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Review

Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies



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ABSTRACT

It is unclear to what extent poor social relationships are related to the development of dementia. A comprehensive systematic literature search identified 19 longitudinal cohort studies investigating the association between various social relationship factors and incident dementia in the general population. Relative risks (RRs) with 95% confidence intervals (CIs) were pooled using random-effects meta-analysis. Low social participation (RR: 1.41 (95% CI: 1.13–1.75)), less frequent social contact (RR: 1.57 (95% CI: 1.32–1.85)), and more loneliness (RR: 1.58 (95% CI: 1.19–2.09)) were statistically significant associated with incident dementia. The results of the association between social network size and dementia were inconsistent. No statistically significant association was found for low satisfaction with social network and the onset of dementia (RR: 1.25 (95% CI: 0.96–1.62). We conclude that social relationship factors that represent a lack of social interaction are associated with incident dementia. The strength of the associations between poor social interaction and incident dementia is comparable with other well-established risk factors for dementia, including low education attainment, physical inactivity, and late-life depression. © 2015 Elsevier B.V. All rights reserved.

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1. Introduction

Dementia has emerged as major public health issue because of high prevalence rates, high burden to patient, carer and society, and high health care costs (Langa et al., 2001; World Health Organization, 2012). In 2010, more than 35 million people worldwide were affected by dementia and this is expected to increase to 115 million people in 2050 (Ferri et al., 2006; Prince et al., 2013). Increased longevity and the aging of the baby boom generation largely contribute to the increased prevalence of dementia (Middleton and Yaffe, 2009; World Health Organization, 2012). The prevalence of dementia approximately doubles with every 5-year increase in age after the age of 60, from 1% among people aged 60 to 25% among people aged \geq 85 years from Western Europe in 2001 (Ferri et al., 2006). An average delay of two years in onset of Alzheimer's disease (AD) could decrease the worldwide prevalence of AD by 22.8 million cases by the year 2050 which would subsequently lower the number of cases that need high level care and associated costs (Brookmeyer et al., 2007). Currently, there is no effective treatment available to cure dementia. Therefore, identification of modifiable risk factors is of utmost importance in order to delay or prevent the onset of dementia (Middleton and Yaffe, 2009). One potentially important modifiable risk factor for incident dementia is the absence of good social relationships. Good social relationships were found to protect against multiple adverse outcomes, including depression (Santini et al., 2014), coronary heart disease (Hemingway and Marmot, 1999), functional decline (Avlund et al., 2004), and mortality (Holt-Lunstad et al., 2010). The definition and operationalization of social relationships differs across studies. Social relationships can for example contain structural features such as the number of one's social ties, but also qualitative aspects such as levels of social support (Seeman et al., 2001). It is important to distinguish between these different aspects of social relationships, because they may influence health through different mechanisms (Cohen, 2004). For example, social integration may have a beneficial effect on health through influencing health behaviors. Whereas social support may benefit health through stress reduction, by providing psychological and material resources needed to cope with stress (Cohen, 2004).

Previous reviews have investigated the influence of social relationships (i.e., socially integrated lifestyle, social engagement, social activities) on incident dementia, but conclusions were contradictory (Di Marco et al., 2014; Fratiglioni et al., 2004; Pillai and Verghese, 2009; Wang et al., 2012; Williams et al., 2010). The reviews did not perform a meta-analysis, did not distinguish between various social relationship factors, or did not take into account the methodological quality of the included studies.

Therefore, our aim is to investigate the relation between social relationships and incident dementia in the general population by conducting a systematic review, including a meta-analysis of longitudinal cohort studies, in which we will take into account different aspects of social relationships (e.g., social network size, social participation, loneliness).

2. Methods

This systematic review was conducted according to the methods of the Cochrane Collaboration (Higgins and Green, 2008) and in addition, we followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009) for the reporting of this systematic review and meta-analysis.

2.1. Systematic search and study selection

A systematic database search in MEDLINE, Embase and PsycINFO was conducted on July 9th 2012. Search strings included suitable indexing terms (i.e., MeSH terms and keywords) on (1) social relationships (e.g., social network; social engagement; loneliness) and (2) dementia (e.g., dementia; Alzheimer's disease; cognitive decline) (see Appendix A). Articles were included if they were peer reviewed articles reporting on an association between social relationships measured at baseline and incident dementia during follow-up in a quantitative way; utilizing a longitudinal prospective cohort study design conducted in the general population. Only articles published in English; Dutch; German or French were included. Two reviewers (JSK and MZ) independently screened title and abstract of all citations identified by the search. Subsequently; the full text of all potentially eligible articles was screened for final selection by the same reviewers. Reference lists of all included articles and relevant reviews on this topic were screened for potentially eligible studies.

2.2. Data extraction and methodological quality assessment

Two reviewers (JSK and MZ) independently extracted the data regarding study population, social relationship assessment, statistical method and results, timing of follow-up measurements, and outcome (incident dementia). The methodological quality of included studies was assessed by the two reviewers (JSK and MZ) independently using the Quality of Prognosis Studies in Systematic Reviews (QUIPS) tool (Hayden et al., 2006) (see Appendix B). Disagreements were resolved in a consensus meeting. In case of persistent disagreement, a third reviewer (NS) made the final decision.

2.3. Statistical analysis

Social relationship factors were categorized into (1) social network size; (2) social participation (e.g., participation in associations or community activities); (3) frequency of social contact (e.g., visiting or receiving phone calls from friends, children or other relatives); (4) loneliness; (5) satisfaction with social network (e.g., satisfied with network interactions or having good relations with others); and (6) other social relationship factors (e.g., composite measures of social relationships measures, perception of reciprocity). Studies including incident (all case) dementia or incident AD as outcome were combined in the meta-analyses. If studies reported the outcomes separately, dementia was included in the meta-analysis.

In case studies reported multiple estimates, the adjusted estimates were used for the meta-analysis. Estimates were preferred that were adjusted for age, depression, alcohol use, education, baseline cognition, and physical functioning (this included at least one of the three following variables: physical activity, functional disability, or at least one of the following chronic disease: traumatic brain injury (TBI), cardiovascular disease, or cerebrovascular accident (CVA)/stroke). Estimates adjusted for these variables were preferred over unadjusted estimates or estimates that were adjusted (also) for other social relationship variables. For the meta-analyses, the relative risk (RR) was used representing the risk of incident dementia among people with poor social relationships (e.g., small social network) compared to people with better social relationships. In case hazard ratio (HR) or odds ratio (OR) were reported in the studies, these were interpreted as relative risk, on the condition that the incidence of dementia among the participants was below 10% (Higgins and Green, 2008; Zhang and Kai, 1998). If social relationship factors were presented as categorical variables (e.g., size of social network: 0-3 persons; 4-7 persons; ≥ 8 persons), the relation between the reference category and the most opposite category (e.g., 0-3 persons versus >8 persons) was used in the meta-analysis. If more follow-up measurements were available from one study, results from the longest follow-up were included in the meta-analyses. In case multiple articles were based on the same dataset, the article was included in the meta-analyses that (in order of importance) reported (1) an adjusted risk estimate (i.e., adjusted for age, depression, alcohol use and physical functioning), (2) largest sample size, or (3) longest follow-up period.

A random-effects method was used to pool effect sizes (Higgins and Green, 2008). Heterogeneity was examined by means of the Q-test and the l^2 index. If the p-value in the Q-test was below 0.05 and/or the I^2 index was higher than 50%, the results of the studies in the pooled analysis were considered to be heterogeneous (Diniz et al., 2013; Higgins and Green, 2008), and no pooled estimate was calculated. Subsequently, sources of heterogeneity were explored by conducting subgroup analyses for differences in study population (i.e., age, gender), timing of follow-up measurements, outcomes (AD versus dementia), measurement of the determinants (i.e., dichotomous, categorical, or continuous), and the methodological quality. Sensitivity analyses were performed to investigate the robustness of the results with regard to (1) the choice of category for the social relationship factors (i.e., the relation between the reference category and the most opposite category), (2) differences in follow-up time (i.e., long (10 years) versus short (5 years)), and (3) the outcome (i.e., AD versus dementia). The extent of publication bias in this meta-analysis was assessed by constructing funnel plots for the relation between various social relationship factors (i.e., social network size, social participation, frequency of social contact, loneliness, and satisfaction with social network) and incident dementia by plotting the natural logarithm of the effect measure (log risk ratio) against the standard error of this measure. Egger's test was used to test asymmetry of the funnel plots; publication bias is likely if *p*-value <0.10 (Egger et al., 1997; Higgins and Green, 2008). All statistical analyses were performed with the program comprehensive meta-analysis (version 2) (Borenstein et al., 2005).

3. Results

Reviewing 8527 titles and abstracts and 133 full articles, resulted in inclusion of 15 articles (Amieva et al., 2010; Andrew and Rockwood, 2010; Boyle et al., 2010; Chen et al., 2011; Crooks et al., 2008; Fabrigoule et al., 1995; Fratiglioni et al., 2000; Gureje et al., 2011; He et al., 2000; James et al., 2011; Lobo et al., 2008; Saczynski et al., 2006; Valenzuela et al., 2011; Wang et al., 2002; Wilson et al., 2007) (see Fig. 1). Screening the references of all articles selected for full-text reading and other relevant reviews resulted in four additional eligible articles (Akbaraly et al., 2009; Karp et al., 2006; Paillard-Borg et al., 2009; Scarmeas et al., 2001). In total 19 articles were included for this systematic review.

Details regarding study characteristics of the included studies are presented in Table 1. The year of the baseline measurements ranged from 1987 to 2010 and duration of follow-up varied between 2 and 15 years. The sample size of the cohorts ranged from 732 to 5447.

The results of the methodological quality assessment of included studies are presented in Table 2. Methodological quality varied from very poor (0% for accounting for alcohol use in the analyses) to excellent (100% for minimizing risk of reverse causation). The most methodological flaws were found for the following quality items: adjustment for potential confounders (alcohol (19 of 19 studies; 100%), depression (12 of 19 studies; 63%), and physical functioning (11 of 19 studies; 58%)). Insufficient information was given for blinding of the outcome assessor for the determinant measurement (15 of 19 studies; 79%) and attrition (i.e., differences between participants and drop outs) (13 of 19 studies; 68%). The inter-rater agreement on the methodological quality was excellent (Higgins and Green, 2008) (overall agreement 89% (303/342); kappa statistic: 0.79).

3.1. Social network size and risk of incident dementia

Eight studies (Amieva et al., 2010; Boyle et al., 2010; Fratiglioni et al., 2000; Gureje et al., 2011; He et al., 2000; James et al., 2011; Saczynski et al., 2006; Wilson et al., 2007) investigated the association between social network size and incident dementia; only two studies (James et al., 2011; Saczynski et al., 2006) found a statistically significant association between small social network size and incident dementia. Three studies based their conclusions on the data from the Rush Memory and Aging Project (Boyle et al., 2010; James et al., 2011; Wilson et al., 2007). We included only the study of Wilson et al. (2007) in the meta-analysis. Unfortunately, the study of Gureje et al. (2011) did not report estimates and could therefore not be included in our meta-analysis. The estimates of five studies (Amieva et al., 2010; Fratiglioni et al., 2000; He et al., 2000; Saczynski et al., 2006; Wilson et al., 2007) were included in our meta-analysis. The results were heterogeneous ($\chi^2 = 11.05$, df=4, p = 0.03, $I^2 = 64\%$) (see Fig. 2). Heterogeneity could not properly be explained because the various studies differed from each other on various aspects (i.e., study population, outcomes, measurement of the determinants, methodological quality).

3.2. Social participation and risk of incident dementia

Eight studies (Fabrigoule et al., 1995; Gureje et al., 2011; He et al., 2000; Karp et al., 2006; Saczynski et al., 2006; Scarmeas et al., 2001; Wang et al., 2002; Wilson et al., 2007) investigated the association between social participation and incident dementia; four studies (Karp et al., 2006; Saczynski et al., 2006; Scarmeas et al., 2001; Wilson et al., 2007) found a statistically significant association between low social participation and incident dementia. Two studies (Karp et al., 2006; Wang et al., 2002) based their conclusions on the data from the Kungsholmen project; both stud-

	Location	Year of Baseline collection ^a	Study duration (years)	N in the analyses	Population ^b	Age mean (SD), range (years)	Women (%)	Social relationship assessment	Adjustment for covariates	Outcome Assessment
Akbaraly et al. (2009)	France	1999–2001	4	5447		73.8 (NA), 65+	60.9	Frequency of social contact	Age, sex, education, depression, hypertension, vascular disease history, hyperc- holesterolemia, baseline cognition, occupational grade, study center, marital status, diabetes, Apolipoprotein E genotype, incapacity in daily life activity	Incident dementia AND Incident AD AND Incident mixed/vascular dementia
Amieva et al. (2010)	France	1988	5–15	2089 ^c	Excluding participants who developed dementia during the first 3 years	73.7 (6.0), 65+	59.9	Social network size, Satisfaction with social network, Other social relationship factors	Age, sex, education, depression, IADL, presence of chronic diseases, baseline cognition, the other social variables (marital status, nature of social network, satisfaction of interactions with other people, feeling of being misunderstood, perception of reciprocity)	Incident dementia AND Incident AD
Andrew and Rockwood (2010)	Canada	1996–1997	5	3776		79.1 (6.4), 70+	60.7	Other social relationship	Age, sex, baseline cognition, frailty	Incident dementia
Boyle et al. (2010)	USA	1997-2008	4	951		80.4 (7.4), NA	74.9	Social network	Unadjusted	Incident AD
Chen et al. (2011)	China	2001 and 2003	Median: 3.9	1307 ^d		NA, 60+	43.5	Frequency of social contact, Loneliness, Satisfaction with social network	Age, sex	Incident dementia
Crooks et al. (2008)	USA	1998–1999	Maximum: 4	1608°		80.6 (3.1), 78+	100	Frequency of social contact, Satisfaction with social network, Other social relationship factors	Age, education, depression, stroke, myocardial infarction, hypertension, baseline cognition, diabetes, Parkinson's disease, hormone use	Incident dementia
Fabrigoule et al. (1995)	France	1988	Maximum: 3	2040		74.8 (6.9), 65– 101	59.8	Social participation, Frequency of social contact	Age, baseline cognition	Incident dementia

Fratiglioni et al. (2000)	Sweden	1987	3	1203 ^r	Excluding participants with MCI at baseline	81.5 (NA), 75– 90+	75.6	Social network size, Frequency of social contact, Satisfaction with social network, Other social relationship factors	Age, sex, education, baseline cognition, (and depression for the other social relationship factor; composite measure of social relationship factors only)	Incident dementia
Gureje et al. (2011)	Nigeria	2003–2004	3	1225		74.5 (8.4), 65– 85+	52.1	Social network size, Social participation, Frequency of social contact	Age, sex, education	Incident dementia
He et al. (2000)	China	1987	10	1160		67.1 (NA), 55– 75+	58	Social network size, Social participation, Frequency of social contact, Loneliness	Age, sex	Incident AD
James et al. (2011)	USA	1997-2010 and 2004-2010	4.4	1294		78.4 (NA), 55– 75+	73.9	Social network size	Unadjusted	Incident AD
Karp et al. (2006)	Sweden	1987–1989	7	732	Excluding participants with MCI at baseline, or who developed dementia during the first 4 years	81.3 (NA), 75– 85+	74.2	Social participation	Age, sex, education, depression, physical functioning, baseline cognition, comorbidity	Incident dementia
Lobo et al. (2008)	Spain	1994	2	1506	Excluding participants with MCI at baseline	73.52 (NA), 55- 80+	56.7	Loneliness	Age, sex, education, irritability, neurovegetative symptoms, sleep problems, lack of concentration, subjective slowness	Incident dementia AND Incident AD
Paillard-Borg et al. (2009)	Sweden	1987–1989	Median: 7.8	732	Excluding participants with MCI at baseline, or who developed dementia during the first 4 years	81.1 (4.9), 75– 85+	74.2	Other social relationship factors	Age, sex, education, depression, physical functioning, baseline cognition, "the physical factor", "the mental factor", comorbidity, living arrangements	Incident dementia

	Location	Year of Baseline collection ^a	Study duration (years)	N in the analyses	Population ^b	Age mean (SD), range (years)	Women (%)	Social relationship assessment	Adjustment for covariates	Outcome Assessment
Saczynski et al. (2006)	USA	1991–1993	4.6	25138		76.8 (4.0), 72+	0	Social network size, Social participation, Frequency of social contact, Other social relationship factors	Unadjusted (only for the association social network size and incident dementia adjusted for: age education, depression, cerebrovascular disease, coronary heart disease, disability, baseline cognition, Apolipoprotein E e4 allele status)	Incident dementia
Scarmeas et al. (2001)	USA	1990	2.9	1772		75.6 (NA), 65+	68.1	Social participation, Frequency of social contact	age, education, occupation, ethnic group	Incident dementia
Valenzuela et al. (2011)	UK	1991–1992	4.1	NA	Excluding participants with dementia at previous interview	76.9 (NA), 65+	60	Other social relationship factors	Age, sex, education, occupational complexity, interview wave, vascular risk factors	Incident dementia
Wang et al. (2002)	Sweden	1987–1989	6.4	732	Excluding participants with MCI at baseline, or who developed dementia during the first 3 years	81.3 (NA), 75– 85+	74.2	Social participation	Age, sex, education, depression, physical functioning, baseline cognition, comorbidity	Incident dementia
Wilson et al. (2007)	USA	2000	3.3	785	-	80.7 (7.1), NA	75.7	Social network size, Social participation, Loneliness	For the association social network size and incident dementia: Age, sex, education, loneliness, social activity For the association social participation and incident dementia: Age, sex, education, loneliness, social network size For the association loneliness and incident dementia: Age, sex education, physical activity	Incident AD

NA: not available; AD: Alzheimer's disease; IADL: instrumental activities of daily living; MCI: mild cognitive impairment.

^a Reflects the baseline measurement included for our analysis.

^b All general population, excluding participants with dementia at baseline.

^c Estimate for social network size based on n = 1337.

Table 1 (Continued)

^d Estimate for frequency of social contact based on n = 560.

^e Estimate for frequency of social contact based on n = 1301 and estimate for satisfaction with network interaction based on n = 1603.

^f Estimate for frequency of social contact based on n = unclear.

^g estimate for social network size based on n = 1064.

Table 2				
Methodological quality assessment per	quality item and	per study	(based on Q	UIPS). ^a

	1. Study participa	tion	2. Study a	attrition	3. Determ measurer	iinant nent	4. Outcom measuren	ne nent	5. Confou	nding mea	asurement	and accour	nt					6. Analysis
							-		Potential	confounde	ers measur	ed	Accounte study des	counted for potential confounders in de udy design or analyses				
Author (year)	1a. Con- secutive series of partici- pants	1b. Adequate participa- tion rate >70%	2a. 70% e data on - dementia at follow- up	2b. No differ- ences between partici- pants and drop outs	3a. using sufficient methods	3b. 70% complete data for social relation- ship factors	4a. Dementia diagnosis	4b. Outcome assessors blinded for the social relation- ship factors	5a1. Age	5A2 Depres- sion	5A3 Alcohol use	5A4 Physical activity, OR func- tional disability OR chronic disease	5b5. Age	5B6 Depres- sion	5B7 Alcohol use	5B8 Physical activity, OR func- tional disability OR chronic disease	5c. Reverse causality	6a. No overfit- ting
Akbaraly et al. (2009)	+	?	+	?	+	+	+	?	+	+	?	+	+	+	_	+	+	+
Amieva et al. (2010)	+	_	?	?	+	+	+	?	+	+	?	+	+	+	_	+	+	?
Andrew and Rockwood (2010)) +	_	+	?	+	_	+	?	+	?	?	?	+	_	_	_	+	+
Boyle et al. (2010)	?	?	+	?	+	?	+	+	+	+	+	+	_	_	_	_	+	+
Chen et al. (2011)	+	+	+	?	?	+	_	?	+	+	+	+	+	_	_	_	+	_
Crooks et al. (2008)	+	+	+	_	+	+	_	?	+	+	?	+	+	+	_	+	+	_
Fabrigoule et al. (1995)	+	_	+	?	+	?	+	?	+	+	+	+	+	_	_	_	+	?
Fratiglioni et al. (2000)	+	+	+	_	+	+	+	?	+	+	?	+	+	+/_ ^b	_	+/_ ^b	+	?
Gureje et al. (2011)	+	+	+	+	+	?	_	?	+	+	+	+	+	_	_	_	+	+
He et al. (2000)	+	+	+	?	?	?	+	?	+	+	+	+	+	_	_	_	+	+
James et al. (2011)	_	?	+	?	+	?	+	?	+	+	+	+	_	_	_	_	+	+
Karp et al. (2006)	+	+	+	+	+	+	+	?	+	+	?	+	+	+	_	+	+	_
Lobo et al. (2008)	+	+	+	_	_	+	+	+	+	+	+	+	+	_	_	_	+	?
Paillard-Borg et al. (2009)	+	+	+	?	+	+	+	?	+	+	?	+	+	+	_	+	+	+
Saczvnski et al. (2006)	_	+	?	?	+	+	+	?	+	+	?	+	+/_ ^c	+/_ ^c	_	+/- ^c	+	?/+ ^d
Scarmeas et al. (2001)	+	_	+	+	+	+	+	+	+	+	+	+	+	_	_	_	+	?
Valenzuela et al. (2011)	+	+	?	?	+	+	_	?	+	+	?	+	+	_	_	+	+	?
Wang et al. (2002)	+	+	+	?	+	+	+	?	+	+	?	+	+	+	_	+	+	_
Wilson et al. (2007)	?	?	+	?	+	+	+	+	+	+	+	+	+	+	_	+	+	+

^a QUIPS: Quality of Prognosis Studies in Systematic Reviews. Judgment: + (Yes) (if the quality item was met, representing low risk of bias); - (No) (if the quality item was not met, representing high risk of bias); ? (Unclear) (if insufficient information was available to judge the potential of bias, representing uncertain risk of bias). Further details about the quality assessment items are presented in Appendix B.

^b For social network size, frequency of social contact, and satisfaction with network: - (No), for the graded summary score and combinations of social relationship factors: + (Yes).

^c For social network size: + (Yes), for social participation, frequency of social contact, and other social relationship factor: – (No).

^d For social network size: ? (Unclear), for social participation, other social relationship factor and frequency of social contact: + (Yes).

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Fig. 1. Flow of study selection.

ies found comparable results. The study of Karp et al. (2006) was included in the meta-analysis. We could not calculate risk measures for the study of Saczynski et al. (2006) and therefore this study was not included in the meta-analysis. The estimates of six studies (Fabrigoule et al., 1995; Gureje et al., 2011; He et al., 2000; Karp et al., 2006; Scarmeas et al., 2001; Wilson et al., 2007) were included in the meta-analysis. The pooled estimate showed that individuals with lower levels of social participation had a statistically significant higher risk to develop dementia compared to individuals with higher levels of social participation (RR: 1.41 (95% CI: 1.13–1.75)) (see Fig. 3).

3.3. Frequency of social contact and risk of incident dementia

Nine studies (Akbaraly et al., 2009; Chen et al., 2011; Crooks et al., 2008; Fabrigoule et al., 1995; Fratiglioni et al., 2000; Gureje et al., 2011; He et al., 2000; Saczynski et al., 2006; Scarmeas et al., 2001) investigated the association between frequency of social con-



Heterogeneity: $\chi^2 = 11.05$, df=4, p=0.03, I²=64%

Fig. 2. Forest plot of social network size and risk of incident dementia.



Heterogeneity: χ²=7.27, df=5, p=0.20, I²=31%



tact and incident dementia; four studies (Crooks et al., 2008; Gureje et al., 2011; Saczynski et al., 2006; Scarmeas et al., 2001) found a statistically significant association between low frequency of social contact and incident dementia. We could not calculate risk measures for the study of Saczynski et al. (2006) and therefore this study was not included in the meta-analysis. The estimates of the other eight studies were included in the meta-analysis. The pooled estimate showed that individuals with lower frequency of social contacts had a statistically significant higher risk to develop dementia compared to individuals with higher frequency of social contacts (RR: 1.57 (95% CI: 1.32–1.85)) (see Fig. 4).

3.4. Loneliness and risk of incident dementia

Four studies (Chen et al., 2011; He et al., 2000; Lobo et al., 2008; Wilson et al., 2007) investigated the association between loneliness and incident dementia; only one study (Wilson et al., 2007) found a statistically significant association between higher level of loneliness and incident dementia. Unfortunately, the study of Lobo et al. (2008) did not report estimates and could therefore not be included in our meta-analysis. The estimates of the other three studies (Chen et al., 2011; He et al., 2000; Wilson et al., 2007) were included in the meta-analysis. The pooled estimate showed that individuals who are lonely had a statistically significant higher risk to develop dementia compared to individuals that are not lonely (RR: 1.58 (95% CI: 1.19–2.09)) (see Fig. 5).

3.5. Satisfaction with social network and risk of incident dementia

Four studies (Amieva et al., 2010; Chen et al., 2011; Crooks et al., 2008; Fratiglioni et al., 2000) investigated the association between satisfaction with social network and incident dementia; only one study (Amieva et al., 2010) reported a statistically significant association between low satisfaction with social network and incident

dementia. The estimates of all four studies were included in the meta-analysis. The pooled estimate showed no statistically significant association between low satisfaction with social network and incident dementia (RR: 1.25 (95% CI: 0.96–1.62)) (see Fig. 6).

3.6. Other social relationship factors and risk of incident dementia

Seven studies (Amieva et al., 2010; Andrew and Rockwood, 2010; Crooks et al., 2008; Fratiglioni et al., 2000; Paillard-Borg et al., 2009; Saczynski et al., 2006; Valenzuela et al., 2011) examined the association between social relationship factors that could not be classified by one of the categories above and incident dementia. Five out of seven studies found a statistically significant association with at least one other social relationship factor measurement and incident dementia (Amieva et al., 2010; Crooks et al., 2008; Fratiglioni et al., 2000; Paillard-Borg et al., 2009; Saczynski et al., 2006). Most of these factors consisted of composite measures of social relationship factors such as a social vulnerability index (Andrew and Rockwood, 2010), Lubben Social Network Scale (Crooks et al., 2008), or a graded sum score of the social network (Fratiglioni et al., 2000). The results are presented in Appendix C.

3.7. Sensitivity analyses

Results of sensitivity analyses showed that for studies defining social relationship factors as a categorical variable (Akbaraly et al., 2009; Amieva et al., 2010; Chen et al., 2011; Crooks et al., 2008; Saczynski et al., 2006), the inclusion of one of the other categories in the meta-analyses did not alter the conclusions. Secondly, sensitivity analyses showed that differences in follow-up time (He et al., 2000) did not alter the conclusions. Also, when pooling the results of studies that measured AD as outcome (He et al., 2000; Wilson et al., 2007; Akbaraly et al., 2009; Amieva et al., 2010), the conclusions were not altered (see Appendix D).



Heterogeneity: χ²=3.79, df=7, p=0.80, I²=0%



Heterogeneity: $\chi^2 = 0.06$, df=2, p=0.97, I²=0%

Fig. 5. Forest plot of loneliness and risk of incident dementia.



Heterogeneity: χ^2 =5.95, df=3, p=0.11, I²=49%

Fig. 6. Forest plot of satisfaction with social network and risk of incident dementia.

3.8. Publication bias

Publication bias was evaluated by Egger's test, which yielded no significant results for social network size (p = 0.14), frequency of social contact (p = 0.95), loneliness (p = 0.12), and satisfaction with social network (p = 0.93). Publication bias was likely for social participation (p = 0.08) (see Appendix E).

4. Discussion

This meta-analysis shows that people with less social participation, less frequent social contact and more feelings of loneliness have an increased risk to develop dementia. Low satisfaction with social network seems to be associated with incident dementia, but results were not statistically significant. There was insufficient evidence to draw firm conclusions about the association between small social network and incident dementia due to large heterogeneity between the studies with regard to the study population, outcomes, measurement of the determinants, and the methodological quality. The results of this review suggest that particularly less social interaction increases the risk of dementia, more than specifically the size or satisfaction with the social network.

Although other systematic reviews also suggest that better social functioning is protective against the development of dementia (Fratiglioni et al., 2004; Pillai and Verghese, 2009; Wang et al., 2012; Williams et al., 2010), the results were contradictory and none of these reviews conducted a meta-analysis. Comparing the results of our meta-analysis to other meta-analyses on well-known risk factors for incident dementia, we found that the magnitude of our findings is quite large and comparable with other wellestablished risk factors for incident dementia, for example; late-life depression and risk of dementia (OR: 1.85 (95% CI: 1.67–2.04)) (Diniz et al., 2013), physical inactivity and risk of AD (RR: 1.82 (95% CI: 1.19–2.78)) (Norton et al., 2014), midlife hypertension and risk of AD (RR: 1.61 (95% CI: 1.16–2.24)) (Norton et al., 2014), low education attainment and risk of AD (RR: 1.59 (95% CI: 1.35–1.86)) (Norton et al., 2014), type 2 diabetes mellitus and risk of AD (OR: 1.57 (95% CI: 1.41–1.75)) (Vagelatos and Eslick, 2013), and smoking and risk of AD (RR: 1.37 (95% CI: 1.23–1.52)) (Beydoun et al., 2014).

4.1. Potential mechanisms underlying the association of social interaction and incident dementia

One potential explanation why more social interaction protects against dementia relates to the 'use it or lose it' theory, which suggests that engagement in intellectual, social and physical activities stimulates the brain. Changes in everyday activities may result in disuse of the brain and relates to atrophy of cognitive functions (Hultsch et al., 1999). Related to the 'use it or lose it' theory is the cognitive reserve theory. The concept of cognitive reserve suggests that social interaction affects brain structure and results in more efficient use of brain networks (Stern, 2012). For instance, stimulating environments and an (socially) engaged lifestyle have been associated with neurogenesis (Fratiglioni et al., 2004; Stern, 2012), and an increase of synaptic density (Fratiglioni et al., 2004; Scarmeas and Stern, 2003). Another potential explanation could be related to stress, which has been associated with a two times increased risk of developing AD due to structural changes in the hippocampus (Fratiglioni et al., 2004; Wilson et al., 2003). The results of brain autopsy of a diseased sample studied by Wilson et al. (2003) suggest that the association between chronic psychological distress as a risk factor for AD is related to neurobiological mechanisms other than the pathological hallmarks of AD such as cortical plaques and tangles (Wilson et al., 2003). Social support and lack of loneliness may work as a buffer against stress (Cohen and McKay, 1984; Cohen, 2004; Fratiglioni et al., 2004; Gierveld, 1998) and thereby protect against dementia. Another pathway through which social interaction may protect against dementia is that the social environment motivates health behaviors and yields multiple sources of information that can help effective use of available health services (Cohen, 2004; Rizzuto and Fratiglioni, 2014). Therefore, the size of the social network may not be as important as long as one has a social network that one can interact with on a regular basis to keep the brain stimulated, to release stress and to contribute to healthy behavior and provide resources to health facilities.

Our study has several strengths. First of all, a thorough systematic literature search was conducted on a broad range of social relationship factors. This made it possible to identify and disentangle different social relationship factors and demonstrate that various social relationship factors are associated individually with incident dementia. A second strength is that by disentangling different social relationship factors we were able to account for a large part of heterogeneity between the studies, allowing us to perform a meta-analysis. Previous systematic reviews often made generalizations about broad categories and investigated multiple lifestyle and leisure activities as risk factors for the development of dementia (Beydoun et al., 2014; Di Marco et al., 2014; Fratiglioni et al., 2004; Wang et al., 2012). Various lifestyle factors (i.e., a socially, mentally and physically active lifestyle) are most likely intertwined with each other and may have a synergistic effect on incident dementia (Fratiglioni et al., 2004; Rizzuto and Fratiglioni, 2014). However, a clear answer was missing in the current literature on whether social relationships are associated with incident dementia and specifically which aspects of social relationships. Therefore, the present meta-analysis was performed and the results can contribute to give direction to further research on lifestyle factors and dementia.

As with any systematic review, there are some methodological challenges that should be considered. First of all, the choice of category for the social relationship factors (i.e., the relation between the reference category and the most opposite category) can be considered as subjective. However, after critical appraisal by performing sensitivity analyses, we found that the comparison of different categories did not alter the conclusions. Secondly, variation between studies was present for the measurement of the social relationship factors (i.e., different questionnaires, cut-off points), timing of follow-up measurements, composition of the study population (i.e., percentage women varied between studies from 0% to 100%), and adjustments of different potential confounders in the analyses. However, these clinical and methodological heterogeneity did not result in heterogeneous study results (except for the association between social network size and incident dementia).

Publication bias was not detected, with exception of studies investigating the relation between social participation and incident dementia. Therefore, the pooled risk estimate for the relation between social participation and incident dementia may be overestimated and should be interpreted with caution. We should mention that Egger's test, in this case, may be underpowered to investigate publication bias, because less than ten studies were included in the funnel plots (Higgins and Green, 2008). Furthermore, most existing cohort studies with dementia as outcome have some information on social relationships. We do not know why potential associations between social relationships and incident dementia have not been published (yet). Prospective registration of observational studies could make researchers methodologically more aware about the consequences of selective publication (Altman, 2014). In addition, this will also improve the methods of the study design and quality of reporting (Altman, 2014).

Additionally, there are methodological challenges involved in older people research that should also be considered. Surveys of older people include high dropout and high proportions of nonresponders. It is likely that this leads to an underestimation of the association between social relationship factors and incident dementia since those who die or drop out are most likely more ill or engage less in healthy lifestyle behaviors than those who participate in the study (Rizzuto and Fratiglioni, 2014). Based on the quality assessment we found that most studies complied with the criterion that of participants with complete data on social relationship factors at baseline, at least 70% have data on cognitive function at follow-up. However, for most studies it was unclear whether there were important differences between participants who completed the study and those who did not (i.e., based on at least age and sex). As a result, we cannot be certain whether the sample ultimately included in the analyzes perhaps consists of a younger (and possibly healthier) population compared to the dropouts, and thereby possibly gives an underestimation of the associations found.

The gold standard to investigate a causal relation between a factor on an outcome would be interventions studies (Wang et al., 2012). Only a limited number randomized controlled trials have recently investigated the effect of a social interaction intervention and cognitive functioning among older people (Yaffe and Hoang, 2013). One study applied an intervention to increase engagement in social activity among lonely older persons. Results showed that after three months the intervention group improved more on cognitive performance compared to the control group (Pitkala et al., 2011). Similarly, an intervention on improving social interaction among Chinese older persons improved cognitive function compared to a control group that did not receive an intervention. However, results were not as significant as those for physical activity (Mortimer et al., 2012). Future research should take into account the interplay among multiple lifestyle factors. An intervention among the general population would therefore probably be most effective if various lifestyle factors are addressed (Fratiglioni et al., 2004). This present systematic review provides evidence that less social interaction is a risk factor for the development of dementia. Therefore, we would recommend that more attention should be paid to social interaction in future lifestyle interventions. Because (modifiable) risk factors for dementia may already occur earlier in the life, future studies applying a life course perspective would be helpful in order to investigate a suitable approach for the prevention of dementia (Rizzuto and Fratiglioni, 2014).

5. Conflict of interest

The authors have no potential conflict of interest to report.

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Appendix A.

Search strings MEDLINE, Embase and PsycINFO

MEDLINE

MH "Cognition Disorders OR MH "Mild Cognitive Impairment OR MH "Dementia+

OR

TI ("cognitive function" OR "cognitive impairment OR "cognitive decline OR "cognitive deficit" OR "cognition loss" OR "cognitive loss" OR "cognitive abilit" OR dement" OR alzheimer" OR "cognition" OR "cognitive status OR "cognitive change OR "cognition change OR "cognitive performance OR "cognitive disfunction") OR AB ("cognitive function" OR "cognitive impairment OR "cognitive decline OR "cognitive deficit" OR "cognition loss" OR "cognitive loss" OR "cognitive abilit" OR dement" OR alzheimer" OR "cognition OR "cognitive status OR "cognitive change OR "cognition OR "cognitive status OR "cognitive change OR "cognition change OR "cognitive performance OR "cognitive disfunction")

AND

MH "Loneliness OR MH "Social Isolation OR MH "Social Support OR MH "Social Participation OR MH "Interpersonal Relations

OR

TI (loneliness OR "social support OR "social isolation OR "social participation OR "social engagement OR "social disengagement OR "social integration OR "personal network" OR "social network" OR "social activit" OR "social tie" OR "social relation" OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "kinship relation" OR "friendship" OR "social influence OR "social vulnerability) OR AB (loneliness OR "social support OR "social disengagement OR "social integration OR "personal network" OR "social network" OR "social integration OR "personal network" OR "social interaction OR "social withdrawal OR "social relation" OR "social interaction OR "social withdrawal OR "social capital OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "social contact OR "social embeddedness OR "family relation" OR "social contact OR

NOT (Animals NOT Human; Animals)

Embase

'cognitive defect'/exp OR 'dementia'/exp

OR

'cognitive function':ab,ti OR 'cognitive functioning':ab,ti OR 'cognitive impairment':ab,ti OR 'cognitive decline':ab,ti OR 'cognitive deficit':ab,ti OR 'cognitive deficits':ab,ti OR 'cognition loss':ab,ti OR 'cognition losses':ab,ti OR 'cognitive loss':ab,ti OR 'cognitive losses':ab,ti OR 'cognitive ability':ab,ti OR 'cognitive abilities':ab,ti OR 'dementia':ab,ti OR 'demented':ab,ti OR 'alzheimer':ab,ti OR 'cognition':ab,ti OR 'cognitive status':ab,ti OR 'cognitive change':ab,ti OR 'cognition change':ab,ti OR 'cognitive performance':ab,ti OR 'cognitive disfunction':ab,ti OR 'cognitive disfunctioning':ab,ti OR 'cognitive disfunctions':ab,ti

AND

'social support'/exp OR 'social isolation'/exp OR 'social participation'/exp OR 'social network'/exp OR 'loneliness'/exp OR 'family relation'/exp OR 'friendship'/exp

OR

loneliness:ab,ti OR 'social support':ab,ti OR 'social isolation':ab,ti OR 'social participation':ab,ti OR 'social engagement':ab,ti OR 'social disengagement':ab,ti OR 'social integration':ab,ti OR 'personal network':ab,ti OR 'personal networks':ab,ti OR 'social network':ab,ti OR 'social networks':ab,ti OR 'social activity':ab,ti OR 'social activities':ab,ti OR 'social tie':ab,ti OR 'social activities':ab,ti OR 'social relation':ab,ti OR 'social relations':ab,ti OR 'social ties':ab,ti OR 'social relation':ab,ti OR 'social relations):ab,ti OR 'social interaction':ab,ti OR 'social withdrawal':ab,ti OR 'social capital':ab,ti OR 'social contact':ab,ti OR 'social embeddedness':ab,ti OR 'family relation':ab,ti OR 'family relations ship':ab,ti OR 'family relationships':ab,ti OR 'family relationship':ab,ti OR 'family relationships':ab,ti OR 'kinship relation':ab,ti OR 'kinship relation':ab,ti OR 'kinship relationship':ab,ti OR 'kinship relat ship relationships':ab,ti OR 'friendship':ab,ti OR 'friendships':ab,ti OR 'social influence':ab,ti OR 'social vulnerability':ab,ti

PsycINFO

DE "Dementia+ OR DE "Neurodegenerative Diseases OR DE "Alzheimer's Disease OR DE "Cognitive Impairment OR DE "Cognitive Ability

OR

TI ("cognitive function" OR "cognitive impairment OR "cognitive decline OR "cognitive deficit" OR "cognition loss" OR "cognitive loss" OR "cognitive abilit" OR dement" OR alzheimer" OR "cognition OR "cognitive status OR "cognitive change OR "cognition change OR "cognitive performance OR "cognitive disfunction") OR AB ("cognitive function" OR "cognitive impairment OR "cognitive decline OR "cognitive deficit" OR "cognition loss" OR "cognitive loss" OR "cognitive abilit" OR dement" OR alzheimer" OR "cognition OR "cognitive status OR "cognitive change OR "cognition oR "cognitive status OR "cognitive change OR "cognition change OR "cognitive status OR "cognitive change OR "cognition change OR "cognitive performance OR "cognitive disfunction")

AND

DE "Social Networks OR DE "Social Support OR DE "Loneliness OR DE "Social Integration OR DE "Social Isolation OR DE "Interpersonal Relationships+

OR

TI (loneliness OR "social support OR "social isolation OR "social participation OR "social engagement OR "social disengagement OR "social integration OR "personal network" OR "social network" OR "social activit" OR "social tie" OR "social relation" OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "kinship relation" OR "friendship" OR "social influence OR "social vulnerability) OR AB (loneliness OR "social support OR "social disengagement OR "social integration OR "personal network" OR "social network" OR "social integration OR "personal network" OR "social interaction OR "social withdrawal OR "social relation" OR "social interaction OR "social withdrawal OR "social capital OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "social interaction OR "social withdrawal OR "social capital OR "social contact OR "social embeddedness OR "family relation" OR "kinship relation" OR "friendship" OR "social influence OR "social vulnerability)

AND Publication Type: Peer Reviewed Journal

Appendix B.

Domain

Methodological quality assessment tool (based on QUIPS).^a

1. Study participationThe study sample1a. The study was performed in a consecutiverepresents theseries of participantspopulation of interest1b. There is adequate participation in the studyon key characteristics,individuals that were recruited, at least 70% agsufficient to limitto participatepotential bias to theto participantsresults2. Study attritionLoss to follow-up (from sample to study2a. Of participants with complete data on socia relationship factors at baseline, at least 70% har poceased people do count as data on dementia	ation a 1a. The study was performed in a consecutive series of participants erest 1b. There is adequate participation in the study. Of istics, individuals that were recruited, at least 70% agrees to participate	•
2. Study attrition Loss to follow-up (from sample to study 2a. Of participants with complete data on socia relationship factors at baseline, at least 70% har gopulation) is not gopulation is not data on dementia at follow-up Deceased people do count as data on dementia	the	
characteristics (i.e., the study data adequately represent the sample), sufficient to limit potential bias follow-up and can be seen as "worst case 2b. There are no important differences between participants who completed the study and thos who did not. Important characteristics are at le age and sex Deaths not included. So it must be a compariso	 (from 2a. Of participants with complete data on social relationship factors at baseline, at least 70% have data on dementia at follow-up beceased people do count as data on dementia at e., the follow-up and can be seen as "worst case 2b. There are no important differences between participants who completed the study and those who did not. Important characteristics are at least age and sex Deaths not included. So it must be a comparison between denseute (not indicate denseute (not indicate denseute)) and 	

those still in the analyses

50

3. Determinant measurem The determinant of interest is adequately measured in study participants to sufficiently limit potential bias	ent 3a. Social relationship factors are assessed using sufficient methods This could include well-known valid and reliable instruments for any social relationship factor described in Appendix A (e.g., Lubben Social Network Scale, Multidimensional Scale of Perceived Social Support, de Jong Gierveld Loneliness Scale, Close Person Inventory). Also assessments using multiple questions to assess social relationship factors are considered sufficient when including relevant questions. Using only one question (if this is not known to be a valid tool to assess the social relationship factor) is designated as insufficient 3b. Of the participating individuals at baseline, at least 70% had complete data for social relationship factors
4. Outcome measurement The outcome of interest is adequately measured in study participants to sufficiently limit potential bias	4a. The outcome incident dementia is based on assessment performed by a multidisciplinary team using set criteria E.g., a neuropsychological test battery is conducted by a neuropsychologist while the diagnosis dementia is made by a psychiatrist of neurologist, based on DSM-criteria or NINCDS-ADRDA-criteria 4b. Outcome assessors are blinded for the social relationship factors
5. Confounding measurem Important potential confounders are appropriately accounted for, limiting potential bias with respect to the determinant of interest	ent and account 5a. Important potential confounders are measured. Important potential confounders should include at least: 1. Age 2. Depression 3. Alcohol use 4. Physical activity, OR functional disability, OR one of the chronic diseases: TBI, cardiovascular disease or CVA/stroke 5b. Important potential confounders are accounted for in de study design (matching for key variables, stratification, or initial assembly of comparable groups) or the analysis (i.e., appropriate adjustment). Important potential confounders should include at least: 5. Age 6. Depression 7. Alcohol use 8. Physical activity, OR functional disability, OR one of the chronic diseases: TBI, cardiovascular disease or CVA/stroke 5c. Reverse causality is minimized either by: -Adjusting for baseline cognitive function -Matching on baseline cognitive function -Excluding patients with baseline cognitive impairments or dementia
The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results.	6a. There is no over fitting (there is a minimum of 10 participants in the smallest group per predictor and outcome variable).

^aQUIPS: Quality of Prognosis Studies in Systematic Reviews. Judgment: + (Yes) (if the quality item was met, representing low risk of bias); - (No) (if the quality item was not met, representing high risk of bias); ? (Unclear) (if insufficient information was available to judge the potential of bias, representing uncertain risk of bias). TBI: traumatic brain injury; CVA: cerebrovascular accident.

Appendix C.

Results (RR (95% CI) and OR (95% CI)) of the associations between other social relationship factors and incident dementia.

	1	
Author (year)	Social relationship factor measurement	Risk of incident dementia
Amieva et al. (2010)	Perception to have received more social support than given Perception of having given more social support than received	RR: 0.45 (95% CI: 0.2–0.9) (p=0.03) RR: 1.05 (95% CI: 0.8–1.3) (p=0.57)
	Nature of the social network (rather friends than as many friends as family members)	RR: 0.95 (95% CI: 0.6–1.3) (<i>p</i> = 0.80)
	(rather family members than as many friends as family members)	(0.89 (95% CI)) (0.6-1.1) (p=0.38)
Androw and Pockwood	Feeling of being misunderstood	RR: 0.70 (95% CI: 0.3–1.2) (p=0.25) OP: 1.02 (05% CI:
(2010)	(including aspects of communication to engage in wider community, living situation, social support, socially oriented activities of daily living and leisure	0.97–1.07) (<i>p</i> =0.50)
	activities) (higher score means higher social vulnerability)	
Crooks et al. (2008)	Stronger social network (higher scores on the Lubben Social Network Scale including the size of the respondent's active social network,	RR: 0.74 (95% CI: 0.57–0.97) (<i>p</i> < 0.05)
Fratiglioni et al. (2000)	perceived social network, and perceived confidant network) Graded sum score of social network including marital status, living arrangements, and frequency and satisfaction with contact with children and close social ties (dichotomized:	RR: 1.6 (95% CI: 1.2–2.1) (p < 0.05)
Paillard-Borg et al. (2009)	poor or limited vs moderate or extensive) Social factor score (social (e.g., contacting and satisfied with contact with children/close friends) and productive (e.g., gardening, cooking) activities) (higher score means higher cocial factor)	RR: 0.79 (95% CI: 0.69–0.99) (<i>p</i> < 0.05)
Saczynski et al. (2006)	Low social engagement in late life (of which existence of a confidant is one indicator)	Statistically significant associated with increased risk of dementia (n < 0.05)
Valenzuela et al. (2011)	Composite measure of social engagement (frequency of contact with children, other relatives, or neighbours, and frequency of attending meetings, clubs and other social events)	OR: 0.7 (95% CI: 0.5–1.1) (ns)

RR: relative risk; CI: confidence interval; OR: odds ratio.

Appendix D.

Results of sensitivity analyses for outcome measure (AD versus

dementia).

Social relationship measure		Pooled estimate (RR (95% CI))	Heterogeneity $(\chi^2; p$ -value; $l^2)$	Number of studies included in meta-analysis	References ^a
Social network size	Total	1.17 (0.92–1.48)	$\chi^2 = 11.05; p = 0.03;$ $l^2 = 64\%$	5	Amieva et al. (2010), Fratiglioni et al. (2000), He et al. (2000), Saczynski et al. (2006), Wilson et al. (2007)
	Dementia as outcome	1.37 (0.82–2.31)	$\chi^2 = 8.2; p = 0.02;$ $l^2 = 75\%$	3	Amieva et al. (2010), Fratiglioni et al. (2000), Saczynski et al. (2006)
	AD as outcome	0.99 (0.89–1.10)	$\chi^2 = 2.3; p = 0.32;$ $l^2 = 12\%$	3	Amieva et al. (2010), He et al. (2000), Wilson et al. (2007)
Social participation	Total	1.41 (1.13-1.75)	$\chi^2 = 7.27; p = 0.20;$ $l^2 = 31\%$	6	Fabrigoule et al. (1995), Gureje et al. (2011), He et al. (2000), Karp et al. (2006), Scarmeas et al. (2001), Wilson et al. (2007)
	Dementia as outcome	1.21 (1.10–1.33)	$\chi^2 = 2.8; p = 0.42;$ $l^2 = 0\%$	4	Fabrigoule et al. (1995), Gureje et al. (2011), Karp et al. (2006), Scarmeas et al. (2001)
	AD as outcome	1.86 (1.24–2.78)	$\chi^2 = 0.31; p = 0.58;$ $l^2 = 0\%$	2	He et al. (2000), Wilson et al. (2007)
Frequency of social contact	Total	1.57 (1.32–1.85)	$\chi^2 = 3.79; p = 0.80;$ $I^2 = 0\%$	8	Akbaraly et al. (2009), Chen et al. (2011), Crooks et al. (2008), Fabrigoule et al. (1995), Fratiglioni et al. (2000), Gureje et al. (2011), He et al. (2000), Scarmeas et al. (2001)
	Dementia as outcome	1.59 (1.31–1.94)	$\chi^2 = 3.6; p = 0.61;$ $l^2 = 0\%$	7	Akbaraly et al. (2009), Chen et al. (2011), Crooks et al. (2008), Fabrigoule et al. (1995), Fratiglioni et al. (2000), Gureje et al. (2011), Scarmeas et al. (2001)
	AD as outcome	1.52 (1.07–2.15)	$\chi^2 = 0.07; p = 0.78;$ $l^2 = 0\%$	2	Akbaraly et al. (2009), He et al. (2000)
Loneliness	Total	1.58 (1.19–2.09)	$\chi^2 = 0.06; p = 0.97;$ $l^2 = 0\%$	3	Chen et al. (2011), He et al. (2000), Wilson et al. (2007)
	Dementia as outcome	1.69 (0.74–3.87)	-	1	Chen et al. (2011)
	AD as outcome	1.57 (1.16–2.11)	$\chi^2 = 0.03; p = 0.87;$ $I^2 = 0\%$	2	He et al. (2000), Wilson et al. (2007)
Satisfaction with social network	Total	1.25 (0.96–1.62)	$\chi^2 = 5.95; p = 0.11;$ $I^2 = 49\%$	4	Amieva et al. (2010), Chen et al. (2011), Crooks et al. (2008), Fratiglioni et al. (2000)
	Dementia as outcome	1.25 (0.96–1.62)	$\chi^2 = 5.95; p = 0.11;$ $I^2 = 49\%$	4	Amieva et al. (2010), Chen et al. (2011), Crooks et al. (2008), Fratiglioni et al. (2000)
	AD as outcome	1.42 (0.77-3.33)	-	1	Amieva et al. (2010)

^aTwo studies measured dementia as well as AD as outcome (Akbaraly et al., 2009; Amieva et al., 2010).

Appendix E.

Funnel plots for (a) social network size, (b) social participation, (c) frequency of social contact, (d) loneliness, and (e) satisfaction with social network.



Log risk ratio



Log risk ratio



Log risk ratio



Log risk ratio

References

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