ranged from 5 to 8, suggesting moderate to high quality-studies. Four studies were qualified as low risk of bias (Rafnsson et al., 2017; Rawtaer et al., 2017; Wilson et al., 2015, 2007) and six studies presented moderate risk of bias (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Sutin et al., 2018; Zhou et al., 2018a).

3.3. Quantitative synthesis

3.3.1. Loneliness and the risk for MCI

Two studies have explored so far the association between loneliness and subsequent MCI (Lobo et al., 2008; Wilson et al., 2015). Unfortunately, the study by Wilson et al. (2015) did not report effect sizes

Table 1
Characteristics of included studies.

Code[1]	First author (year)	Location	Sample size, % women	Follow-up period	Mean age (SD), age range	Loneliness measurement	Outcome	Adjustment for covariates	Results (effect size; 95% CI)
1	Chen, R (2011)	China	1307, 43.5%	7.5 years	NA, 65+ years	Feeling lonely vs not feeling lonely (binary)	Incident dementia	Age and sex	OR = 1.69 (0.79, 3.89)
2	He, YL (2000)	China	1203, 58.0%	10 years	NA, 55+	NA	Incident AD	Age and sex	RR = 1.63 (0.93, 2.86)
3	Holwerda, T (2014)	The Netherlands	2173, 63.1%	3 years	NA, 65-86 years	Do you feel lonely or do you feel very lonely? (single question; binary)	Incident dementia	Age, sex, level of education, marital status, living situation (alone), depression, cardiovascular and other medical conditions, cognitive function, ADL/IADL and social support	OR = 1.64 (1.05, 2.56)
4a	Lobo, A (2008)	Spain	1506, 55.2%[2]	3 years	73.6 (8.7) [2], 55+ years	Item on loneliness from the GMS (single question; binary)	Incident dementia	Age, sex, educational level, and 23 non-cognitive symptoms (worry, anxiety, tension, irritability, anhedonia, among others)	OR = 3.25 (0.92, 11.5)[3]
4b	Lobo, A (2008)	Spain	1654, 55.2%[2]	3 years	73.6 (8.7)[2], 55+ years	Item on loneliness from the GMS (single question; binary)	Incident MCI	Age, sex, educational level, irritability, neurovegetative symptoms, sleep problems, lack of concentration and subjective slowness	OR = 2.05 (1.31, 4.97)
5	Rafnsson, SB (2017)	England	6677, 55.7%	8 years	66.0 (9.4), 52-90 years	Short form of the Revised UCLA Loneliness Scale (continuous)	Incident dementia	Age, sex, level of education, marital status, wealth, hypertension, diabetes, stroke, cancer, coronary health disease, mobility, depression, baseline cognitive function, social isolation and close relationships	OR = 1.36 (1.03, 1.80)
6	Rawtaer, I (2017)	Singapore	1601, 64.5%	8 years	64.9 (6.8), 55+	Do you feel that at the present moment you are not at all lonely or fairly lonely or very lonely? (single Likert scale question; binary in regression models)	Incident MCI and dementia	Age, sex, ethnicity, smoking, alcohol consumption, dyslipidemia, hypertension, diabetes, obesity, stroke/heart disease, APOE-e4 allele carrier, depression, physical activities, social activities, productive activities, living status, marital status and satisfaction with life.	HR = 1.02 (0.66, 1.57)
7	Sutin, AR (2018)	United States	12,030, 60%	10 years	67.30 (10.45)	Short form of the Revised UCLA Loneliness Scale (continuous)	Incident dementia	Age, sex, years of education, race, ethnicity, hypertension, diabetes, smoking, physical activity, BMI, social isolation, depressive symptoms	HR = 1.19 (1.05, 1.33)
8	Wilson, RS (2007)	United States	792, 75.7%	6 years	80.7 (7.1), 50+	Modified version of the De Jong-Gierveld Loneliness Scale (continuous)	Incident AD	Age, sex, level of education social activity, social network, physical activity, cognitive activity, depressive symptoms, income, race/ethnicity, disability and vascular risk factors	RR = 1.51 (1.07, 2.15)
9	Wilson, RS (2015)	United States	529, 78.9%	10 years	81.4 (7.1), 50+	Modified version of the De Jong-Gierveld Loneliness Scale (continuous)	Incident MCI	Age, sex, and education, depressive symptoms, social network size, social interaction frequency, negative social interactions	NA
10	Zhou, Z (2017)	China	7867, 54.9%	3 years	83.1 (10.9), 65+ years	Do you often feel lonely? (single Likert scale question; continuous)	Incident dementia	Age, sex, type of area (rural), level of education, living situation, marital status, social support, institutionalization, exercise, smoking, alcohol consumption, nut and milk intake, stroke, cerebrovascular diseases, hypertension, diabetes, cognitive function and ADL	OR = 1.15 (1.04, 1.28)

Note = Articles that reported effect sizes for different outcomes were considered separately.
1Studies ordered by alphabetical author´s name.
2Data referred to the overall sample included in this article.
3Data provided by the authors of the study.
Abbreviations= AD Alzheimer´s Disease; ADL Activities of Daily Living; BMI Body Mass Index; APOE-e4 Apolipoprotein e4; CI Confidence Interval; IADL Instrumental Activities of Daily Living; HR Hazard ratio; MCI Mild Cognitive Impairment; NA Not Available; OR Odds ratio; RR Relative risk; SD Standard Deviation; UCLA University of California Los Angeles Loneliness Scale.

Table 2
The Newcastle-Ottawa Scale for assessing the quality of included studies.

Study (code)	Study selection				Comparability	Outcome			Overall risk[1]
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Chen R, 2011 (1)	*	*		*	*	*	*		**6**
He YL, 2000 (2)	*	*		*	*	*	*		**6**
Holwerda T, 2014 (3)	*	*		*	**	*			**6**
Lobo A, 2008 (4a, 4b)	*	*		*	*	*			**5**
Rafnsson SB, 2017 (5)	*	*	*	*	**		*		**7**
Rawtaer I, 2017 (6)	*	*		*	**	*	*		**7**
Sutin, AR (7)	*	*	*	*	**		*	*	**8**
Wilson RS, 2007 (8)		*	*	*	**	*	*	*	**8**
Wilson RS, 2015 (9)		*	*	*	*	*	*	*	**7**
Zhou Z, 2017 (10)	*	*		*	**			*	**6**
Total	8	10	4	10	16	7	7	4	

Notes: a study can be given a maximum of one star for each fulfilled item within the Study selection and Outcome categories. A maximum of two stars can be assigned for Comparability. Detailed information about the quality review can be found in Appendix C. Study codes correspond to those listed in Table 1.
1Scores range from 0 to 9. Scores < 5 were considered as low-quality studies; scores 5–6 as moderate-quality studies; scores $\geq$ 7 indicated high-quality studies.

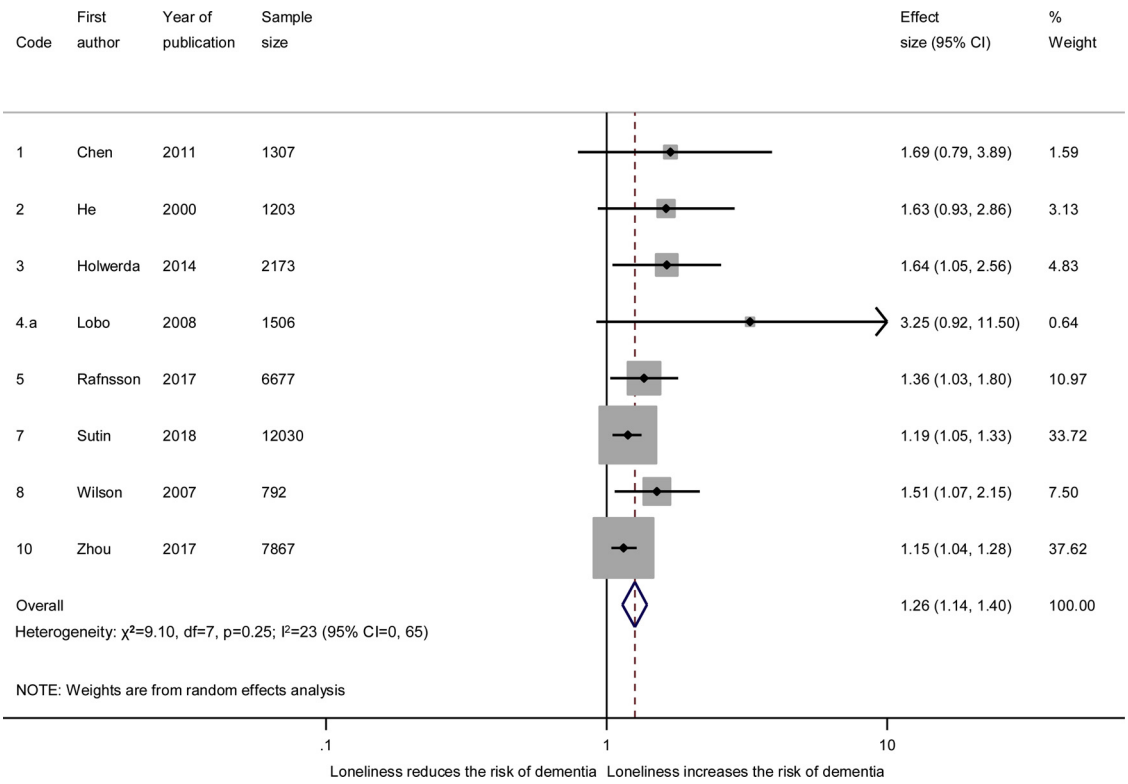

Fig. 2. Forest plot of the effect of loneliness on incident dementia.
Notes = An inverse-variance weighted random-effect meta-analysis is displayed. Effect size corresponds to relative risk.
Study codes correspond to those listed in Table 1.
Abbreviations = CI: Confidence Interval; Df: Degrees of Freedom.

and the authors were unable to provide these data. Therefore, we could not conduct a meta-analysis. In Lobo and colleagues´ study (2008), 208 MCI cases were identified at follow up (12.6%). A significant effect of loneliness (OR = 2.05; 95% CI = 1.31, 4.97) for increasing risk of MCI was found (Table 1).

3.3.2. Loneliness and the risk for dementia

Pooled estimates from the association between loneliness and dementia are displayed in Fig. 2. This meta-analysis included data from eight independent studies (n = 33,555) assessing either incident all-cause dementia or AD (Chen et al., 2011; He et al., 2000; Holwerda et al., 2014; Lobo et al., 2008; Rafnsson et al., 2017; Sutin et al., 2018; Wilson et al., 2007; Zhou et al., 2018a). Lonely individuals or individuals reporting greater feelings of loneliness had an increased risk of dementia (overall RR = 1.26; 95% CI = 1.14, 1.40). The level of heterogeneity was moderate with wide CIs (I^2 = 23%; 95% CI = 0, 65) and the Cochran Q test was not significant ($\chi 2(7) = 9.10$, p = 0.25).

3.3.3. Loneliness and the risk of combined outcomes (MCI and dementia)

The work by Rawtaer et al. (2017) was the only study exploring MCI and dementia simultaneously as a single outcome. Of the 1601 cognitively healthy individuals at baseline, a total of 163 individuals developed MCI-dementia at follow up. Feelings of loneliness were not associated with subsequent MCI-dementia (HR = 1.02; 95% CI = 0.66, 1.57).

3.3.4. Publication bias

Visual examination of contour-enhanced funnel plot suggests that studies on loneliness and dementia (data from section 3.3.2.) are perceived to be missing in areas of statistical significance (in grey), which would indicate that the cause of asymmetry may be more likely to be associated with factors other than publication bias (Fig. 3). The limited number of included studies (n = 8) did not support statistical testing for asymmetry.

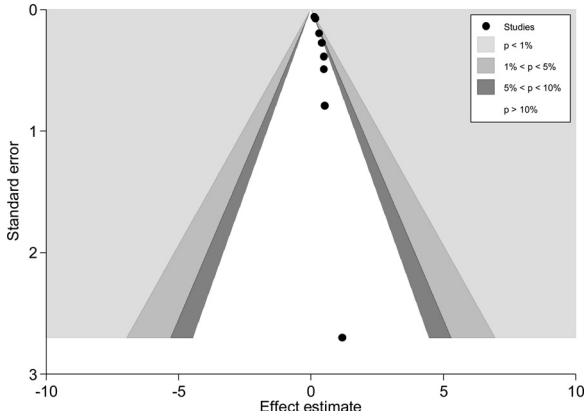

Fig. 3. Contour-enhanced funnel plot for loneliness and the risk of dementia.
Note = Effect estimate corresponds to relative risk.

3.3.5. Sensitivity analyses

The main results (section 3.3.2.) remained unchanged in sensitivity analysis removing two studies exclusively on AD (He et al., 2000; Wilson et al., 2007) (RR = 1.22 [95% CI = 1.10, 1.36]; I^2 = 22 [95% CI = 0, 66]). Likewise, none of the study characteristics assessed in sensitivity analyses (i.e. studies using validated questionnaires for loneliness, high to moderate risk of bias, longer follow-up period and adjusting for depression) revealed a different effect on the relationship between loneliness and risk of dementia (RR = 1.23 to RR = 1.29), indicated by the overlapping CIs of these effect estimates as compared with the main results (Table 3).

Table 3
Sensitivity analysis for the association between loneliness and dementia based on study characteristics.

Analyses	Studies included in meta-analysis (code)	Pooled estimate (RR, 95% CI)	Heterogeneity between studies	
			Cochran's Q test (χ^2(df); *p value*)	I^2 (%, 95% CI)
Studies exclusively on all-cause dementia	1, 3, 4.a, 5, 7, 10	1.22 (1.10, 1.36)	6.42 (5); 0.27	22 (0, 66)
Loneliness measurement (validated questionnaires)	5, 7, 9	1.24 (1.11, 1.39)	2.11 (2); 0.35	5 (0, 90)
Follow-up period (+5 years)	1, 2, 5, 7, 8	1.26 (1.13, 1.39)	3.54 (4); 0.47	0 (0, 79)
Depression adjustment (yes)	3, 5, 7, 8	1.29 (1.13, 1.47)	3.56 (3); 0.31	16 (0, 87)
Risk of bias (moderate)	1, 2, 3, 4.a, 10	1.23 (1.09, 1.38)	6.78 (5); 0.23	26 (0, 69)

Abbreviations = CI: Confidence Intervals; df: Degrees of Freedom; RR = Relative Risk.
Note = Study codes correspond to those listed in Table 1.

4. Discussion

4.1. Summary of results and comparison with previous work

A small number of longitudinal observational studies that explored the association between loneliness and subsequent MCI or dementia was identified, demonstrating the existence of an important gap in the literature. Our study results showed that loneliness was associated with an increased risk of incident dementia based on a meta-analysis. Several sensitivity analyses further revealed the robustness of the main findings: the effect of loneliness on dementia risk did not seem to be largely affected by the exposure measurement, duration of follow-up, depression adjustment or risk of bias (23%–29% increased risk). While we found a stronger association between loneliness and dementia with longer follow-ups, which may suggest that loneliness could be a causal risk factor rather than a prodrome of dementia, this hypothesis is not supported by the overlapping CIs of effect estimates nor by previous researchers claiming that it is more likely that loneliness compromises neural responses that affects how dementia-related pathologies are clinically expressed (Rozzini et al., 2008; Wilson and Bennett, 2017).

We were unable to conduct meta-analyses with MCI as the outcome since there were only two longitudinal studies of which one did not provide effect sizes (Lobo et al., 2008; Wilson et al., 2015), but limited evidence suggests a potential effect of loneliness on MCI. In addition, some recent cross-sectional studies exploring this association have reported conflicting results (Kwon et al., 2017; Yu et al., 2016).

Our findings are in line with previous studies showing a detrimental effect of loneliness on subsequent cognitive decline or dementia (Boss et al., 2015; Cacioppo and Hawkley, 2009; Gow and Mortensen, 2016; Kuiper et al., 2015, 2016; Rozzini et al., 2008; Shankar et al., 2013; Tilvis et al., 2004; Wang et al., 2011; Zhong et al., 2016, 2017). In addition, the influence of loneliness on risk for dementia is comparable in size with other well-established risk factors for cognitive decline and dementia, including diabetes (RR = 1.5; 95% CI = 1.33, 1.79), physical inactivity (RR = 1.4; 95% CI = 1.16, 1.67) and hearing loss at midlife (RR = 1.9; 95% CI = 1.38, 2.73) (Livingston et al., 2017). Yet, our understanding about the implications of loneliness on dementia remains superficial as compared with the current evidence on other recognized risk factors.

4.2. Strengths and limitations

There are several strengths related to our research. First, we performed a comprehensive systematic search including a variety of databases combined with manual searching, using a broad range of search terms and covering all languages and years. Second, independent reviewers completed study selection, with a high level of inter-rater agreement. Third, included studies were conducted in population samples from both Eastern and Western countries, which might enable us to generalise our findings to diverse regions and cultures. Additionally, these studies were performed in community-dwelling individuals, and can thus be generalised to the general population. Therefore, the results of these studies may have direct relevance in terms of public health policy.

Our study results should nevertheless be interpreted in the light of the study limitations. This meta-analysis is essentially limited to the small number of included studies, which shows that literature relating loneliness with MCI and dementia is notably insufficient. Still, most studies were recent population-based studies and their overall methodological quality was moderate to high. In addition, we only selected articles published in peer-reviewed journals. However, it was decided not to include grey literature (i.e. material not formally published) since its inclusion does not guarantee the reduction of publication bias (Martin et al., 2005). Furthermore, we were not able to retrieve the necessary information from one study with insufficient data (Wilson et al., 2015), despite having contacted the authors. Even though our exhaustive literature search was highly sensitive, selective reporting may have occurred (i.e. observational studies exploring the effect of some exposures on MCI and dementia, may have included loneliness as a potential covariate without reporting any risk estimate in their publications). Although loneliness may vary over time in some individuals, studies included in this meta-analysis did not account for the persistence of loneliness, which may have compromised our results. However, a recent study by Zhong and colleagues (2016) showed that both transient and chronic loneliness were significantly associated with poorer cognitive function after 6 years of follow-up in 2995 older adults from China. Moreover, there was heterogeneity among studies in the way MCI and dementia were ascertained, leading to potential misclassification. However, incidence rates were consistent among studies, suggesting that diagnostic bias is unlikely to have largely affected our results. In the same line, there may be attribution bias. For example, those who died during the follow-up period may have had MCI or dementia before death. This may have led to an underestimation of the true association of loneliness on MCI and dementia risk. As with other reviews, potentially unobserved variables, such as CR, could have also confounded the findings of this study. Importantly, this research involved longitudinal observational studies so causality cannot be inferred. In addition, our findings do not rule out a potential reverse causal direction. As noted earlier, loneliness may appear either as a behavioural manifestation of cognitive deterioration or as an early sign of an underlying pathology contributing to MCI and dementia (Hawkley and Cacioppo, 2010; Wilson and Bennett, 2017). In order to minimize this possibility, all studies excluded individuals with cognitive impairment or dementia at study entry and some of them further adjusted for participants' cognitive status at baseline in the statistical models. Because the I^2 statistic values showed poor precision (wide CIs) when the number of studies in the meta-analysis was small, the conclusion on the level of between-study heterogeneity should be interpreted cautiously. Further, the small number of studies involved in the present work together with the uncertainty around the I^2 statistic limited us from conducting subgroup or meta-regression analyses to explore the influence of potential effect modifiers' (Higgins and Thompson, 2004; von Hippel, 2015). Nevertheless, we performed a series of sensitivity analyses to support the robustness of the main pooled estimates. Likewise,

statistical testing for asymmetry was precluded as these tests are often underpowered and may yield misleading results when less than 10 studies are included (Higgins and Green, 2008). Altogether, these are common statistical limitations of most meta-analyses (Davey et al., 2011; Ioannidis et al., 2007).

4.3. Conclusions

Individuals, as social beings, have a vital need to belong. As such, unsatisfying social relationships have important implications for physical and mental health (Heinrich and Gullone, 2006). Understanding the deleterious effect of loneliness on cognitive function, specifically on MCI and dementia, may serve to design environmental and psychological interventions that could prevent or delay the onset of these neuropsychiatric diseases. Adequate interventions that enhance community participation and the maintenance of social relationships represent an affordable strategy not only to potentially reduce MCI and dementia risk but also to fulfill a feeling of meaningfulness in life. Based on the meta-analysis, loneliness was found to be significantly associated with the incidence of dementia. Despite the rising interest in loneliness at both scientific and societal levels, more research is highly needed. In order to draw more accurate conclusions, future studies should preferably use validated scales for loneliness that account for the history of participants' feelings of loneliness, evaluate potential cases of MCI and dementia through comprehensive assessments done by clinical experts and perform analysis adjusting for factors that are likely to have an influence on the above-mentioned association.

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Conflict of interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2019.03.002.

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