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Lifetime determinants of cognitive ageing, dementia and early death

Social relationships and cognitive decline: a systematic review and meta-analysis of longitudinal cohort studies

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Abstract

Background: Although poor social relationships are assumed to contribute to cognitive decline, meta-analytic approaches have not been applied. Individual study results are mixed and difficult to interpret due to heterogeneity in measures of social relationships. We conducted a systematic review and meta-analysis to investigate the relation between poor social relationships and cognitive decline.

Methods: MEDLINE, Embase and PsycINFO were searched for longitudinal cohort studies examining various aspects of social relationships and cognitive decline in the general population. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled using random effects meta-analysis. Sources of heterogeneity were explored and likelihood of publication bias was assessed. We stratified analyses according to three aspects of social relationships: structural, functional and a combination of these.

Results: We identified 43 articles. Poor social relationships predicted cognitive decline; for structural (19 studies): pooled OR: 1.08 (95% CI: 1.05–1.11); functional (8 studies): pooled OR: 1.15 (95% CI: 1.00–1.32); and combined measures (7 studies): pooled OR: 1.12 (95% CI: 1.01–1.24). Meta-regression and subgroup analyses showed that the heterogeneity could be explained by the type of social relationship measurement and methodological quality of included studies.

Conclusions: Despite heterogeneity in study design and measures, our meta-analyses show that multiple aspects of social relationships are associated with cognitive decline.

As evidence for publication bias was found, the association might be overestimated and should therefore be interpreted with caution. Future studies are needed to better define the mechanisms underlying these associations. Potential causality of this prognostic association should be examined in future randomized controlled studies.

Key words: Cognitive decline, social relationships, meta-analysis

Key Messages

- We identified 43 articles investigating various aspects of social relationships; structural, functional and a combination of structural and functional.
- This meta-analysis shows that poor social relationships are associated with cognitive decline.
- There was substantial clinical and methodological heterogeneity between studies.
- Future studies are needed to better define the mechanisms underlying the associations between poor social relationships and cognitive decline.

Introduction

Late-life cognitive impairment and dementia are considered a major public health concern because of high prevalence rates and high economic and social burden.[1,2] Decline in cognitive functioning is considered part of normal ageing. However, there are substantial individual differences in the rate and timing of cognitive decline.[3,4] Furthermore, some cognitive functions (i.e. processing speed, executive function, memory) decline from middle age onwards, whereas other cognitive functions (i.e. verbal ability and general knowledge) are less age related.[3,5] Accelerated cognitive decline and a deviation from population norms based on age and education level may result in a classification of mild cognitive impairment (MCI) or dementia.[6] MCI is conceptualized as a prodromal state between a preclinical stage of dementia and dementia.[7] A clinical diagnosis of MCI is based on a cognitive concern expressed by the patient, an informant or a clinician about a change in cognition, compared with the person's previous level. In addition, the individual's performance of cognitive functioning is in at least one cognitive domain lower than would be expected from the person's age and educational level. In general, these cognitive changes are sufficiently mild and independence of daily living is maintained. Furthermore, there should be no evidence of dementia[5] that is characterized by more severe decline in cognitive functioning which also interferes with independence in everyday activities.[7,8] Prevalence rates of accelerated cognitive decline vary between 3% and 42%.[9] People with cognitive impairment have higher risk to develop disabilities in instrumental activities of daily living[10] and dementia.[6,11] Currently, no effective treatments for cognitive impairments or dementia are available.[12,13] Interventions aimed to prevent cognitive decline at the very early or preclinical phases could be beneficial in slowing the process of cognitive decline.[7,14] In order to develop preventive treatments or strategies, it is important to identify factors that might cause cognitive impairment or accelerate cognitive decline.[11]

Various (modifiable) risk factors for cognitive decline have been identified, including cardiovascular disease,[15] diabetes,[16] physical inactivity,[17,18] smoking,[19] and excessive alcohol use.[20] Another potentially important modifiable risk factor for cognitive decline is the absence of (good) social relationships. We previously showed that poor social relationships, and in particular less social interaction, are an important risk factor for the development of dementia.[21] Social relationships can generally be classified by structural and functional aspects.[22–24] Structural aspects relate to the structure of the social network, such as the size of the social network and the frequency of contact between members of the social network. Functional aspects relate to the function of the social network and the purpose of the relationships, such as someone's perception of the quality of the support provided by their network, practical aid or social support.[24,25] Social relationships play an important role in the protection against depression,[26] coronary heart disease,[27] functional decline[28] and mortality.[22] Previous reviews on the relation between poor social relationships and cognitive decline also point to an influence of various social relationship aspects (i.e. socially integrated lifestyle, loneliness, social engagement, social activities) on cognitive decline, but conclusions are contradictory.[18,29–32] These reviews examined only a limited number of social relationship aspects, did not take into account the methodological quality of the included studies or only included

cross-sectional studies. Furthermore, none of the previous systematic reviews performed a meta-analysis, nor distinguished between structural and functional aspects of social relationships.

Therefore, we investigate the relation between poor social relationships and the development of cognitive decline in the general population, by conducting a systematic review and meta-analysis of longitudinal cohort studies in which we consider both structural and functional aspects of social relationships.

Methods

This systematic review was conducted according to the methods of the Cochrane Collaboration[33] and, in addition, we followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[34] for the reporting of this systematic review and meta-analysis.

Systematic search and study selection

A systematic database search in MEDLINE, Embase and PsycINFO was conducted on 9 July 9 2012. Search strings included suitable indexing terms (i.e. MeSH terms and keywords) on: (i) social relationships (e.g. social network, social engagement, loneliness); and (ii) cognitive decline (e.g. cognitive impairment, cognitive decline, cognitive function) (see Supplementary material A, available as Supplementary data at *IJE* online). Two reviewers (J.S.K. and M.Z.) 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. Disagreements were resolved in consensus meetings. In case of persistent disagreements, a third reviewer (N.S.) made the final decision. Reference lists of all included articles and relevant reviews on this topic were screened to locate articles not identified in the database searches. Articles were included if they: (i) were peer reviewed;(ii) reported an association between social relationships measured at baseline and a change in cognitive functioning between baseline and follow-up in a quantitative way; and (iii) utilized a longitudinal prospective cohort study design conducted in the general population. Only articles published in English, Dutch, German or French were included. Studies focusing only on dementia as outcome were excluded from this review. The overall percentage agreement and Cohen's kappa were calculated to evaluate inter-rater agreement for inclusion of eligible articles.

Data extraction and methodological quality assessment

The same two reviewers (J.S.K. and M.Z.) independently extracted the data regarding study population, social relationship assessment, statistical methods and results, timing of follow-up measurements, and cognitive functioning. Where possible, estimates adjusted for potential confounders were used for the meta-analyses. In this respect, age, depression, alcohol use, education, baseline cognition and physical functioning [this included at least one of the three following variables: (i) physical activity; (ii) functional disability; or (iii) at least one of the following chronic diseases: traumatic brain injury (TBI), cardiovascular disease or cerebrovascular accident (CVA)/stroke], were considered potential confounders.

The methodological quality of included studies was assessed by the two reviewers (J.S.K. and M.Z.) independently using the Quality of Prognosis Studies in Systematic Reviews (QUIPS) tool[35] (see Supplementary material B, available as Supplementary data at *IJE* online). Disagreements were resolved in consensus meetings. The overall percentage agreement and Cohen's kappa were calculated to evaluate inter-rater agreement on the methodological quality of the included studies.

Statistical analysis

For the meta-analysis, the analyses were stratified by calculating a pooled estimate separately for: (i) structural aspects of social relationships (i.e. social network size, social activity); (ii) functional aspects of social relationships (i.e. social support, loneliness, satisfaction with household members); and (iii) a combination of structural and functional aspects of social relationships (i.e. composite scores of structural and functional social relationships measures combined). In case social relationship factors were presented as categorical variables [36] the categories were dichotomized in such a way that the lowest category (poor social relationships) was tested against the other categories combined, and the odds ratio based on the new two-by-two table was used. The odds ratio (OR) was used to calculate pooled estimate, representing the risk of developing cognitive impairment among people with poor social relationships (e.g. small social network) compared with people with better social relationships. In case other estimates than ORs were presented in the article, we transformed those estimates to ORs and the accompanying 95% confidence intervals (CIs) where possible in order to include the study results in the meta-analysis. Relative risks (RRs) and hazard ratios (HRs) were interpreted as ORs. Unstandardized and standardized regression coefficients were converted to logORs and subsequently to ORs[33,37–41] (see Supplementary material C, available as Supplementary data at *IJE* online). If *P*-values were reported as $P < 0.05$, we assumed a *P*-value of 0.05 in order to calculate the standard error and subsequently 95% CI. If *P*-values were

reported as $P > 0.05$, we assumed a P-value of 0.53 (i.e. the average of 0.05 and 1.00) in order to calculate a 95% CI.[42] In case information was missing in the article to calculate OR and 95% CI (i.e. estimate, P-value, standard error or standard deviation of the determinant or outcome), the authors of the article were contacted and requested additional information.

When multiple articles were based on the same study (i.e. same participants), we selected the results of the article based on the following criteria (in order of importance): (i) reported an estimate useful for the meta-analysis; (ii) determinant measured as a composite measure of social relationship factors, or most compatible with the other studies; (iii) outcome measured as global cognitive functioning, or most compatible with the other studies; (iv) longest follow-up duration; and (v) largest sample size.

A random effects method was used to pool effect sizes.[33] Heterogeneity was examined by means of the Q-test and the I^2 index. If the P-value in the Q-test was below 0.05 or the I^2 index was higher than 50%, the results of the studies in the pooled analysis were considered to be heterogeneous.[33] All statistical analyses were performed with the program Comprehensive Meta-Analysis (version 3).[43]

Meta-regression, subgroup analyses and sensitivity analyses

Sources of heterogeneity were explored by conducting univariable random effects meta-regression[33,34] for the following pre-specified characteristics: (i) type of social relationship measurement (i.e. for structural aspects: social activity and social network size; for functional aspects: social/emotional support, loneliness and satisfaction with household members); (ii) outcome measurement, based on (a) incident cognitive impairment versus a continuous measure of cognitive decline; (b) global cognitive functioning versus specific domains of cognitive functioning; (c) and results based on two measurements of cognitive functioning (baseline and follow-up) versus more than two measurements; (iii) timing of follow-up measurement (≤ 3 years, 4-7 years, ≥ 8 years); (iv) risk for cognitive decline at baseline, based on (a) health status at baseline (all community-dwelling versus cognitively healthy versus cognitively and physically/mentally healthy); (b) age at baseline (≤ 65, 66–74, ≥ 75); and (v) the individual methodological quality items. If less than 10 studies were included in the meta-analysis, sources of heterogeneity were not explored by meta-regression but by conducting subgroup analyses for the same pre-specified characteristics as mentioned above.[33,34] In case the incidence of cognitive decline was larger than 10%, we interpreted RRs or HRs also as ORs. This might result in an underestimation of the actual OR (95% CI).[45] Therefore, sensitivity analyses were conducted by excluding these studies from the meta-analyses.

Publication bias

In order to assess the likelihood of publication bias, we constructed funnel plots for the relation between the various social relationship aspects (i.e. structural, functional and the combined aspects of social relationship factors) and cognitive decline by plotting the natural logarithm of the effect measure (log odds ratio) against the standard error of this measure. We used Egger's method to statistically test asymmetry of the funnel plots. Publication bias was assumed likely in case $P < 0.10$.[46]

Results

Identification of studies

Reviewing 8527 titles and abstracts, and 133 full articles, resulted in 36 articles that met inclusion criteria for this systematic review[47-82] (see Figure 1). Screening the references of all included articles and other relevant reviews resulted in seven additional eligible articles included in this review.[36,83-88] In total, 43 articles were included in this systematic review. The inter-rater agreement for inclusion of eligible articles was good (overall agreement: 90% (133/148); Cohen's kappa 0.76). Details regarding study characteristics of the included articles are summarized in Table 1. Briefly, the duration of follow-up varied between 1 and 15 years. The sample size of the cohorts ranged between 66 and 16638.

Methodological quality

The results of the methodological quality assessment of the studies included in the systematic review are presented in Supplementary material D (available as Supplementary data at *IJE* online). Scores on individual methodological quality items varied from poor (only 19% of the studies accounted for alcohol use in the analyses) to excellent (100% of the studies measured age). Most methodological limitations (i.e. high risk of bias in over 50% of the studies) were found for the following item: 'adjustments for potential confounders' (i.e. alcohol use and depression). Insufficient information (i.e. unclear risk of bias in over 50% of the studies) was given for the following methodological quality items: study attrition (i.e. differences between participants and drop-outs), complete data of social relationship measures at baseline, blinding of the outcome assessor for the determinant measurement, and measurement of alcohol use, making it impossible to determine the likelihood of bias. The inter-

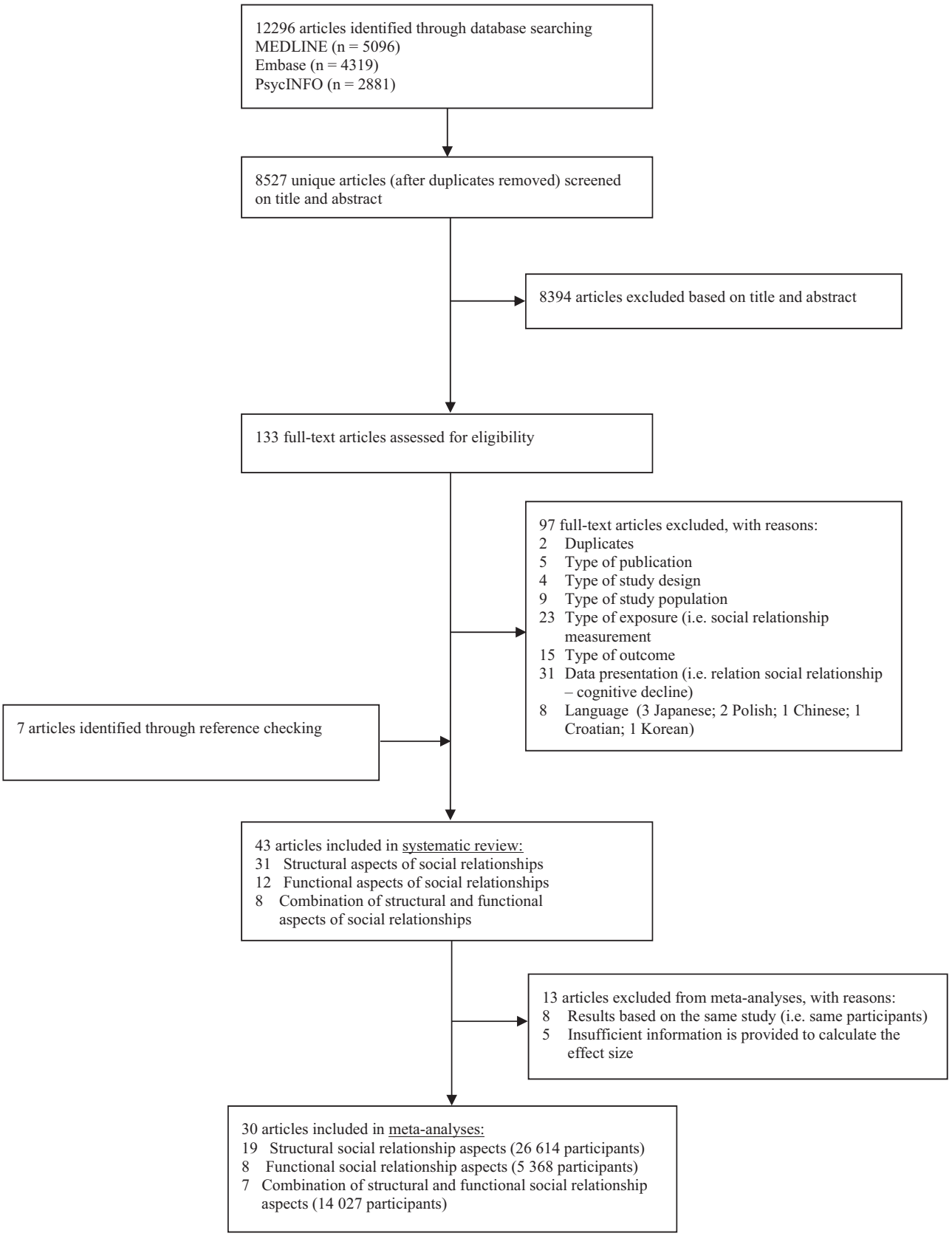

Figure 1 Flow of study selection.

Table 1. Characteristics and results of studies included in systematic review for: a) structural aspects of social relationships, b) functional aspects of social relationships, and c) combination of structural and functional aspects of social relationships

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS

Study characteristics				Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
Aartsen *et al.* 2002[83]	The Netherlands	6	1693	Inclusion: - 55 to 85 years old - Being in the population register of one of 11 municipalities in the Netherlands - Oversampling of older and male participants	68.7 (8.3), 55–85	55	Age, sex, education, functional ability, baseline cognition	Cognitive decline (measured with MMSE (continuous; range 0–30), at baseline and at follow-up)	**Structural:** *Social activity*. Continuous, based on 3 parameters combined (visiting church services, visiting neighbourhood associations, visiting meetings of an organization for helping older adults, neighbours, and handicapped persons)	No association (data not shown)	na[b]
Albert *et al.* 1995[84]	USA	Range: 2.0–2.5	1192[c]	Inclusion: - Community dwelling - 70 to 79 years old Exclusion: - Cognitive impairment at baseline - Functional deficits or serious illness at baseline	74.3 (2.7), 70–79	55	Age, sex, education, psychiatric symptoms, alcohol use, physical performance, foot-tapping time, number of chronic conditions, cholesterol, dehydroepiandrosterone sulphate, baseline cognitive function, race, income, smoking, efficacy scale score, peak expiratory flow rate, cortisol/microgram creatinine, waist-hip ratio, life satisfaction score, strenuous work in everyday life, strenuous work and recreation, moderate work and recreation, light work and recreation, BMI	Cognitive decline (measured with Boston Naming Test, Delayed Recognition Span Test, Similarities subtest of the Wechsler Adult Intelligence Scale-Revised, figure copying (continuous; range 0–89), at baseline and at follow-up)	**Structural:** *Social network size*. Continuous, range: 0–30. Higher scores indicate more friends and relatives felt close to	No association (data not shown)	na[d]
Barnes *et al.* 2004[49]	USA	Mean: 5.3 Maximum: 6	3899	Inclusion: - 65+ years old - Living in geographically defined area in south Chicago	73.9 (6.5), 65+	62	Age, sex, race *Additional adjustments for physical activity, number of depressive symptoms, and number of chronic medical conditions did not alter the results in the original paper (data not shown)*	Annual rate of cognitive decline (measured with East Boston Story, Symbol Digit Modalities Test, MMSE (continuous; raw test scores were converted to z scores and then averaged), at baseline, and at 3- and 6-year follow-up)	**Structural:** *Social activity*. Continuous, based on 4 parameters (attending religious services, going to a museum, participation in activities or groups outside the home, a part-time or full-time job). Range: 0–8. Higher scores indicate higher social activity	β*: 0.009 (SE: 0.001)	1.06 (1.04–1.07)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
Bassuk *et al.* 1999[50]	USA	12	710	Inclusion: - 65+ years old - Living in New Haven, Connecticut in 1982 Exclusion: - Cognitive impairment at baseline - Being institutionalized	Range: 65+	63	Age, sex, education, depression, alcohol use, physical disability, cardiovascular profile, regular physical activity, baseline cognition, ethnicity, income, housing, sensory impairment, smoking status	Incident cognitive impairment (measured with SPMSQ (range 0–10). Cognitive decline was defined as transition to a lower SPMSQ category (from high (9 or 10) to medium (7 or 8) or low (0 to 6) or from medium to low). Measured at baseline, and at 3-, 6- and 12-year follow-up)	**Structural:** *Social disengagement.* Continuous, based on 6 parameters (having a spouse, monthly visual contact with at least three relatives or friends, yearly non-visual contact with at least 10 relatives or close friends, church attendance at least once per month, membership in other groups, regular participation in recreational and social activities). Range: 1–4. Higher scores indicate more social disengagement	12-year follow-up: OR: 1.33 (95% CI: 1.03 to 1.72)	1.33 (1.03–1.72)
Béland *et al.* 2005[51]	Spain	6	519	Inclusion: - 65+ years old - Living in Leganés, a suburban municipality located 8 km outside Madrid	75.6 (6.9), 65–100	58	Age, sex, education, depression, functional limitations, stroke	Cognitive decline (measured with Leganés Cognitive Test (continuous; range 0–32), at baseline, and at 2-, 4- and 6-year follow-up)	**Structural:** *Social activity.* Continuous, based on 4 parameters combined (membership in a community association, at least monthly attendance of religious services, at least monthly attendance at a community center with recreational activities for seniors, frequenting, at least monthly, a public square or outdoor meeting place). Range: 0–4. Higher scores indicate more social activity	B: 0.0065 (SE: 0.0061)	na[e]
Bosma *et al.* 2002[85]	Netherlands	3	818	Inclusion: - 50+ years old at follow-up (3 years after baseline) - In register of one of the 15 family practices	62.8, 49–81	Unclear	Age, sex, education, baseline cognition, length of follow-up interval	Cognitive decline (measured with MMSE (continuous; range 0–30), at baseline and at follow-up)	**Structural:** *Social activity.* Dichotomous (no engagement in organizational membership (e.g. clubs) activity versus at	B: 0.08 ($P > 0.05$) Additional information from author: SE: 0.106	1.09 (0.88–1.34)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				Exclusion: - Developed dementia between baseline and first follow-up - Chronic neurological pathology (e.g. dementia, cerebrovascular disease, epilepsy, parkinsonism and malignancies related to the nervous system) - Mental retardation - Chronic psychotropic drug use					least 1 h/week engagement in activity)		
Boyle *et al.* 2010[52]	USA	Mean: 4.0 (SD: 1.58) Maximum: 8	698	Inclusion: - Agreeing to detailed annual clinical evaluations and organ donation at the time of death - Valid baseline score on the purpose of life questionnaire - At least 1 follow-up clinical evaluation Exclusion: - MCI at baseline	80.4 (7.4)	75	None	Incident MCI (measured with a clinical diagnosis of MCI, at baseline, and at 2-, 3-, 4-, 5-, 6-, 7-, and 8-year follow-up)	**Structural**: *Social network size*. Continuous, range: 0–66. Higher scores indicate more children, family, and friends seen at least once a month	- Mean (SD) social network size in 413 participants (of 698) who did not develop MCI: 7.0 (6.3) - Mean (SD) social network size in 285 participants (of 698) who did develop MCI: 6.6 (6.1) $P = 0.25$	na[f]
Cherry *et al.* 2010[53]	USA	Maximum: 13 months	66	Inclusion: -Tested within the 8-month period prior to the storms Rita and Katrina -Belong to age group 45 to 64, 65 to 89, or 90+ -MMSE score $\geq$ 25 -Residing in one of 8 parishes within approximately 40-mile radius of Baton Rouge, LA Exclusion: - Neurological impairment as a result of stroke or adult dementia	74.9, 45–90+	49	House evacuees in your home, experiencing changes in your workplace or job-related duties	Cognitive decline (measured with Forward Digit Span subtest of the WAIS (continuous change score), at baseline and at follow-up)	**Structural:** *Social activity*. Continuous, (participation in clubs and social organizations). Higher scores indicate more social activity	B: 0.61, $P = 0.03$	na[b]
Chi *et al.* 2000[54]	China	3	260	Inclusion: - 70+ years old - Community-dwelling - Chinese	76.1 (4.9), 67–95	49	Age, sex, education, IADL, frequency of exercise, baseline cognition, being literate, chronic illness,	Cognitive decline (measured with SPMSQ (continuous; range 0–10), at	**Structural:** *Number of relatives respondents felt close to*. Continuous, range: 0–5. Higher	B: 0.05 (SE: 0.07)	1.17 (0.77–1.77)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- On the registered list of the Social Welfare Department Exclusion: - Moving from study area			somatic complaints, sight, hearing, self-rated health, smoking, satisfaction with household members, number of friends felt close to	baseline and at follow-up)	scores indicate more relatives felt close to		
Ertel *et al.* 2008[55]	USA	6	16638	Inclusion: - 50+ years old - US adults - Interviewed in 1998 Exclusion: - Scoring in the lowest 10th percentile on memory scores at baseline - Being institutionalized	64.5 (0.1), 51–99	58	Age, age^2, sex, education, depression, mobility, ADL, IADL, wealth, income, race, health conditions, large muscle index	Rate of cognitive decline (measured with immediate and delayed recall of a 10-word list (continuous sum score), at baseline, and at 2-, 4- and 6-year follow-up)	**Structural:** *Social engagement.* Continuous, based on 5 parameters combined (marital status, volunteer activities, contact with parents, contact with children, contact with neighbours). Range: 0–5. Higher scores indicate more social engagement	B: 0.04 (95% CI: 0.03 to 0.05), $P < 0.01$	na[b]
Ghisletta *et al.* 2006[86]	Switzerland	5	529	Inclusion: - 80 to 85 years old - Community dwelling - Living in French-speaking region of Switzerland	83.4 (2.6), 80–85	52	Age, sex, socioeconomic status, problems with hearing, problems with vision, general health (including general health and ADL to be categorized into good health and robust, satisfactory health, frail, and bad health)	Cognitive decline (measured with Cross-Out test of the revised Woodcock-Johnson Psycho-Educational Battery (continuous), at baseline, and at 2-, 3-, 4- and 5-year follow-up)	**Structural:** *Social activity.* Continuous, based on 4 parameters combined (with which frequency participants engaged in visit coffee/tea rooms or restaurants, participate in trips or outings, attend cultural events (theatre, music, cinema), attend local fairs or celebrations). Higher scores indicate higher social activity	β: 0.058 (SE: 0.122)	1.24 (0.52–2.95)
Glei *et al.* 2005[56]	Taiwan	Maximum: 7 3 intervals; 3, 6, 7	2387	Inclusion: - 60+ years old in 1989 - Taiwanese	71.8 (5.2), 55-76	44	Age, sex, education, depression, number of ADL difficulties, number of IADL difficulties, number of mobility limitations, number of failed cognitive tasks, year of survey, occupational status index, dissatisfaction with economic situation, social activity, marital	Cognitive decline (measured with five questions from SPMSQ (range 0–5). Cognitive impairment at each wave was modelled as function of each respondent's level of cognitive impairment and characteristics at the previous survey date. Measured at baseline,	**Structural:** *Social network size.* Continuous, range: 0–46. Higher scores indicate higher number of close relatives with at least weekly contact	B: -0.001 (SE: 0.003)	na[g]

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
							status, number of friends/neighbours with at least weekly contact, number of other relatives with at least weekly contact	and at 3-, 6- and 7-year follow-up)			
Green *et al.* 2008[58]	USA	Mean: 10.9 Maximum: 12	874	Inclusion: - 18+ years old in 1981 - Living in East Baltimore	47.3 (12.0)	63	Age, sex, education, depression, lifetime alcohol misuse or dependence, cerebrovascular disease or risk, ADL disabilities, race, household income	Cognitive decline (measured with MMSE (continuous; range 0–30), at baseline and follow-up)	**Structural:** *Social network size.* Continuous, based on 2 parameters (number of relatives outside the home, number of friends and neighbours with whom the respondent communicated by telephone or visits during the past 6 months) and 6 categories (0, 1, 2–3, 4–5, 6–10, ≥11). Range: 0–10. Higher scores indicate larger social network	β: 0.028 (95% CI: -0.037 to 0.093)	na[h]
Hill *et al.* 2006[60]	USA	8	2472	Inclusion: - 65+ years old - Mexican-origin - Residing in Texas, California, New Mexico, Arizona or Colorado	72.3 (6.1), 65–107	58	Age, sex, education, depression, alcohol use, functional disability, hypertension, history of stroke, history of heart attack, baseline cognition, church attendance, hearing impairments, vision impairments, current smoker, diabetes, English language proficiency	Cognitive decline (measured with MMSE (continuous; range 0–30), at baseline, and at 3-, 6- and 8-year follow-up)	**Structural:** *Social disengagement.* Continuous, based on 4 parameters combined (marital status, monthly contact with family and friends, secular group memberships, living arrangements). Range: 0–4. Higher scores indicate more social disengagement.	β: 0.01, $P > 0.05$	na[d]
Holtzman *et al.* 2004[61]	USA	Mean: 12.4 Maximum: 15	341	Inclusion: -50+ years old at baseline - Living in eastern Baltimore Exclusion: - MMSE score < 28 at wave 1	61.3 (6.9), 50–81	69	Age, sex, education, lifetime presence of alcohol disorder, change in physical disability, cardiovascular disease status, baseline cognition, change in dysphoria, race, change in social network size	Cognitive decline (measured with MMSE (continuous; range 0–30), at baseline and follow-up)	**Structural:** *Social network size.* Continuous, based on 2 parameters combined (number of relatives and family members outside the household, number of friends and neighbours with whom the	β: 0.14, $P = 0.006$	1.67 (1.15–2.43)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
									respondent kept in touch by phone or visits). Range: 0–10. Higher scores indicate higher social activity		
Hughes *et al.* 2008[62]	USA	Mean: 4.9 Range: 4.6 – 5.3	217	Inclusion: - 65+ years old - Living in one of the two tracts in Charlotte County Exclusion: - Modified MMSE score < 82 at baseline - Living in congregate living site or long-term care facility	72.4 (6.2), 65+	52	Age, sex, education, attrition status, residency status, neuroticism, extraversion, openness, agreeableness, conscientiousness, years of follow-up in time, marital status, social network of friends, emotional support, instrumental support, informational support, satisfaction with support, negative social interactions	Cognitive decline (measured with Modified MMSE (continuous; range 0–100), at baseline and follow-up)	**Structural:** *Social network of family.* Continuous, based on 3 parameters combined (number of contacts with family per month, frequency of contact per month with closest relative, and number of close relatives). Higher scores indicate larger social network of family	β: 0.09, $P = 0.17$	1.39 (0.87–2.23)
Iwasa *et al.* 2012[63]	Japan	5	567	Inclusion: - 70 to 84 years old - Invited for a health check-up in Tokyo	75.8 (3.5), 70–84	50	Age, sex, education, depression, presence of chronic disease (at least one disease among diabetes, heart disease and stroke), IADL, baseline cognition, smoking, hearing deficit	Cognitive decline, dichotomized (measured with MMSE (range 0–30), calculated by subtracting baseline MMSE score from follow-up MMSE score (cut-off: -3). Measured at baseline and follow-up)	**Structural:** *Social activity.* Dichotomous, no versus yes engagement in social activities	OR: 1.45 (95% CI: 0.89 to 2.34)	1.45 (0.89–2.34)
James *et al.* 2011a[64]	USA	Mean: 4.5 (SD: 1.6) Maximum: 8	954	Inclusion: - Older persons - Living in one of the houses, or places where recruitment took place - Agreeing to detailed annual clinical evaluations and organ donation at the time of death Exclusion: - Dementia at baseline - MCI at baseline	78.4, 55–75+	74	None	Incident MCI (measured with clinical diagnosis of MCI, at baseline and follow-up)	**Structural:** *Social network size.* Continuous. Higher scores indicate more children, family and friends seen at least once a month	- Mean social network size MCI: data not reported - Mean social network size not MCI: data not reported F(df1, df2): 0.03 (1, 950) ; $P = 0.87$	na[f]
James *et al.* 2011b[65]	USA	Mean: 5.2 (SD: 2.8) Range: 0.4–12.3	1138	Inclusion: - 65+ years old	79.6 (7.5), 65+	74	Age, sex, education, depression, disability, physical activity, age*time,	Annual rate of cognitive decline (measured with Logic Memory, East	**Structural:** *Social activity.* Continuous, based on 6 parameters combined	β^*: 0.034 (SE: 0.007)	1.08 (1.05–1.11)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- Living in one of the 40 retirement or subsidized housings in Chicago Exclusion: - Dementia at baseline			sex*time, race, race*time, education*time, social networks, chronic conditions, neuroticism, extraversion, cognitive activity	Boston Story, Word List, Boston Naming Test, Verbal fluency, 15-item reading test, Digit Span Forward and Backward, Digit Ordering, Symbol Digit Modalities Test, Number Comparison, Stroop Test, Judgment of Line Orientation, Standard Progressive Matrices (continuous; raw test scores were converted to z scores and then averaged). Measured at baseline and at 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11- and 12-year follow-up (i.e. participants underwent between 2 and 13 annual evaluations))	(how often during the past year did you involve in social activities: go to restaurants, go on day trips or overnight trips, do unpaid community or volunteer work, visit relatives' or friends' houses, participate in groups, such as senior centre, Knight of Columbus, Rosary Society, or something similar, attend church or religious services). Higher scores indicate higher social activity		
Lee *et al.* 2009[66]	South-Korea	2	977	Inclusion: - 65+ years old - Living in a household in Suwon City	73.0 (5.7), 65+	61	Age, sex, education, heart disease, hypertension, stroke, physical activity, marital status, lifetime occupation, diabetes mellitus, smoking, vegetable consumption	Cognitive decline (measured with Korean version of MMSE (continuous; range 0–30), at baseline, and at 1- and 2-year follow-up)	**Structural:** *Social activity.* Dichotomous, upper quartile versus lower quartiles, based on (frequency of meeting or telephoning friends, neighbours, or relatives, attending church or other forms of religious service, going to movies, sports, or cultural exhibition). Higher scores indicate more social activity	B: 0.626 (SE: 0.187) Additional information from author: SD outcome: 4.55	1.24 (1.09–1.41)
Monastero *et al.* 2007[87]	Sweden	Mean: 3.4 (SD: 0.5)	718	Inclusion: - 75–95 years old on 1 October 1987 - Inhabitant of Kungsholmen district in Stockholm	80.4, 75–95	74	Age, sex, education, depression, ADL disability, fitness activities, time to first follow-up, chronic disease, psychoses,	Incident CIND (measured with MMSE (range 0–30; cut-off: 1 SD below age- and education-specific mean of the test.	**Structural:** *Social activity.* Dichotomous, no/infrequent versus frequent participation, based on 4 parameters (attending	OR: 1.6 (95% CI: 1.0 to 2.6)	1.6 (1.0–2.6)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				Exclusion: - Dementia at baseline - Dementia at first follow-up - CIND at baseline - MMSE score < 20 at baseline			psychotropic drug use, social activities, social network, mental activities, productive activities	Dementia cases were ascertained by specialists according to DSM-III-R criteria. Measured at baseline and follow-up)	the theatre, concerts or art exhibitions; travelling; playing cards/games; or participating in social groups or a pension organization)		
Niti *et al.* 2008[68]	Singapore	Median: 1.5 Range: 1 - 2	1635	Inclusion: - 55+ years old - Living in a geographically defined area in the South-East region of Singapore	66.0 (7.3), 55–93	65	Age, sex, education, depression, alcohol use, hypertension, cardiac diseases, stroke, physical functional status, physical activity, baseline cognition, number of medical illnesses, diabetes, smoking, apolipoprotein E4 genotype, productive activity	Cognitive decline, dichotomized (measured with MMSE (range 0–30), defined as a decline of ≥ 1point between baseline and follow-up. Measured at baseline and follow-up)	**Structural:** *Social activity.* Dichotomous, frequent engagement in at least one social activity yes versus no, based on 8 parameters (participation in religious services, visiting cinemas, restaurants or sports events; day or excursion trips, playing cards or parlour games, senior citizen club activities, group recreational activities like karaoke or social dancing)	OR: 0.85 (95% CI: 0.59 to 1.22)	1.18 (0.82–1.69)
Seeman *et al.* 2001[70]	USA	Mean: 7.4 (SD: 4.7 months)	706	Inclusion: - 70 to 90 years old - Living in Durham (NC), East Boston (MA), or New Haven (CT) -Exclusion: *Physical limitation at baseline:* - Reported disability on the 7-item ADL-Scale (Katz) - More than one reported mild disability on eight items tapping gross mobility and range of motion - Not able to hold a semi-tandem balance for at least 10 s	74.2, 70–79	55	Age, education, depression, baseline cognition, income, ethnicity, number of chronic conditions, lung function, amount of strenuous leisure activity, amount of strenuous house/yard maintenance activity, self-efficacy, marital status, number of close ties, number of group participation, instrumental support, demands/conflicts with network, support provided to others	Cognitive decline (measured with Boston Naming Test, Delayed Recognition Span Test, Similarities subtest of the WAIS-Revised, figure copying (continuous; range 0–89), at baseline and follow-up)	**Structural:** *Social activity.* Continuous, based on 3 parameters (meetings of clubs or other groups, religious services, other activities with religious groups). Higher scores indicate more social activity	B: -0.13, $P = 0.70$	na[d]

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- Not able to stand from a seated position five times within 20 s *Cognitive limitations at baseline:* - Score < 6 on the SPMSQ - Score < 3 on the delayed recall of a short story							
Shatenstein *et al.* 2012[71]	Canada	3	1208	Inclusion: - In the Quebec Medicare database for the regions of Montreal Laval and Sherbrooke - English- or French-speaking - Able to walk one block or climb one floor without rest Exclusion: - 3MS score ≤ 79 at baseline - Disabilities in ADL - Heart failure ≥ class II - COPD requiring oxygen therapy or oral steroids - Inflammatory digestive disease - Cancer treated either by radiation therapy, chemotherapy or surgery in the previous 5 years - Parkinson disease - Thrombosis or cerebral haemorrhage - Muscular dystrophy - Epilepsy	74.2, 67–84	53	Age, sex, education, depression, alcohol use, functional autonomy, family income, waist circumference, mental function autonomy, regular vitamin-mineral supplement user, Canadian Healthy Eating Index, daily energy intake	Rate of cognitive decline (measured with Modified MMSE (range 0–100), at baseline, and at 1-, 2- and 3-year follow-up)	**Structural:** *Social activity.* Continuous, based on various parameters combined (Social Activities Questionnaire which evaluates 19 types of valued activities such as shopping, attending cultural events, travelling, and participating in community organizations). Higher scores indicate higher social activity	β: 0.005 (SE: 0.001)	1.02 (1.01–1.03)
Small *et al.* 2012[72]	Canada	Mean: 9.3	952	Inclusion: - 55+ years old - Community-dwelling - Corrected vision and hearing sufficient to engage the study procedures Exclusion: - Alzheimers disease or other dementia at intake - Psychiatric condition (with medications)	68.6 (6.7), 55–94	63	Unclear whether age, gender, years of education and self-reported health are included as covariates in the analyses	Cognitive decline (measured with 40 questions on recall of world knowledge and vocabulary test from the Educational Testing Service Kit of Factor Referenced Test (continuous, scores were standardized). Measured at baseline, and at 3-, 6-,	**Structural:** *Social activity.* Continuous, based on various parameters (for example, attending concerts, visiting friends). Higher scores indicate greater frequency of activity	B: 0.39 (SE: 0.16)	1.13 (1.02–1.24)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- History of serious cardiovascular or cerebrovascular disease				9- and 12-year follow-up)			
Thomas 2011[74]	USA	3	Women: 1103 Men: 539	Inclusion: - 60+ years old - White and African American adults	Women: 70.1, 60–95 Men: 69.4, 60–92	Separate analyses for women and men	Age, age^2, education, cognitive limitations at baseline, physical limitations at baseline, race, marital status, employment status, income, number of waves in which respondents participated	Cognitive decline (measured with five questions from SPMSQ (continuous; range 0–5), at baseline and follow-up)	**Structural:** *Social engagement.* Continuous, based on 5 parameters (talking on the phone with friends/family, visiting with friends/family, attending meetings/programmes of groups or organizations, attending religious services, volunteering). Higher scores indicate more frequent participation in social activities	Women: β: -0.133, $P < 0.01$ Men: β: -0.059, $P > 0.05$	Women: 1.63 (1.12–2.37) Men: 1.24 (0.63–2.42)
Van Ness *et al.* 2003[77]	USA	3 and 6	3-year follow-up: 1847 6-year follow-up: 1245	Inclusion: - 65+ years old - Males and residents of public and private elderly housing were oversampled Exclusion: - Being institutionalized	74.6 (6.9), 65–85+	58	Age, sex, education, depression, functional disability, hypertension, stroke, baseline cognition, smoking, religious attendance, religious preference, race, income, marital status	Incident cognitive impairment (measured with SPMSQ (range 0–10) and dichotomized as cognitive function intact (0–1 errors) versus cognitive dysfunction (≥ 2 errors). Measured at baseline, and at 3- and 6-year follow-up)	**Structural:** *Social disengagement index.* Continuous, range 0–3. Higher scores indicate more social engagement	6-year follow-up: OR: 0.88 (95% CI: 0.75 to 1.04)	na[d]
Wang *et al.* 2006[88]	China	Mean: 4.7 (SD: 0.5)	5437	Inclusion: - 55+ years old - From nine randomly selected communities at Chongqing and long-term residents in these communities. Exclusion: - Cognitive impairment at baseline (not normal baseline MMSE scores) - Severe aphasia - Hearing and visual impairment precluding a reliable assessment of cognitive function - Serious or terminal illness	63.4, 55+	48	Age, sex, education, depressive symptoms, alcohol use, ADL scores, medical conditions, baseline MMSE score, occupation, smoking, participation in other activities (i.e. cognitive and physical)	Incident cognitive impairment (measured with Chinese MMSE (range 0–30; cut-off points of 17 (illiteracy), 20 (≤ 6 years of education), and 24 (> 6 years of education). Measured at baseline, and at 1, 2-, 3-, 4- and 5-year follow-up)	**Structural:** *Social activity.* Continuous, calculated as hours spent per week of visiting friends or relatives. Higher scores indicate more hours per week	HR: 1.04 (95% CI: 0.91 to 1.20)	1.04 (0.91–1.20)

(continued)

Table 1. Continued

A) STRUCTURAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author (reference)	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- Previous long-lasting mental retardation - History of severe head trauma or surgery, and gas poisoning - Schizophrenia							
Yen *et al.* 2010[80]	Taiwan	Maximum: 10	6-year follow-up: 1554 10-year follow-up: 1142	Inclusion: - 60+ years old - Living in Taiwan Exclusion: - Dementia at baseline - Cognitive impairment at baseline	69.8 (4.9), 64+	59	Age, sex, education, depression, stroke, ADL disability, IADL disability, functional limitation, diabetes, self-perceived health	Incident cognitive impairment, at 6 and/or 10 years of follow-up [measured with 9-item SPMSQ (range 0–9; dichotomized as cognitive impairment, ≥ 4 errors, versus no cognitive impairment, < 4 errors. Measured at baseline, and at 6- and 10-year follow-up]	**Structural:** *Social activity.* Dichotomous, joining in organized group activity: yes versus no	OR: 0.98 (95% CI: 0.71 to 1.35)	1.02 (0.74–1.41)
Zhang 2006[81]	China	2	3867	Inclusion: - 80–105 years old - Living in one of the parts of China where recruitment was done Exclusion: - MMSE score < 18 at baseline	83.8, 80–105	59	Age, sex, no formal education, number of ADL disabilities, rural residence, non-agricultural occupations, marital status, frequent sibling visits	Incident cognitive impairment (measured with Chinese MMSE (range 0–30; cut-off point of < 18), at baseline and follow-up)	**Structural:** *Frequent children visits.* Continuous. Range: 0–5. Higher scores indicate more frequent visits.	OR: 0.95, $P < 0.05$	1.05 (1.01–1.11)
Zunzunegui *et al.* 2003[82]	Spain	4	Women: 264 Men: 293	Inclusion: - 65+ years old - Living in Legánes, a suburb of Madrid Exclusion: - ≥ 5 errors in 8-item version of SPMSQ - Visual impairment (unable to see 23-point characters)	Range: 65+	Separate analyses for women and men	Age, education	Incident cognitive impairment (measured with SPMSQ, the Barcelona Test, EPESE short story recall (cut-off scores for incident cognitive impairment: change score of > 1SD: range -8 to -23). Measured at baseline and follow-up)	**Structural:** *Social integration.* Continuous, based on 3 parameters (membership in a community association, at least monthly attendance of religious services, visits to the community centre for elderly people). Range: 0–3. Higher scores indicate better social integration	Women: OR: 0.73 (95% CI: 0.47–1.13) Men: OR: 0.68 (95% CI: 0.45–1.04)	Women: 1.37 (0.89–2.13) Men: 1.47 (0.96–2.22)

(continued)

Table 1. Continued

B) FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
Albert *et al.* 1995[84]	USA	Range: 2.0-2.5	1192[c]	Inclusion: - 70 to 79 years old - Community dwelling Exclusion: - Cognitive impairment at baseline - Functional deficits or serious illness at baseline	74.3 (2.7), 70-79	55	Age, sex, education, psychiatric symptoms, alcohol use, physical performance, foot-tapping time, number of chronic conditions, cholesterol, dehydroepiandrosterone sulphate, baseline cognitive function, race, income, smoking, efficacy scale score, peak expiratory flow rate, cortisol/microgram creatinine, waist-hip ratio, life satisfaction score, strenuous work in everyday life, strenuous work and recreation, moderate work and recreation, light work and recreation, BMI	Cognitive decline (measured with Boston Naming Test, Delayed Recognition Span Test, Similarities subtest of the Wechsler Adult Intelligence Scale-Revised, figure copying (continuous; range 0-89), at baseline and follow-up)	**Functional:** *Emotional support*. Continuous	No association (data not shown)	na[i]
Bassuk *et al.* 1999[50]	USA	12	710	Inclusion: - 65+ years old - Living in New Haven, CT, in 1982 Exclusion: - Cognitive impairment at baseline - Being institutionalized	Range: 65+	63	Age, sex, education, depression, alcohol use, physical disability, cardiovascular profile, regular physical activity, baseline cognition, ethnicity, income, housing, sensory impairment, smoking status	Incident cognitive impairment (measured with SPMSQ (range 0-10). Cognitive decline was defined as transition to a lower SPMSQ category [from high (9 or 10) to medium (7 or 8) or low (0 to 6) or from medium to low]. Measured at baseline, and at 3-, 6- and 12-year follow-up)	**Functional:** *Emotional support*. Dichotomous, yes versus no	No association (data not shown)	na[i]
Chi *et al.* 2000[54]	China	3	260	Inclusion: - 70+ years old - Community-dwelling	76.1 (4.9), 67-95	49	Age, sex, education, IADL, frequency of exercise, baseline cognition, being	Cognitive decline [measured with SPMSQ	**Functional:** *Satisfaction with household members*. Continuous.	B: -0.02 (SE :0.08)	1.06 (0.69-1.63)

(continued)

Table 1. Continued

B) FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- Chinese - On the registered list of the Social Welfare Department Exclusion: - Moving from study area			literate, chronic illness, somatic complaints, sight, hearing, self-rated health, smoking, number of relatives felt close to, number of friends felt close to	(continuous; range 0-10), at baseline and follow-up]	Range: 0-5. Higher scores indicate more satisfaction		
Graves *et al.* 1999[57]	USA	2	717	Inclusion: - 65+ years old - Living within King County in November 1991 - Of at least 50% Japanese heritage Exclusion: - Dementia at baseline	71.5, 65-95+	56	Age, sex, education, baseline cognition, follow-up time, apolipoprotein E status, low income, choice reaction time, acculturation factor 1 and 2, diagnosed history of heart attack, stroke, or high blood pressure	Incident cognitive impairment (measured with CASI (range 0-100). Dichotomized as cognitive decline ($\geq$ 5.15 points decline on CASI) versus no cognitive decline ($<$ 5.15 points decline, no change, or CASI score). Measured at baseline and follow-up)	**Functional:** *Social support*. Continuous summed score. Range: 4-21. Higher scores indicate less support	OR: 0.90 (95% CI: 0.76 to 1.04)	1.11 (0.96-1.32)
Green *et al.* 2008[58]	USA	Mean: 10.9 Maximum: 12	874	Inclusion: - 18+ years old in 1981 - Living in East Baltimore	47.3 (12.0)	63	Age, sex, education, depression, lifetime alcohol abuse or dependence, cerebrovascular disease or risk, ADL disabilities, race, household income	Cognitive decline (measured with MMSE (continuous; range 0-30), at baseline and follow-up)	**Functional:** *Emotional support*. Continuous, based on 3 parameters combined (how much does your partner really care about you, how much can you rely on your partner for help with a serious problem, how much can you relax and be yourself around your partner).Range: 0-27. Higher scores indicate more social support	β: -0.004 (95% CI: -0.047 to 0.040), P = 0.862	1.02 (0.86-1.19)
Hughes *et al.* 2008[62]	USA	Mean: 4.9 Range: 4.6-5.3	217	Inclusion: - 65+ years old - Living in one of the two tracts in Charlotte County	72.4 (6.2), 65+	52	Age, sex, education, attrition status, residency status, neuroticism, extraversion, openness,	Cognitive decline (measured with Modified MMSE (continuous;	**Functional:** *Emotional support*. Continuous, based on 4 parameters combined (frequency in the	β: -0.05, P = 0.45	0.83 (0.52-1.34)

(continued)

Table 1. Continued

B) FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS											
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				Exclusion: - Modified MMSE score < 82 at baseline - Living in congregate living site or long-term care facility			agreeableness, conscientiousness, years of follow-up in time, marital status, social network of family, social network of friends, instrumental support, informational support, satisfaction with support, negative social interactions	range 0-100), at baseline and follow-up)	past month of others providing support in difficult times, providing comfort, listening or talking about private feelings, and showing interest or concern). Higher scores indicate more emotional support.		
Lobo *et al.* 2008[67]	Spain	2	1654	Inclusion: - 55+ years old - Living in Zaragoza *For MCI cases at wave 2:* - An abnormal score in the memory items of both the MMSE and the GMS at wave 2 - Scores in the normal range on two indices of ADL at wave 2 Exclusion: - Dementia at baseline (based on DSM-IV-TR or cut-off on GMS and/or MMSE standard threshold) *For MCI cases at wave 2:* - Dementia according to GMS at wave 2 - MMSE score below threshold point at wave 2 *For non-cases at wave 2:* - Other GMS cases in particular depression and anxiety at wave 2	73.5 (9.8), 55-80+	58	Age, sex, education, irritability, neurovegetative symptoms, sleep problems, lack of concentration, subjective slowness	Incident MCI (measured with GMS-Agecat, MMSE. Incident MCI by *Petersen et al.*'s criteria. Measured at baseline and follow-up)	**Functional:** *Loneliness.* Dichotomous, yes versus no	OR: 2.05 (95% CI: 1.31 to 3.19)	2.05 (1.31-3.19)
Seeman *et al.* 2001[70]	USA	Mean: 7.4 (SD: 4.7 months)	706	Inclusion: - 70 to 90 years old	74.2, 70-79	55	Age, education, depression, baseline cognition, income, ethnicity, number	Cognitive decline (measured with Boston Naming Test, Delayed	**Functional:** *Emotional support*. Continuous, based on 6 parameters	B: 1.26, $P = 0.07$	1.33 (0.98-1.82)

(continued)

Table 1. Continued

B) FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS

	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
				- Living in Durham (NC), East Boston (MA), or New Haven (CT) -Exclusion: *Physical limitations at baseline:* - Reported disability on the 7-item ADL-Scale (Katz) - More than one reported mild disability on eight items tapping gross mobility and range of motion - Not able to hold a semi-tandem balance for at least 10 s - Not able to stand from a seated position five times within 20 s *Cognitive limitations at baseline:* - Score < 6 on the SPMSQ - Score < 3 on the delayed recall of a short story			of chronic conditions, lung function, amount of strenuous leisure activity, amount of strenuous house/yard maintenance activity, self-efficacy, marital status, number of close ties, number of group participations, instrumental support, demands/conflicts with network, support provided to others	Recognition Span Test, Similarities subtest of the WAIS-Revised, figure copying (continuous; range 0-89), at baseline and follow-up)	combined (how often do spouse/children/close friends and relatives make you feel loved and cared for? How often are spouse/children/close friends and relatives willing to listen when you need to talk about your worries or problems?)Higher scores indicate more emotional support		
Tilvis *et al.* 2000[75]	Finland	10	148	Inclusion: - Born in 1904, 1909 or 1914 - Home-dwelling	Range: 75-85	Unclear	Poor health	Cognitive decline, dichotomized (measured with MMSE (range 0-30). Dichotomized as cognitive decline (drop in MMSE >4 points) versus no cognitive decline. Measured at baseline and follow-up)	**Functional:** *Loneliness.* Dichotomous, yes versus no	OR: 2.12, $P = 0.004$	na[j]
Tilvis *et al.* 2004[76]	Finland	10	149	Inclusion: - Born in 1904, 1909 or 1914 - Living in Helsinki - In the census register in 1989	78.2, 75-85	74	Age	Cognitive decline, dichotomized (measured with MMSE (range 0-30). Dichotomized as cognitive decline (drop in MMSE >4 points) versus no cognitive decline. Measured at baseline,	**Functional:** *Loneliness.* Dichotomous, yes versus no	10-year follow-up: RR: 3.0 (95% CI: 1.4 to 6.8)	3.0 (1.4 - 6.8)

(continued)

Table 1. Continued

B) FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS										
	Study characteristics			Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
								and at 1, 5, and 10 year follow-up)			
Watfa *et al.* 2011[78]	France	Mean: 4.1 Range: 1-6.2	687	Inclusion: - 60+ years old - Apparently good state of health - Consulting for a health check-up at the preventive medical center in Nancy Exclusion: - Known dementia at baseline	65.6 (5.1), 60+	45	Age, sex, baseline cognition, nervousness, inability to decide, painful event, despair, feelings of being surrounded by strange (incomprehensible) things, sense of being elderly	Cognitive decline (measured with French MMSE (range 0-30). Annual change in MMSE: difference between second and first MMSE measurement / follow-up time). Measured at baseline and follow-up)	**Functional:** *Difficulty in social relations.* Dichotomous, yes versus no	B: 0.25 (SE: 0.10)	na[b]
Wilson *et al.* 2007[79]	USA	Mean: 3.3 Range: 1-4 2-5 annual assessments	791	Inclusion: - Agreement to annual in-home clinical evaluations and brain donation at death Exclusion: - Dementia at baseline	80.7 (7.1)	76	Age, sex, education, time (in years since baseline), time^2, loneliness, age*-time, Sex*time, education level*time	Annual rate of cognitive decline (measured with Logical Memory Story A, East Boston Story, Word List Memory, Word List Recall, Word List Recognition, Digit Span Forward and Backward, Digit Ordering). Number Comparison, Symbol Digit Modalities Test, Stroop Test, Judgment of Line Orientation, Standard Progressive Matrices (continuous; raw test scores were converted to z scores and then averaged). Measuredat baseline, and at 1, 2, 3, and 4 year follow-up)	**Functional:** *Loneliness.* Continuous, based on the modified de Jong-Gierveld scale. Range: 1-5. Higher scores indicate more loneliness	β*:- 0.01 (SE: 0.01)	1.02 (0.98-1.07)

(continued)

Table 1. Continued

C) COMBINATION OF STRUCTURAL AND FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS										
Study characteristics				Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
Andrew *et al.* 2010[47]	Canada	5	2391	Inclusion: - Being 65+ at inclusion - Community-dwelling - Oversampling of those aged 75+ at inclusion Exclusion: - Dementia at baseline - Being institutionalized ≥ 6 months - Left study area - Not fluent English or French	79.1 (6.4), 70+	61	Age, sex, baseline cognition, frailty	Incident cognitive impairment (measured with Modified MMSE (range 0-100). Incident cognitive decline: decline of ≥ 5 points. Measured at baseline and follow-up)	**Combination:** *Social vulnerability index*. Continuous. Range: 0-40. Higher scores indicate higher social vulnerability	OR: 1.03 (95% CI: 1.00 to 1.06)	1.03 (1.00-1.06)
Barnes *et al.* 2007[48]	USA	Maximum 15	6502	Inclusion: -65+ -Women -Living in one of the four metropolitan areas in the USA -Able to walk Exclusion: -Undergone bilateral hip replacement or had earlier hip fracture -Developed major cognitive decline at follow-up	71.7 (5.3), 65-99	100	Age, education, baseline cognition, study site	Incident minor cognitive impairment (measured with Modified MMSE (range 0-26). Cognitive decline was based on the slope between baseline and follow-up (or death) measurements (optimal cognitive function (slope ≥ 0 point/year) versus minor cognitive decline (slope < 0 but > lowest tertile). Measured at baseline, and at 6-, 8-, 10- and 15-year follow-up)	**Combination:** *Lubben Social Network Scale*. Dichotomous, lowest tertile versus highest two tertiles	OR: 1.20 (95% CI : 1.01 to 1.43)	1.20 (1.01-1.43)
Green *et al.* 2008[58]	USA	Mean: 10.9 Maximum: 12	874	Inclusion: - 18+ years old in 1981 - Living in East Baltimore	47.3 (12.0)	63	Age, sex, education, depression, lifetime alcohol misuse or dependence, cerebrovascular disease or risk, ADL disabilities, race, household income	Cognitive decline (measured with MMSE (continuous; range 0-30), at baseline and follow-up)	**Combination**: *Social network*. Continuous, based on 3 parameters combined (network size, frequency of contact and emotional support). Range: 0-47. Higher scores indicate better social network	β: 0.005 (95% CI: -0.023 to 0.033), P = 0.721	0.98 (0.89-1.09)
Haug 1989[59]	USA	9	502	Inclusion: - 65+ years old - Enlisted in Medicare in Cleveland, OH	81.7, 74-99	69	Age, education, baseline cognition	Cognitive decline, dichotomized (measured with SPMSQ (continuous; range 0-10) at baseline and follow-up)	**Combination**: *Index of Social Resources*. Continuous, based on 6 parameters combined (household composition,	β: -0.11, $P < 0.05$	1.49 (1.00-2.24)

(continued)

Table 1. Continued

C) COMBINATION OF STRUCTURAL AND FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS											
Study characteristics				Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women (%)				Original from paper	OR (95% CI) for in meta-analysis
									children in the area, number of phone contacts and social visits, frequent feelings of loneliness, having a confidant, perceived availability of care if needed). Higher scores indicate more extensive social resources		
Ho *et al.* 2001[36]	China	3	Men: 519 Women: 469	Inclusion: - 70+ years old - Registration with the Old Age Allowance (OAA) Schema, or being registered for Disability Allowance. Exclusion: - Cognitive impairment at baseline	Women: 78.1, 70 - 90+ Men: 77.0, 70-90+	Separate analyses for women and men	Stratified by sex	Incident cognitive impairment (measured with Clifton Assessment Procedure for the Elderly (range 0-12, cutoff: 7) , at baseline and follow-up)	**Combination**: *Social support*. 3 categories, based on various parameters combined (contact with friends/relative/neighbours, participation in community/ religious activities. (Questions adopted from the Lubben Social Network Scale.) Score < 9 versus ≥ 15, and score 9-14 versus ≥ 15. Higher scores indicate more social support.	Women, social support score < 9 versus ≥ 15: OR: 1.2 (95% CI: 0.6 to 2.2) Men, social support score < 9 versus ≥ 15: OR: 2.8 (95% CI: 1.1 to 6.7)	Women, social support score < versus > 9: 1.69 (1.02-2.80)Men, social support score < 9 versus > 9: 5.41 (2.68-10.95)
Monastero *et al.* 2007[87]	Sweden	Mean: 3.4 (SD: 0.5)	718	Inclusion: - 75 to 95 years old on October 1 1987 - Inhabitant of Kungsholmen district in Stockholm Exclusion: - Dementia at baseline - Dementia at first follow-up - CIND at baseline - MMSE score < 20 at baseline	80.4, 75-95	74	Age, sex, education, depression, ADL disability, fitness activities, time to first follow-up, chronic disease, psychoses, psychotropic drug use, social activities, social network, mental activities, productive activities	Incident CIND (measured with MMSE (range 0-30; cutoff: 1 SD below age- and education-specific mean of the test. Dementia cases were ascertained by specialists according to DSM-III-R criteria. Measured at baseline and follow-up)	**Combination**: *Graded summary score*. Dichotomous, limited/ poor social network versus moderate/extensive social network, based on various parameters (measures of marital status, living arrangements and frequency and satisfaction with contacts with children and close social ties)	OR: 0.8 (95% CI: 0.4 to 1.5)	0.8 (0.4-1.5)
Plehn *et al.* 2004[69]	USA	Mean: 3.6 Range: 3.2-4.3	96	Inclusion: - 55+ years old - community dwelling (living in senior centre, community centre, home for adults, retirement community in rural/central Virginia)	75.6 (7.9), 55+	78	None	Cognitive decline, dichotomized (measured with Mattis Dementia Rating Scale, Fuld Object Memory Evaluation, MMSE (cutoff: ≥ 1 SD drop at follow-up on at	**Combination**: *Social engagement*. Continuous, higher scores indicate poorer engagement	- Mean (SD) of participants who remained cognitively stable: 6.3 (1.8) (n = 84)	na[b]

(continued)

Table 1. Continued

C) COMBINATION OF STRUCTURAL AND FUNCTIONAL ASPECTS OF SOCIAL RELATIONSHIPS											
Study characteristics				Population characteristics[a]			Adjustment for covariates	Outcome	Social relationship assessment	Results	
Author	Country	Study duration (years)	*N* in the analyses	In- and ex-clusion criteria	Age mean (SD), range (years)	Women *n* (%)				Original from paper	OR (95% CI) for in meta-analysis
				- < 10 years of education - Lived most their lives (particular during school years) in a rural area Exclusion: - Dementia at baseline Self-reported presence of: - Chronic or severe psychiatric disorder - Extensive psychotropic drug use - Long-term substance misuse history - History of electroconvulsive therapy - History of neurological disease (e.g. CVA) - History of head injury with loss of consciousness				least three of the subtests. Measured at baseline and follow-up)		- Mean (SD) of participants who cognitively declined: 8.1 (3.3) ($n = 12$)	
Stoykova *et al*. 2011[73]	France	Mean: 9.2 (SD: 6.6) Maximum: 20	2052	Inclusion: - 65+ years old - Community dwelling - Being on the electoral roll in the south-west of France (Gironde and Dordogne) Exclusion: - Dementia at baseline - Dementia at any of the follow-up measures	74.6 (6.7), 65+	54	Age, sex, education, depression, functional abilities, presence of chronic diseases, marital status	Cognitive decline (measured with MMSE (continuous; range 0-30), at baseline, and at 1, 3, 5, 8, 10, 13, 15, 17, and 20 year follow-up)	**Combination**: *Social network index*. Continuous, based on 4 parameters (social network size, satisfaction with relationships, perception of being understood by other people, participation in social activities). Range: 0-4. Higher scores indicate worse social network	β: 0.01 (SE: 0.01)	1.04 (0.97-1.11)

SD, standard deviation; OR, odds ratio; CI, confidence interval; MMSE, Mini Mental State Examination; na, not applicable; BMI, body mass index; β*, partially standardized regression coefficient; SE, standard error; SPMSQ, Short Portable Mental Status Questionnaire; B, unstandardized regression coefficient; MCI, mild cognitive impairment; WAIS, Wechsler Adult Intelligence Scale; IADL, Instrumental Activities of Daily Living; ADL, Activities of Daily Living; β, standardized regression coefficient; CIND, cognitive impairment, no dementia; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders IV – text revision; CASI, Cognitive Abilities Screening Instrument; GMS, Geriatric Mental State; RR, relative risk; CVA, cerebrovascular accident.

[a]all general population;

[b]insufficient information to extract the effect size;

[c]$N = 611$ (exploratory sample) + $n = 581$ (confirmatory sample);

[d]same study as Bassuk *et al*. (1999);

[e]same study as Zunzunegui *et al*. (2003);

[f]same study as James *et al*. (2011b);

[g]same study as Yen *et al*. (2010);

[h]same study as Holtzman *et al*. (2004);

[i]same study as Seeman *et al*. (2001);

[j]same study as Tilvis *et al*. (2004).

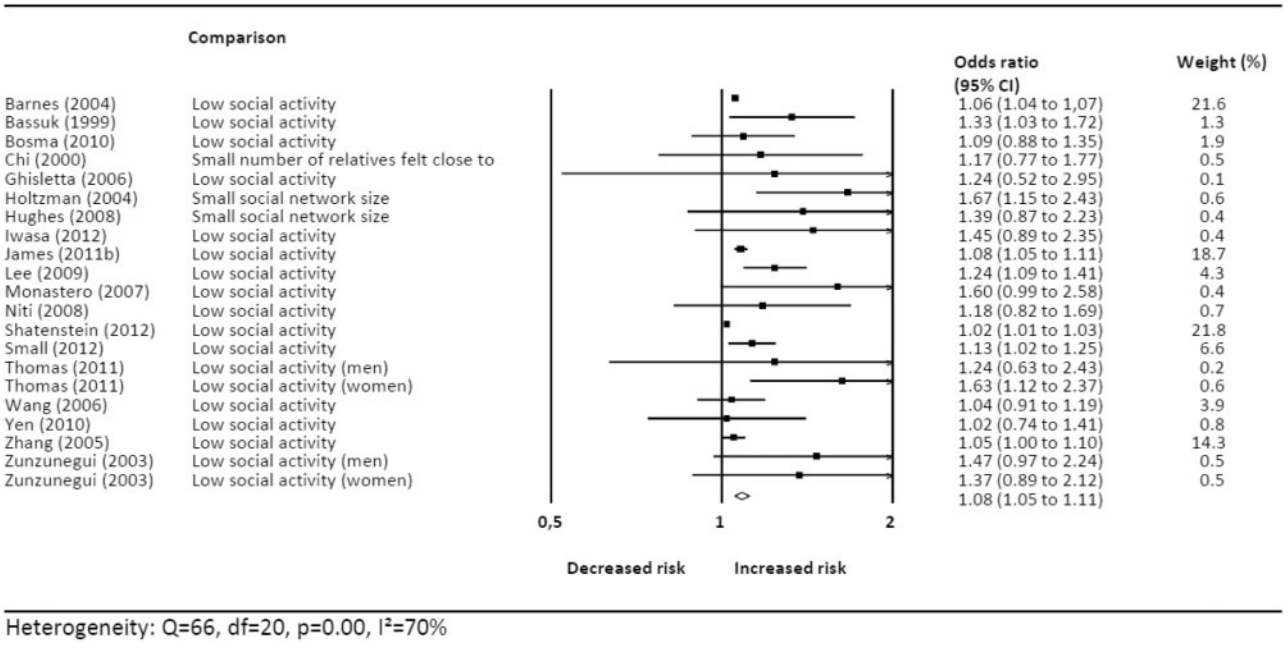

Figure 2. Forest plot of structural aspects of social relationships as predictor of cognitive decline.

rater agreement on the internal validity items was very good (overall agreement 92% (712/774); Cohen's kappa 0.85).

Association between social relationships and cognitive decline

Structural aspects of social relationships

In total, 31 articles[49–56,58,60–66,68,70–72,74,77,80–88] investigated the association between structural aspects of social relationships and cognitive decline in the general population. On average, participants were 71.6 years old at baseline (range: 47 to 107). The mean duration of follow-up of these studies was 5.5 years (range: 1 to 15). The average sample size of the cohorts was 1534 (range: 66 to 16638). Most studies were performed in North America (17/31), eight in Asia and six in Europe; 14 articles[50–52,56,58,60,61,64,65,70,77,80,82,84] based their conclusions on data from the same study populations (using the same data), of which we included only one article from each study in the meta-analysis.[50,61,65,80,82] Unfortunately, three articles[53,55,83] did not report sufficient data to calculate the OR and 95% CI and could not therefore be included in the meta-analysis. The results of 19 articles[49,50,54,61-63,65,66,68,71,72,74,80–82,85–88] were included in the meta-analysis, showing that poor structural social relationships are associated with cognitive decline [OR: 1.08 (95% CI: 1.05-1.11)] (see Figure 2).

As results were heterogeneous ($I^2 = 70\%$, $P = 0.00$ from Q-test), sources of heterogeneity were explored. The meta-regression showed that the following characteristics affected the magnitude of the association (see Table 2): (i) type of social relationship measurement (social activity versus social network size); (ii) the following methodological quality items: 2a (study attrition); 3a (measurement of the determinant); 4a (measurement of the outcome); and 6a (statistical over-fitting). With regard to the type of social relationship measurement, we found a stronger association between a small social network and cognitive decline[54,61,62] [OR: 1.42 (95% CI: 1.11-1.80)]; heterogeneity: $I^2 = 0\%$, $P = 0.46$ from Q-test] than between low social activity and cognitive decline[49,50,63,65,66,68,71,72,74,80–82,85–88] [OR: 1.08 (95% CI: 1.04-1.11)]; heterogeneity : $I^2 = 71\%$, $P = 0.00$ from Q-test] ($P = 0.03$ from meta-regression). With regard to the individual methodological quality items, the (pooled) estimate of studies with high risk or unclear risk of bias on the item 2a,(attrition bias)[54,61,62,66,68,86], item 4a (measurement of the outcome)[61] and item 6a (statistical over-fitting)[82,87] showed a stronger association between poor structural social relationships and cognitive decline than the pooled estimate of studies with low risk of bias on these quality items (overestimation) ($P = 0.00$, $P = 0.02$, $P = 0.02$, respectively, from meta-regression). For only one methodological quality item (3a; measurement of the determinant), we found opposite results. The pooled estimate of studies with high risk or unclear risk of bias regarding the measurement of the determinant (item 3a)[54,63,71,80,81,85] [(OR: 1.02 (95% CI: 1.01-1.03); heterogeneity : $I^2 = 0\%$, $P = 0.52$ from Q test], was smaller than the pooled estimate of studies with low risk of bias on this quality item[49,50,61,62,65,66,68,72,74,82,86–88] [OR: 1.12 (95% CI:

Table 2. Univariate random effects meta-regression (methods of moments) and subgroup analyses for structural social relationships aspects

Variable	Number of studies	OR (95% CI)	*P*-value for heterogeneity*	*P*-value from meta-regression†
Social relationship measurement				
Low social activity	18	1.08 (1.04-1.11)	0.00; $I^2 = 71\%$	
Small social network size	3	1.42 (1.11-1.80)	0.46; $I^2 = 0\%$	**0.03**
Outcome measurement				
Incident cognitive impairment	7	1.13 (1.02-1.25)	0.14; $I^2 = 38\%$	
Cognitive decline (continuous)	14	1.08 (1.04-1.12)	0.00; $I^2 = 76\%$	0.94
Global cognitive decline or a combination of domains	18	1.08 (1.05-1.11)	0.00; $I^2 = 71\%$	Reference
Perceptual speed	1	1.24 (0.52-2.95)	na	0.75
Semantic memory	1	1.13 (1.03-1.25)	na	0.44
Two measurements	13	1.27 (1.13-1.43)	0.03; $I^2 = 47\%$	Reference
More than two measurements	8	1.06 (1.03-1.10)	0.00; $I^2 = 82\%$	0.08
Timing of follow-up measurement				
Continuous	21	1.08 (1.05-1.11)	0.00; $I^2 = 70\%$	0.10
$\leq$ 3 years	8	1.09 (1.02-1.16)	0.01; $I^2 = 60\%$	Reference
4-7 years	9	1.07 (1.04-1.11)	0.16; $I^2 = 32\%$	0.71
$\geq$ 8 years	4	1.22 (1.03-1.43)	0.13; $I^2 = 47\%$	0.09
Health status at baseline				
All community-dwelling	8	1.19 (1.06-1.35)	0.06; $I^2 = 49\%$	Reference
Cognitively healthy	7	1.10 (1.03-1.18)	0.05; $I^2 = 52\%$	0.30
Cognitively and physically and/or mentally healthy	6	1.08 (1.01-1.17)	0.07; $I^2 = 52\%$	0.60
Age				
Continuous	21	1.08 (1.05-1.11)	0.00; $I^2 = 70\%$	0.11
$\leq$ 65	3	1.16 (0.94-1.44)	0.07; $I^2 = 63\%$	Reference
66-74	12	1.08 (1.04-1.12)	0.00; $I^2 = 76\%$	0.74
$\geq$ 75	6	1.07 (1.04-1.11)	0.36; $I^2 = 8\%$	0.71
Methodological quality items				
1a Low risk of bias	13	1.09 (1.04-1.14)	0.00; $I^2 = 77\%$	
1a Unclear or high risk of bias	8	1.08 (1.05-1.10)	0.80; $I^2 = 0\%$	0.90
1b Low risk of bias	9	1.19 (1.07-1.33)	0.04; $I^2 = 50\%$	
1b Unclear or high risk of bias	12	1.09 (1.04-1.14)	0.00; $I^2 = 70\%$	0.50
2a Low risk of bias	15	1.07 (1.04-1.10)	0.00; $I^2 = 72\%$	
2a Unclear or high risk of bias	6	1.27 (1.14-1.41)	0.76; $I^2 = 0\%$	**0.00**
2b Low risk of bias	2	1.12 (0.88-1.44)	0.20; $I^2 = 40\%$	
2b Unclear or high risk of bias	19	1.11 (1.06-1.16)	0.00; $I^2 = 67\%$	0.50
3a Low risk of bias	15	1.12 (1.07-1.18)	0.01; $I^2 = 56\%$	
3a Unclear or high risk of bias	6	1.02 (1.01-1.03)	0.52; $I^2 = 0\%$	**0.04**
3b Low risk of bias	5	1.06 (1.02-1.10)	0.19; $I^2 = 35\%$	
3b Unclear or high risk of bias	16	1.13 (1.07-1.19)	0.00; $I^2 = 69\%$	0.30
4a Low risk of bias	20	1.08 (1.05-1.11)	0.00; $I^2 = 66\%$	
4a Unclear or high risk of bias	1	1.67 (1.15-2.43)	na	**0.02**
4b Low risk of bias	1	1.08 (1.05-1.11)	na	
4b Unclear or high risk of bias	20	1.08 (1.05-1.12)	0.00; $I^2 = 67\%$	0.96
5a1 Low risk of bias	21	1.08 (1.05-1.11)	0.00; $I^2 = 70\%$	
5a1 Unclear or high risk of bias	0	na	na	na
5a2 Low risk of bias	15	1.08 (1.04-1.11)	0.00; $I^2 = 75\%$	
5a2 Unclear or high risk of bias	6	1.11 (1.02-1.21)	0.16; $I^2 = 38\%$	0.70
5a3 Low risk of bias	8	1.14 (1.03-1.25)	0.01; $I^2 = 66\%$	
5a3 Unclear or high risk of bias	13	1.08 (1.05-1.11)	0.09; $I^2 = 37\%$	0.83
5a4 Low risk of bias	20	1.08 (1.05-1.11)	0.00; $I^2 = 70\%$	

(continued)

Table 2. Continued

Variable	Number of studies	OR (95% CI)	*P*-value for heterogeneity*	*P*-value from meta-regression†
5a4 Unclear or high risk of bias	1	1.39 (0.87-2.23)	na	0.30
5b5 Low risk of bias	20	1.08 (1.05-1.11)	0.00; $I^2 = 70\%$	
5b5 Unclear or high risk of bias	1	1.13 (1.02-1.25)	na	0.44
5b6 Low risk of bias	12	1.07 (1.03-1.10)	0.00; $I^2 = 77\%$	
5b6 Unclear or high risk of bias	9	1.14 (1.06-1.23)	0.13; $I^2 = 36\%$	0.18
5b7 Low risk of bias	5	1.14 (1.00-1.30)	0.02; $I^2 = 65\%$	
5b7 Unclear or high risk of bias	16	1.09 (1.06-1.12)	0.05; $I^2 = 39\%$	0.27
5b8 Low risk of bias	18	1.08 (1.04-1.11)	0.00; $I^2 = 72\%$	
5b8 Unclear or high risk of bias	3	1.13 (1.04-1.23)	0.65; $I^2 = 0\%$	0.34
5c Low risk of bias	21	1.08 (1.05-1.11)	0.00; $I^2 = 70\%$	
5c Unclear or high risk of bias	0	na	na	na
6a Low risk of bias	18	1.08 (1.04-1.11)	0.00; $I^2 = 70\%$	
6a Unclear or high risk of bias	3	1.47 (1.14-1.90)	0.90; $I^2 = 0\%$	**0.02**

na, not applicable.
*Based on Q value. †Boldface is $P < 0.05$.

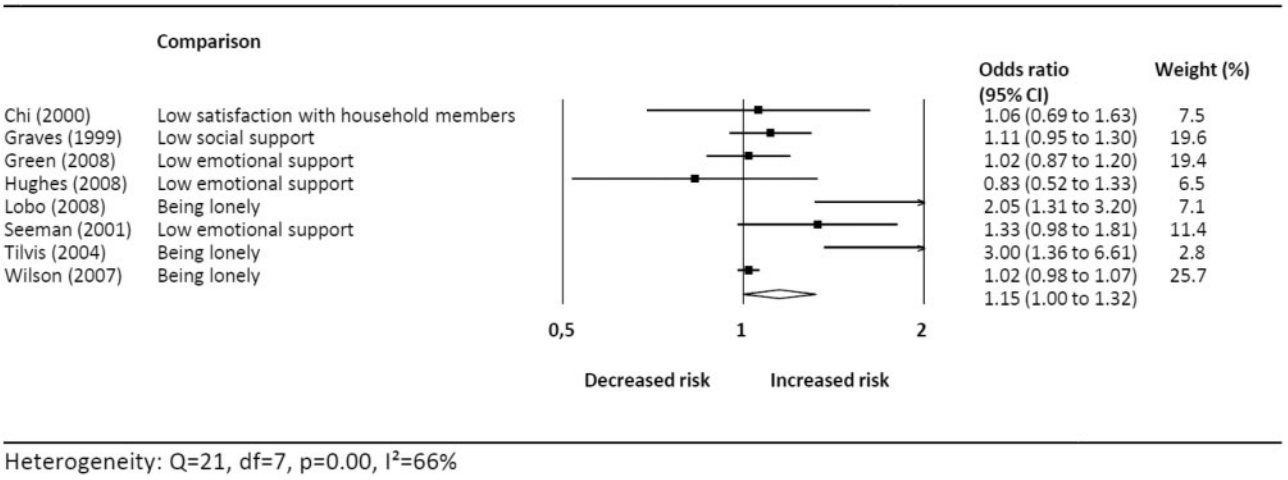

Figure 3. Forest plot of functional aspects of social relationships as predictor of cognitive decline.

1.07–1.18); heterogeneity: $I^2 = 56\%$, $P = 0.01$ from Q-test] ($P = 0.04$ from meta-regression).

Furthermore, one study[88] reported an HR (95% CI) which was interpreted as OR (95% CI) in our meta-analysis. Since the incidence of cognitive impairment was larger than 10% (i.e. 10.9%), a sensitivity analysis was performed by excluding this study. This did not change the magnitude of the association [OR: 1.08 (95% CI: 1.05-1.12)].

Functional aspects of social relationships

In total, 12 articles[50,54,57,58,62,67,70,75,76,78,79,84] investigated the association between functional aspects of social relationships and cognitive decline in the general population. On average, participants were 71.6 years old at baseline (range: 55 to 95). The mean duration of follow-up of these studies was 6.0 years (range: 1 to 12). The average sample size of the cohorts was 675 (range: 148 to 1654). Most studies were performed in North America (7/12), four in Europe and one in Asia. Five articles[50,70,75,76,84] based their conclusions on data from the same study populations (using the same data), of which we included only one article from each study in the meta-analysis.[70,76] Unfortunately, one article[78] did not report sufficient data to calculate the OR and 95% CI and could not therefore be included in the meta-analysis. The results of eight articles[54,57,58,62,67,70,76,79] were included in the meta-analysis, showing that poor functional social relationships were associated with cognitive decline [OR: 1.15 (95% CI: 1.00-1.32)]. However, results were heterogeneous ($Q = 21$; $P = 0.00$; $I^2 = 66\%$) (see Figure 3).

Overall, while exploring sources of heterogeneity by subgroup analyses, we found that many of the pre-specified characteristics affected the presence and magnitude of an association between poor functional social relationships

Table 3. Subgroup analyses for functional social relationships aspects

Variable	Number of studies	OR (95% CI)	*P*-value for heterogeneity*
Social relationship measurement			
Low social/emotional support	4	1.08 (0.96-1.22)	0.32; $I^2 = 15\%$
Being lonely	3	1.71 (0.88-3.32)	0.00; $I^2 = 88\%$
Low satisfaction with household members	1	1.06 (0.69-1.63)	na
Outcome measurement			
Incident cognitive impairment	2	1.45 (0.80-2.64)	0.01; $I^2 = 85\%$
Cognitive decline (continuous)	6	1.08 (0.94-1.25)	0.06; $I^2 = 53\%$
Global cognitive decline or a combination of domains	8	1.15 (1.00-1.32)	0.00; $I^2 = 66\%$
Two measurements	7	1.22 (1.00-1.49)	0.01; $I^2 = 65\%$
More than two measurements	1	1.02 (0.98-1.07)	na
Timing of follow-up measurement			
$\leq$ 3 years	3	1.30 (0.91-1.86)	0.04; $I^2 = 70\%$
4-7 years	3	1.06 (0.88-1.27)	0.17; $I^2 = 43\%$
$\geq$ 8 years	2	1.30 (0.91-1.86)	0.01; $I^2 = 85\%$
Health status at baseline			
All community-dwelling	3	1.27 (0.82-1.99)	0.03; $I^2 = 71\%$
Cognitively healthy	2	1.03 (0.98-1.07)	0.32; $I^2 = 0.7\%$
Cognitively and physically and/or mentally healthy	3	1.32 (0.84-2.08)	0.02; $I^2 = 73\%$
Age			
$\leq$ 65	1	1.02 (0.87-1.20)	na
66-74	4	1.25 (0.94-1.65)	0.03; $I^2 = 67\%$
$\geq$ 75	3	1.26 (0.82-1.93)	0.03; $I^2 = 72\%$
Methodological quality items			
1a Low risk of bias	5	1.28 (1.00-1.65)	0.01; $I^2 = 72\%$
1a Unclear or high risk of bias	3	1.06 (0.88-1.27)	0.17; $I^2 = 43\%$
1b Low risk of bias	5	1.40 (1.02-1.91)	0.00; $I^2 = 74\%$
1b Unclear or high risk of bias	3	1.02 (0.98-1.07)	0.41; $I^2 = 0\ \%$
2a Low risk of bias	5	1.30 (1.04-1.62)	0.00; $I^2 = 80\%$
2a Unclear or high risk of bias	3	1.01 (0.87-1.16)	0.70; $I^2 = 0\%$
2b Low risk of bias	1	1.11 (0.95-1.30)	na
2b Unclear or high risk of bias	7	1.18 (0.98-1.41)	0.00; $I^2 = 70\%$
3a Low risk of bias	5	1.04 (0.98-1.10)	0.35; $I^2 = 10\%$
3a Unclear or high risk of bias	3	1.76 (0.99-3.14)	0.03; $I^2 = 72\%$
3b Low risk of bias	4	1.52 (1.02-2.27)	0.00; $I^2 = 84\%$
3b Unclear or high risk of bias	4	1.05 (0.94-1.17)	0.67; $I^2 = 0\%$
4a Low risk of bias	8	1.15 (1.00-1.32)	0.00; $I^2 = 66\%$
4a Unclear or high risk of bias	0	na	na
4b Low risk of bias	2	1.39 (0.71-2.75)	0.00; $I^2 = 89\%$
4b Unclear or high risk of bias	6	1.13 (0.95-1.33)	0.08; $I^2 = 49\ \%$
5a1 Low risk of bias	8	1.15 (1.00-1.32)	0.00; $I^2 = 66\%$
5a1 Unclear or high risk of bias	0	na	na
5a2 Low risk of bias	6	1.23 (1.01-1.49)	0.00; $I^2 = 74\%$
5a2 Unclear or high risk of bias	2	1.05 (0.84-1.31)	0.25; $I^2 = 23\%$
5a3 Low risk of bias	2	1.40 (0.71-2.77)	0.00; $I^2 = 88\%$
5a3 Unclear or high risk of bias	6	1.11 (0.96-1.29)	0.04; $I^2 = 56\%$
5a4 Low risk of bias	7	1.17 (1.01-1.36)	0.00; $I^2 = 70\%$
5a4 Unclear or high risk of bias	1	0.83 (0.52-1.33)	na
5b5 Low risk of bias	8	1.15 (1.00-1.32)	0.00; $I^2 = 66\%$
5b5 Unclear or high risk of bias	0	na	na
5b6 Low risk of bias	3	1.04 (0.95-1.13)	0.25; $I^2 = 28\%$

(continued)

Table 3. Continued

Variable	Number of studies	OR (95% CI)	*P*-value for heterogeneity*
5b6 Unclear or high risk of bias	5	1.32 (0.94-1.86)	0.01; $I^2 = 72\%$
5b7 Low risk of bias	1	1.02 (0.87-1.20)	na
5b7 Unclear or high risk of bias	7	1.20 (1.00-1.44)	0.00; $I^2 = 71\%$
5b8 Low risk of bias	4	1.03 (0.98-1.07)	0.42; $I^2 = 0\ \%$
5b8 Unclear or high risk of bias	4	1.43 (0.91-2.23)	0.00; $I^2 = 79\%$
5c Low risk of bias	7	1.20 (1.00-1.44)	0.00; $I^2 = 71\%$
5c Unclear or high risk of bias	1	1.02 (0.87-1.20)	na
6a Low risk of bias	7	1.18 (0.98-1.41)	0.00; $I^2 = 70\%$
6a Unclear or high risk of bias	1	1.11 (0.95-1.30)	na

na, not applicable.
*Based on Q value.

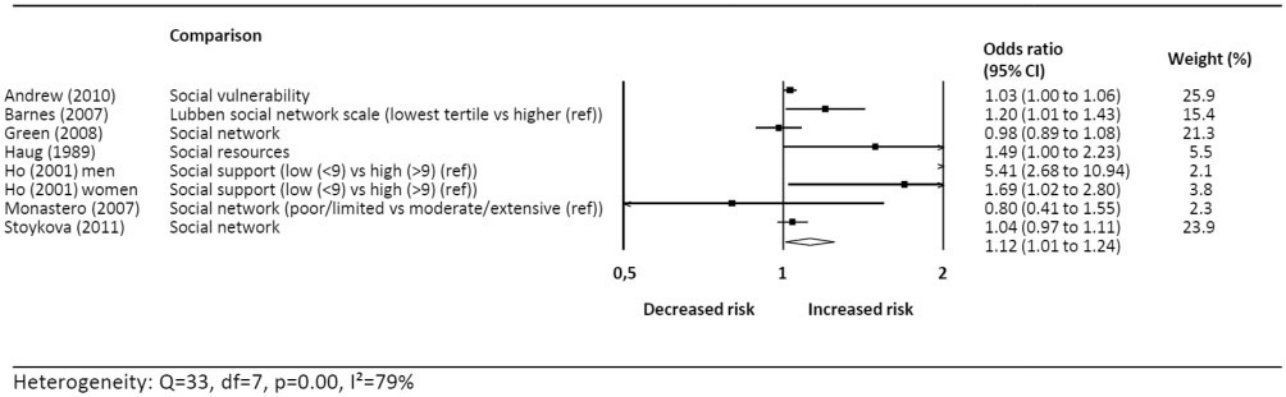

Figure 4. Forest plot of combination of structural and functional aspects of social relationships as predictor of cognitive decline.

and cognitive decline (see Table 3). Our subgroup analyses showed that heterogeneity could partially be explained by the following individual methodological quality items: 1b (study participation); 2a (study attrition); and 3b (measurement of the determinant). Remarkably, the pooled estimate of studies with low risk of bias on these quality items (i.e. item 1b,[54,58,67,70,76] item 2a[57,67,70,76,79] and item 3b[67,70,76,79]) showed a stronger association between poor functional social relationships and cognitive decline than the pooled estimate of studies with high risk or unclear risk of bias on these quality items.

Furthermore, one study[76] reported an RR (95% CI) which was interpreted as OR (95% CI) in our meta-analysis. However, the incidence of cognitive impairment was larger than 10% (i.e. 34% to 44%). Excluding this study from the meta-analysis (sensitivity analysis) showed that the association became smaller [OR: 1.10 (95% CI: 0.98-1.24)].

A combination of structural and functional aspects of social relationships

In total, eight articles[36,47,48,58,59,69,73,87] investigated the association between a combination of structural and functional aspects of social relationships and cognitive decline in the general population. On average, participants were 73.6 years old at baseline (range: 47 to 99). The mean duration of follow-up of these studies was 7.4 years (range: 3 to 20). The average sample size of the cohorts was 1569 (range: 96 to 6502). Most studies were performed in North America (5/8), two in Europe and one in Asia. Unfortunately, one article[69] did not report sufficient data to calculate the OR and 95% CI and could not therefore be included in the meta-analysis. The results of seven articles[36,47,48,58,59,73,87] were included in the meta-analyses, showing that poor structural and functional social relationship aspects combined are associated with cognitive decline [(OR: 1.12 (95% CI: 1.01-1.24)]. As the results were heterogeneous ($Q = 33$; $P = 0.00$; $I^2 = 79\%$) (see Figure 4), we conducted subgroup analyses to explore sources of this heterogeneity.

By performing subgroup analyses to explore sources of heterogeneity, we found that many of the pre-specified characteristics affected the presence and magnitude of an association between poor structural and functional social relationship aspects combined and cognitive decline (see Table 4). Furthermore, heterogeneity could (partially) be explained by the following individual methodological quality items: 1b (study participation); 3b (measurement of the determinant); and 5b6 and 5b8 (adjustment for

Table 4. Subgroup analyses for combination of structural and functional social relationships aspects

Variable	Number of studies	OR (95% CI)	*P*-value for heterogeneity*
Outcome measurement			
Incident cognitive impairment	5	1.37 (1.01-1.86)	0.00; $I^2 = 86\%$
Cognitive decline (continuous)	3	1.04 (0.94-1.15)	0.12; $I^2 = 53\%$
Global cognitive decline or a combination of domains	6	1.04 (0.99-1.09)	0.17; $I^2 = 35\%$
Information/orientation	2[1]	2.94 (0.94-9.19)	0.00; $I^2 = 86\%$
Two measurements	6	1.23 (1.01-1.50)	0.00; $I^2 = 83\%$
More than two measurements	2	1.09 (0.96-1.25)	0.13; $I^2 = 56\%$
Timing of follow-up measurement			
$\leq$ 3 years	2[1]	2.94 (0.94-9.19)	0.00; $I^2 = 86\%$
4-7 years	2	1.03 (1.00-1.06)	0.45; $I^2 = 0\%$
$\geq$ 8 years	4	1.07 (0.97-1.19)	0.07; $I^2 = 57\%$
Health status at baseline			
All community-dwelling	2	1.15 (0.77-1.72)	0.05; $I^2 = 74\%$
Cognitively healthy	5	1.38 (1.01-1.89)	0.00; $I^2 = 85\%$
Cognitively and physically and/or mentally healthy	1	1.03 (1.00-1.06)	na
Age			
$\leq$ 65	1	0.98 (0.89-1.08)	na
66-74	1	1.20 (1.01-1.43)	na
$\geq$ 75	6	1.18 (1.01-1.37)	0.00; $I^2 = 83\%$
Methodological quality items			
1a Low risk of bias	8	1.08 (1.00-1.16)	0.01; $I^2 = 62\%$
1a Unclear or high risk of bias	0	na	na
1b Low risk of bias	2	0.98 (0.88-1.08)	0.55; $I^2 = 0\%$
1b Unclear or high risk of bias	6	1.20 (1.05-1.37)	0.00; $I^2 = 84\%$
2a Low risk of bias	7	1.18 (1.03-1.34)	0.00; $I^2 = 81\%$
2a Unclear or high risk of bias	1	0.98 (0.98-1.08)	na
2b Low risk of bias	2[1]	2.94 (0.94-9.19)	0.00; $I^2 = 86\%$
2b Unclear or high risk of bias	6	1.04 (0.99-1.09)	0.17; $I^2 = 35\%$
3a Low risk of bias	8	1.12 (1.01-1.24)	0.00; $I^2 = 79\%$
3a Unclear or high risk of bias	0	na	na
3b Low risk of bias	3	1.08 (0.96-1.21)	0.23; $I^2 = 32\%$
3b Unclear or high risk of bias	5	1.27 (1.03-1.57)	0.00; $I^2 = 86\%$
4a Low risk of bias	8	1.12 (1.01-1.24)	0.00; $I^2 = 79\%$
4a Unclear or high risk of bias	0	na	na
4b Low risk of bias	0	na	na
4b Unclear or high risk of bias	8	1.12 (1.01-1.24)	0.00; $I^2 = 79\%$
5a1 Low risk of bias	8	1.12 (1.01-1.24)	0.00; $I^2 = 79\%$
5a1 Unclear or high risk of bias	0	na	na
5a2 Low risk of bias	6	1.20 (0.99-1.45)	0.00; $I^2 = 83\%$
5a2 Unclear or high risk of bias	2	1.17 (0.83-1.65)	0.07; $I^2 = 69\%$
5a3 Low risk of bias	4	1.52 (1.04-2.22)	0.00; $I^2 = 89\%$
5a3 Unclear or high risk of bias	4	1.04 (0.99-1.08)	0.28; $I^2 = 21\%$
5a4 Low risk of bias	6	1.20 (0.99-1.45)	0.00; $I^2 = 83\%$
5a4 Unclear or high risk of bias	2	1.17 (0.83-1.65)	0.07; $I^2 = 69\%$
5b5 Low risk of bias	6	1.04 (0.99-1.01)	0.17; $I^2 = 35\%$
5b5 Unclear or high risk of bias	2[1]	2.94 (0.94-9.20)	0.01; $I^2 = 86\%$
5b6 Low risk of bias	3	1.02 (0.96-1.08)	0.49; $I^2 = 0\%$
5b6 Unclear or high risk of bias	5	1.49 (1.11-2.00)	0.00; $I^2 = 87\%$
5b7 Low risk of bias	1	0.98 (0.89-1.08)	na
5b7 Unclear or high risk of bias	7	1.18 (1.03-1.34)	0.00; $I^2 = 81\%$
5b8 Low risk of bias	3	1.02 (0.96-1.08)	0.49; $I^2 = 0\ \%$

(continued)

Table 4. Continued

Variable	Number of studies	OR (95% CI)	*P*-value for heterogeneity*
5b8 Unclear or high risk of bias	5	1.49 (1.11-2.00)	0.00; $I^2 = 87\%$
5c Low risk of bias	7	1.18 (1.03-1.34)	0.00; $I^2 = 81\%$
5c Unclear or high risk of bias	1	0.98 (0.89-1.08)	na
6a Low risk of bias	7	1.13 (1.01-1.26)	0.00; $I^2 = 81\%$
6a Unclear or high risk of bias	1	0.80 (0.41-1.55)	na

na: not applicable.
*based on Q-value.
[1]Both results from Ho *et al.* (2001).

depression and physical functioning in the analyses). The pooled estimate of studies with high risk or unclear risk of bias on the individual methodological quality items (i.e. item 1b[36,47,48,59,73]; 3b[36,47,58,59] and items 5b6 and 5b8[58,73,87]) showed a stronger association between poor social relationships and cognitive decline than the pooled estimate of studies with low risk of bias on these quality items.

Publication bias

It is likely that the results of this review are slightly overestimated due to publication bias [Egger's test: structural aspects of social relationships ($P = 0.00$), functional aspects of social relationships ($P = 0.08$) and combination of structural and functional aspects of social relationships ($P = 0.09$] (see Figure 5).

Discussion

This systematic review and meta-analysis shows that poor social relationships are associated with cognitive decline. Nonetheless, substantial heterogeneity in results was found. A priori planned subgroup analyses showed that the distinction between structural, functional and a combination of structural and functional aspects of social relationships explained some of this heterogeneity. All associations between social relationships and cognitive decline were in the same direction (i.e. poor social relationships are associated with a higher risk of cognitive decline). However, as the operationalization of the social aspects varied (i.e. dimensional, categorical), no firm conclusions can be drawn about the strength of the association and thus the relative importance of the different social relationship aspects. The remaining heterogeneity was due to differences in the methodological quality of the included studies (i.e. study participation, study attrition, measurement of the determinant, measurement of the outcome, adjustment for potential confounders and statistical over-fitting).

Strengths and limitations

Our study has several strengths. First of all, a comprehensive systematic literature search was conducted on a broad range of social relationship factors, which enabled us to differentiate between structural and functional aspects of social relationships. Previous systematic reviews have investigated the relation between multiple lifestyle and leisure activities with cognitive decline.[17,30,31] However, a clear answer on whether and which aspects of social relationships are associated with cognitive decline was still missing. The results of this meta-analysis can contribute to give direction to further research on lifestyle factors and cognitive decline, taking into account the social relationship factors. A second strength is that by transforming all estimates to ORs, we were able to compare the results in a quantitative way and conduct meta-analyses, which has not been done in previous reviews.

This systematic review and meta-analysis also faced some methodological challenges. First, we found clinical, methodological and statistical heterogeneity between studies. Sources of heterogeneity were explored by conducting meta-regression and subgroup analyses, but this only explained some of the heterogeneity between studies. Second, the last search dates from July 2012 and since then new articles have been published on this topic.[89–92] Within our review, we did not find a relation between the year of publication and the effect size. Furthermore, the results of the recently published articles are comparable to the results of the studies included our review, showing for example associations for social isolation,[92] loneliness,[89,92] low social participation[91] and negative social interaction[90] with cognitive decline. Therefore, it seems unlikely that adding recently published articles to our study alters our conclusion. Third, we detected possible publication bias for all three aspects of social relationships. Therefore, the pooled risk estimates may be overestimated and should be interpreted with caution. However, in the case of the functional aspects and the combination of structural and functional aspects of social relationships, Egger's test may be underpowered to investigate publication bias, because less

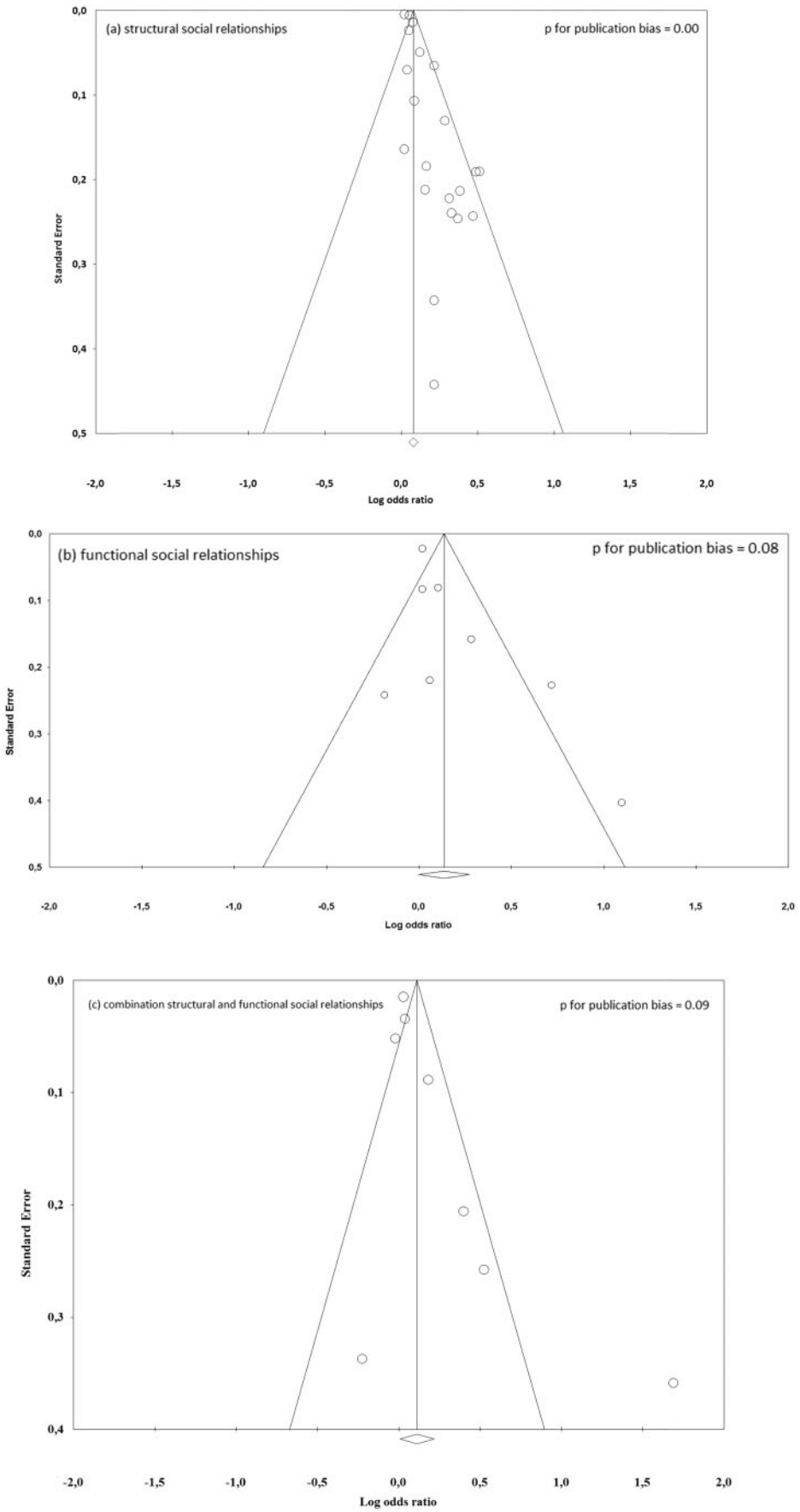

Figure 5. Funnel plots for (a) structural, (b) functional, and (c) combination of structural and functional aspects of social relationships.

than 10 studies were included in the funnel plots.[33] Observational studies are subject to publication bias, because studies of outcomes with positive results and a strong association are more likely to be published.[93] Prospective registration of observational studies could make the scientific community as a whole (e.g. researchers, editors, peer reviewers and publishers) methodologically more aware about the consequences of selective publication.[94] It is suggested that journals strongly encourage prospective registration of diagnostic and prospective studies and that editors and reviewers check the protocol on a registry when reviewing the manuscript.[94] In addition, this will also improve the methods of the study design and quality of reporting.[94] Finally, selective reporting may have biased our results. Some studies included in our systematic review were not primarily aimed to investigate the association between social relationships and cognitive decline, but these studies used an exploratory approach to investigate multiple risk factors for cognitive decline. As a consequence of such an approach, the determinant `social relationships' fell out of the final model if no association was found with cognitive decline. In these studies, the association between social relationships and cognitive decline was not reported at all, or no risk estimate was reported. Furthermore, it is likely that most existing cohort studies with cognitive decline as outcome also collected information on social relationships. However, we do not know why potential associations between social relationships and cognitive decline have not been published (yet).

Potential mechanisms for influence of social relationships on cognitive decline

Poor social relationships may influence cognitive decline through multiple pathways, which could explain why multiple aspects of social relationships were found to be associated with cognitive decline. One theory explaining why poor social relationships may be related to cognitive decline is the 'use it or lose it' theory.[95] This theory suggests that the brain can be seen as a muscle and that engagement in intellectual, social and physical activities stimulates the brain. Decrease in engagement in everyday activities may result in disuse of the brain which in turn may relate to decline of cognitive functions.[95] In addition, the stress-buffering hypothesis suggests that social relationships are beneficial in stressful situations. Stress has been associated with cognitive decline and the development of Alzheimer's disease due to structural changes in the hippocampus.[30,96] Social relationships may prevent or modulate responses to stressful events that are damaging to health.[23] The main-effect hypothesis suggests that social relationships have a protective effect on health through several pathways. General normative guidance about health behaviours obtained from the social network may influence health by motivating positive health behaviour, such as physical activity and non-smoking,[23] Additionally, integration in a social network may directly produce a positive psychological state, which may also increase motivation for positive health behaviour. Social resources may yield multiple sources of information that can help to make effective use of the available health institutions, which for example may help increase regular exercise or may moderate alcohol intake.[23] These positive health behaviours, such as physical activity and non-smoking, are shown to have a beneficial effect on cognitive functioning,[17,18] and a positive psychological state may modulate the neuroendocrine response to stress, which affects the brain.[23,30] The main-effect hypothesis appears to be related mainly to structural aspects of social relationships,[23] Having a small social network may, for example, limit the access to multiple healthy lifestyle sources.[23] On the other hand, the stress-buffering hypothesis appears to be more related to functional aspects of social relationships.[23] Subjective feelings of social support and integration may be beneficial for cognitive functioning particularly in stressful situations, through stress reduction and lowering levels of stress hormones like cortisol which have been shown to negatively affect cognitive functioning.[23,30,70]

Social relationships and other health-related lifestyle factors

In the current systematic review and meta-analysis, the variables age, depression, alcohol use and physical functioning were considered as potential confounders related to social relationships and cognitive decline. However, not all studies adjusted for these confounders (e.g. Boyle *et al.* 2010,[52] Cherry *et al.* 2010,[53] Ho *et al.* 2001,[36] James *et al.* 2011[64] and Plehn *et al.* 2004[69]). Therefore, residual confounding (i.e. the effect of an unmeasured factor) likely plays a role.[97,98] Furthermore, measurement errors in confounders may also lead to residual confounding.[98,99] Finally, in observational studies residual confounding by unknown characteristics can never be excluded.[99] Subgroup analyses showed that the association between social relationships (combined) and cognitive decline was not present or of smaller magnitude among studies that adjusted for potential confounders (i.e. depression, alcohol use, physical functioning) compared with studies that did not adjust for these potential confounders. This indicates that results of studies that were not adjusted for depression, alcohol and physical functioning overestimated the effect of poor social relationships (combination of structural and functional) on cognitive decline, and that part of

the association is explained by depression, alcohol use and physical functioning. The combined aspects of social relationships are the most comprehensive measurements of social relationships, including both structural and functional aspects of social relationships. Particularly subjective feelings regarding social relationships, such as feelings of loneliness, may be affected by the presence of depressive symptoms.[100] Furthermore, higher levels of physical functioning may have a beneficial effect on the social network and vice versa.[101] There is still discrepancy in the role of alcohol consumption in the relation between social relationships and cognitive decline. The complexity of alcohol consumption is that it changes over the life course; it initially increases in volume during adolescence and is followed by a more stable period during mid life before it declines in volume at older age.[102] Furthermore, the relation between social relationship factors (i.e. social occasions, loneliness) and the reasons for changing alcohol consumption (increase versus reduction) are contradictory and are age- and gender-dependent.[103] Moreover, it is known that very heavy drinkers are often under-represented in population-based studies[104] and that being an alcohol abstainer might also be an indicator of poor health.[105]

In addition to the potential role of residual confounding, social relationships are likely intertwined with other health-related lifestyle factors (i.e. a socially, mentally and physically active lifestyle) that may have a synergistic effect on cognitive decline.[30,106] Therefore, researchers should be aware of the connectivity between various lifestyle factors and should take this into account in future research. For instance, the findings of the recent Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER trail) support the effectiveness of a multi-domain prevention approach.[107] In this study, a 2-year multi-domain intervention (i.e. diet, exercise, cognitive training, social stimulation and vascular risk monitoring) was effective on various lifestyle-related risk factors (i.e. BMI, dietary habits, physical activity) and on preservation of cognitive function among older persons (aged 60-77 years) with an increased risk for dementia and cognitive decline, compared with general health advice.[107]

Cognitive decline measurements

There were large differences between the included studies in how they measured cognitive decline, which could explain the large (methodological) heterogeneity between included studies. The Mini Mental State Examination (MMSE) was used in many studies to measure cognitive functioning. Subsequently, cognitive decline was calculated and presented as a continuous measure (change score) or as dichotomous measure, in which a cut-off point was used. Although the MMSE is a widely used instrument to measure cognitive functioning, it should be kept in mind that it is a screening instrument to identify individuals with cognitive impairments and it is characterized by its strong ceiling effect.[108] The earliest stages of cognitive decline are difficult to detect with this tool, particularly among individuals with higher education levels.[108] Other studies included in our systematic review used multiple cognitive tests to compute a composite measure of multiple domains of cognitive functioning, or a diagnosis of Mild Cognitive Impairment (MCI) was made. These differences between studies make it difficult to compare the study results.

Reverse causality

While studying the relation between social relationships and cognitive decline, the possibility of reverse causality should be taken into account. Social networks often change and decrease in later life.[109] Previous research showed that a decline in physical and cognitive functioning is associated with loss of relationships.[110] Therefore, reverse causality (i.e. cognitive decline may not be the consequence but rather the cause of poor social relationships) cannot be excluded.[31,95,97,106] In the current systematic review, we attempted to partially address the risk of reverse causality in two ways. First, reverse causality is more likely when unhealthy participants are included in the study population. Multiple studies reduced the risk of reverse causality by excluding participants with cognitive impairments or dementia at baseline. If reverse causality is present, one would expect larger associations for studies including less healthy participants. No substantial differences were found in results of studies including different study populations (i.e. all community-dwelling versus cognitively healthy, versus cognitively and physically and/or mentally healthy at baseline), which reduces the risk of reverse causality. For the combination of structural and functional aspects of social relationships, we even found a stronger association between poor social relationships and cognitive decline for studies that only included cognitively healthy participants at baseline, compared with studies that did not apply these inclusion criteria (i.e. all community-dwelling). Second, a longer interval between the baseline measurement of social factors and cognitive decline would ensure one could be more confident about the temporality and causality of the relation. For the functional and combined aspects of social relationships, we found no substantial differences in results between studies with longer versus shorter follow-up time. For the structural aspects of social relationships, we even found a stronger association for studies with a longer follow-up period ($\geq$ 8

years), which also reduces the possibility of reverse causality. Nonetheless, despite these findings, it is very difficult to exclude the possibility of reverse causality. Therefore, reverse causality may still play a role in the relation between social relationships and cognitive decline.[97]

Potential causality of the association between social relationships and cognitive decline

Randomized controlled trials (RCTs) would be best suited to investigate a causal relation between poor social relationships and cognitive decline. Multiple RCTs among older adults have shown that it is possible to reduce loneliness and increase social support. Intervention programmes were also shown to help increase development of new friendships.[111] There are only a few RCTs that recently investigated interventions focusing on improving social relationships and aiming to improve or maintain cognitive functioning.[112] One RCT assigned participants to multiple intervention groups, including a social intervention on improving social interaction between people. Results showed that participants in this intervention group showed improvement on multiple, but not all, domains of cognitive functioning.[113] The functional aspects of social relationships as reported in our systematic review (i.e. social support, loneliness, low satisfaction with household members) relate to the quality of social relationships,[24] albeit this relationship might differ between the different functional aspects. Nonetheless, based on the results found in our systematic review and emphasized by others, we would recommend that interventions to improve social relationships should not merely aim to increase the number or frequency of social contacts, but also aim to improve the quality of the relationships.[89,112] Such studies, however, will be very complex. First, the duration of the intervention and when these should be offered during the lifespan is unknown.[112] Second, effectiveness probably also depends on psychosocial characteristics (e.g. personality profile), psychiatric disorders (e.g. depression) and social factors (e.g. financial restraints), which argues for the need of complex interventions.

Conclusions and future research directions

This present systematic review provides evidence that multiple aspects (i.e. structural, functional and a combination) of poor social relationships are associated with cognitive decline. However, studies differ from each other on multiple aspects and more standardized measures for social relationships and cognitive decline are needed in order to compare results between studies. Future research should take into account the interplay among multiple lifestyle factors,[30] in which social relationships have an important contribution. Therefore, we recommend that more attention is paid to the social relationship aspects in future observational studies and lifestyle interventions.

Supplementary Data

Supplementary data are available at *IJE* online.

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