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# Associations between social connections and cognition: a global collaborative individual participant data meta-analysis



Suraj Samtani, Gowsaly Mahalingam, Ben Chun Pan Lam, Darren M Lipnicki, Maria Fernanda Lima-Costa, Sergio Luís Blay, Erico Castro-Costa, Xiao Shifu, Maëlen Guerchet, Pierre-Marie Preux, Antoine Gbessemehlan, Ingmar Skoog, Jenna Najar, Therese Rydberg Sterner, Nikolaos Scarmeas, Ki-Woong Kim, Steffi Riedel-Heller, Susanne Röhr, Alexander Pabst, Suzana Shahar, Katya Numbers, Mary Ganguli, Erin Jacobsen, Tiffany F Hughes, Michael Crowe, Tze Pin Ng, Jane Maddock, Anna Marseglia, René Mélis, Dorota Szcześniak, Henrik Wiegmann, Myrra Vernooij-Dassen, Yun-Hee Jeon, Perminder S Sachdev, Henry Brodaty, on behalf of the SHARED consortium for the Cohort Studies of Memory in an International Consortium (COSMIC)\*



## Summary

**Background** Poor social connections (eg, small networks, infrequent interactions, and loneliness) are modifiable risk factors for cognitive decline. Existing meta-analyses are limited by reporting aggregate responses, a focus on global cognition, and combining social measures into single constructs. We aimed to investigate the association between social connection markers and the rate of annual change in cognition (ie, global and domain-specific), as well as sex differences, using an individual participant data meta-analysis.

**Methods** We harmonised data from 13 longitudinal cohort studies of ageing in North America, South America, Europe, Africa, Asia, and Australia. Studies were eligible for inclusion if they had baseline data for social connection markers and at least two waves of cognitive scores. Follow-up periods ranged from 0 years to 15 years across cohorts. We included participants with cognitive data for at least two waves and social connection data for at least one wave. We then identified and excluded people with dementia at baseline. Primary outcomes were annual rates of change in global cognition and cognitive domain scores over time until final follow-up within each cohort study analysed by use of an individual participant data meta-analysis. Linear mixed models within cohorts used baseline social connection markers as predictors of the primary outcomes. Effects were pooled in two stages using random-effects meta-analyses. We assessed the primary outcomes in the main (partially adjusted) and fully adjusted models. Partially adjusted models controlled for age, sex, and education; fully adjusted models additionally controlled for diabetes, hypertension, smoking, cardiovascular risk, and depression.

**Findings** Of the 40 006 participants in the 13 cohort studies, we excluded 1392 people with dementia at baseline. 38 614 individual participants were included in our analyses. For the main models, being in a relationship or married predicted slower global cognitive decline ( $b=0.010$ , 95% CI 0.000–0.019) than did being single or never married; living with others predicted slower global cognitive ( $b=0.007$ , 0.002–0.012), memory ( $b=0.017$ , 0.006–0.028), and language ( $b=0.008$ , 0.000–0.015) decline than did living alone; and weekly interactions with family and friends ( $b=0.016$ , 0.006–0.026) and weekly community group engagement ( $b=0.030$ , 0.007–0.052) predicted slower memory decline than did no interactions and no engagement. Never feeling lonely predicted slower global cognitive ( $b=0.047$ , 95% CI 0.018–0.075) and executive function ( $b=0.047$ , 0.017–0.077) decline than did often feeling lonely. Degree of social support, having a confidante, and relationship satisfaction did not predict cognitive decline across global cognition or cognitive domains. Heterogeneity was low ( $I^2=0.00–15.11\%$ ) for all but two of the significant findings (association between slower memory decline and living with others [ $I^2=58.33\%$ ] and community group engagement,  $I^2=37.54–72.19\%$ ), suggesting robust results across studies.

**Interpretation** Good social connections (ie, living with others, weekly community group engagement, interacting weekly with family and friends, and never feeling lonely) are associated with slower cognitive decline.

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## Introduction

The 2020 *Lancet* Commission on dementia prevention estimated that tackling social isolation could prevent

4% of dementia cases worldwide.<sup>1</sup> Social isolation is one aspect under the umbrella term social health.<sup>2</sup> Social connections, a key concept for social health, have

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## Research in context

### Evidence before this study

To identify gaps in the literature, we searched Web of Science and PsycINFO for meta-analyses published in English between Jan 1, 2012, and May 5, 2022, with the keywords "(dementia OR alzheimer\* OR cognitive dysfunction OR cognitive decline)" AND "(social OR connection\* OR relationship\* OR friend\* OR family OR network OR activit\* OR interaction\* OR health OR behav\* OR support OR participat\* OR isolat\*)". Social isolation is a modifiable risk factor for dementia, accounting for about 4% of preventable cases worldwide. Recent meta-analyses have examined several facets of social health. One of these studies reported that poor social health structure and function predicted greater cognitive decline. Another study examined individual social connection markers separately and found that low social participation, infrequent social contact, and loneliness were associated with increased risk of dementia. However, these meta-analyses used aggregated (not individual-level) data from studies with different covariates. Furthermore, most studies focused on global cognition, ignoring potential associations between social connections and specific cognitive domains. Sex differences in the link between social connections and domain-specific cognitive changes are also underexplored.

components pertaining to structure (eg, social networks and living situation), function (eg, social support), and quality (eg, loneliness and relationship quality).<sup>3</sup> Socially stimulating environments promote neuroprotective mechanisms,<sup>4</sup> and social connections are theorised to contribute to cognitive reserve,<sup>5</sup> whereby the brain actively copes with neuropathology by using alternative pre-existing or compensatory cognitive processes.<sup>6</sup> Bridging (ie, loose social ties providing cognitive stimulation) and bonding (ie, close social ties buffering stress and influencing function of the neuroendocrine system and the hypothalamic–pituitary–adrenal axis) pathways have been proposed to lead from social connections to cognitive health.<sup>4</sup>

Meta-analyses show associations between poor social connections and increased risk of cognitive decline. A meta-analysis of 43 studies reported that poorer social connection indicators pertaining to both structure and function predicted greater cognitive decline.<sup>7</sup> However, this meta-analysis combined various social connection markers and so could not reach definitive conclusions about specific markers. Another meta-analysis of 39 studies reported that social activity and social support were associated with decline in global cognition and specific cognitive domains.<sup>8</sup> Frequent social activity was associated with improved memory, executive function, visuospatial ability, and processing speed, whereas frequent social support was associated only with improved memory.<sup>8</sup> Existing meta-analyses are limited by the use of aggregated data from studies that adjust

Finally, existing meta-analyses have primarily included data from North America and Europe.

### Added value of this study

To our knowledge, this study is the largest individual participant data meta-analysis of the association between social connections and cognition. We showed that good social connections slow cognitive decline not only in global cognition, as previous studies have shown, but also specifically for memory and language. Additionally, we showed that being in a relationship or married was associated with slower memory decline than being single or never married, but only for women. Results from this study are consistent with previous research from Europe and North America, but we included studies from South America, Africa, Asia, and Australia, including low-income and middle-income countries.

### Implications of all the available evidence

Good social health structure and quality appear to slow the annual rate of cognitive decline. There should be greater emphasis on preserving or enhancing older adults' social relationships. We showed effects for specific cognitive domains, and future research could further explore the bidirectional pathways between cognitive domains and social connections.

differently for potential confounders (eg, one study did not adjust for confounders<sup>9</sup> and another study adjusted for only demographic variables and baseline cognition<sup>10</sup>). Furthermore, existing evidence about social connection markers and cognitive decline is mainly from North America and Europe, and these meta-analyses have not included loneliness, which is associated with increased cognitive decline in some cohort studies.<sup>11</sup>

Sex differences are important to investigate because women have faster cognitive decline than do men in global cognition and executive function.<sup>12</sup> One study reported that increased memory decline was associated with baseline social isolation (ie, a combination of living situation, frequency of social contact, and membership of community or religious groups at baseline) for men and accumulated social isolation (ie, social isolation across multiple waves of the study) for women.<sup>13</sup> Interaction with community groups has been associated with slower cognitive decline for men than for women.<sup>14</sup> Scientific literature on sex differences in the associations between social connection function or quality and cognitive decline, however, is sparse. For instance, social support was reportedly protective against memory decline for only men in one study,<sup>15</sup> whereas high baseline loneliness was associated with cognitive decline for only women in another cohort study.<sup>16</sup>

We aimed to investigate the association between various social connection markers and cognition (ie, global and domain-specific), as well as sex differences, using an individual participant data meta-analysis, which

has fewer limitations than does a traditional meta-analysis. First, we hypothesised that improved social connections (eg, in terms of social structure, function, and quality) are associated with a decreased rate of global cognitive decline. Second, we hypothesised that markers of improved social connection structure are associated with slow decline across all cognitive domains, whereas markers of improved social connection function and connection quality are associated specifically with slow memory decline.<sup>8</sup> Finally, we hypothesised that sex differences exist in the association between social connection markers and cognitive function. Specifically, improved baseline social connection structures (eg, being in a relationship and high interaction frequency) are associated with a slow rate of cognitive decline only for men, given previous research.<sup>13,17,18</sup>

## Methods

### Contributing studies and participants

We collected and harmonised data from 13 longitudinal cohort studies of ageing from around the world: Bambuí Cohort Study of Ageing (Bambuí, Brazil);<sup>19</sup> China Longitudinal Aging Study (CLAS, China);<sup>20</sup> English Longitudinal Study of Ageing (ELSA, England, UK);<sup>21</sup> Epidemiology of Dementia in Central Africa (EPIDEMCA, Central African Republic and Republic of the Congo);<sup>22</sup> Gothenburg H70 Birth Cohort Studies (the H70 study, Sweden);<sup>23</sup> Hellenic Longitudinal Investigation of Aging and Diet (HELIAD, Greece);<sup>24</sup> Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD, South Korea);<sup>25</sup> Leipzig Longitudinal Study of the Aged (LEILA75+, Germany);<sup>26</sup> Neuroprotective Model for Healthy Longevity among Malaysian Older Adults Towards Using Ageing (LRGS TUA, Malaysia);<sup>27</sup> Sydney Memory and Ageing Study (MAS, Australia);<sup>28</sup> Monongahela-Youghogheny Healthy Aging Team (MYHAT, USA);<sup>29</sup> Puerto Rican Elderly Health Conditions Study (PREHCO, Puerto Rico);<sup>30</sup> and Singapore Longitudinal Study of Ageing (SLAS, Singapore).<sup>31</sup> We identified studies for inclusion from the Cohort Studies of Memory in an International Consortium (COSMIC) for the Social Health and Reserve in the Dementia Patient Journey (SHARED) consortium. ELSA was identified through a literature search of the longitudinal studies with multiple social connection variables and was not part of COSMIC. Studies were eligible if they had baseline data for social connection markers and at least two waves of cognitive scores (sample characteristics of cohorts are provided in the appendix p 4). We did not apply any date restrictions. Within each study, we included participants who had social data for at least one wave and cognitive data for at least two waves. We excluded participants with dementia at baseline. We conducted an individual participant data meta-analysis to examine the associations between baseline social connections (ie, relationship status, living situation, frequency of interactions with family and friends, engagement in community groups, social support, having

a confidante, relationship satisfaction, and loneliness) and change in cognition over time (ie, global cognition, memory, language, and executive function). We used the STROBE reporting checklist to describe our study (appendix pp 1–2).

The project was approved by the University of New South Wales Sydney Human Research Ethics Committee (HC200268). The contributing cohorts had previous ethics approval (appendix p 3). Written informed consent was exclusively or predominantly obtained from participants in all studies, including consent to share data with other scientific research (appendix p 3). For EPIDEMCA, consent was obtained from family when the participant was unable to express their consent. For both EPIDEMCA and LRGS TUA, verbal consent and thumbprint mark was obtained from people who were illiterate. Further participant consent for this study was not deemed necessary as only fully de-identified data were shared with the analysis team.

### Procedures

We completed a COSMIC studies data request to collect data from twelve cohorts, and applied for access to ELSA data separately. We requested data for participants with social data for at least one wave and cognitive data for at least two waves. We collected data for cognitive scores and diagnoses, physical health and lifestyle risk factors for cognitive decline or dementia, and any social variables. The data were shared and stored in a secure OneDrive folder with multifactor authentication. The data were queried and confirmed by SSa and GM via descriptive statistics and visual analyses and cross-checked with original studies where discrepancies, errors, or outliers were noticed.

Global cognition, memory, language, and executive function measures, including descriptive statistics and proportion of missing data, are shown in the appendix (pp 5–6). Total scores for cognitive screening tests (ie, the Mini-Mental State Examination in most cohorts) were used to assess global cognition, rather than creating a composite of domain scores. The standardisation process for global cognition and cognitive domain scores is described in the appendix (p 8).

Covariates that were included in the models were harmonised in line with previous research by COSMIC.<sup>32</sup> The measures and harmonisation protocols used for the covariates are described in the appendix (pp 9–13). We controlled for age, sex, and education in the main (partially adjusted) models using data from all 13 cohorts. In fully adjusted models, we also controlled for previous history of diabetes, hypertension, smoking, cardiovascular disease risk (ie, previous history of angina, myocardial infarction, and any other heart disease), and depression. Fully adjusted models included ten cohorts with data available for the aforementioned covariates (ie, Bambuí,<sup>19</sup> CLAS,<sup>20</sup> ELSA,<sup>21</sup> the H70 study,<sup>23</sup> HELIAD,<sup>24</sup> KLOSCAD,<sup>25</sup> LEILA75+,<sup>26</sup> LRGS TUA,<sup>27</sup> MAS,<sup>28</sup> and MYHAT<sup>29</sup>).

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See Online for appendix

We harmonised social connection markers (ie, relationship status, living situation, engagement in community groups, interactions with family and friends, having a confidante, relationship satisfaction, and loneliness) by consensus among multiple authors (SSa, GM, DML, Y-HJ, MV-D, and HB) using as many potential questionnaire responses as possible. The measures and harmonisation protocols that were used for the social connection markers are described in the appendix (pp 14–21). Data for relationship status and living situation were derived mostly from demographic questions, and data for social interactions with family and friends, having a confidante, and relationship satisfaction were derived from single questions. Data for engagement with community groups were obtained from single questions that represented different community groups across studies (eg, whether participants played cards, games, bingo, or mahjong in the SLAS study<sup>31</sup> and whether participants attended meetings of retirement clubs or other clubs in the H70 study<sup>23</sup>).

Loneliness frequency data were available in only four studies,<sup>21,23,26,27</sup> of which only LRGS TUA<sup>27</sup> used a validated loneliness scale (UCLA 3-item Loneliness Scale).<sup>33</sup> To allow comparison across response options for loneliness, we used similar items from ELSA<sup>21</sup> (ie, how often the respondent feels lonely: “hardly ever or never”, “some of the time”, “often”), the H70 study<sup>23</sup> (“Feeling lonely”: “never”, “seldom/sometimes”, “often”), LEILA75+<sup>26</sup> (“I felt lonely”: “rarely or none of the time, less than 1 day”, “some or a little, 1–2 days”, “occasionally or a moderate amount, 3–4 days”, “most or all the time, 5–7 days”), and LRGS TUA<sup>27</sup> (“How often do you feel that you lack companionship?”: “hardly ever”, “some of the time”, “often”).

### Outcomes

The primary outcomes were the annual rates of change in global cognition and cognitive domain scores over time until final follow-up within each cohort study. The secondary outcomes were the sex differences in the association between social connection structure and the annual rates of change in global cognition and cognitive domain scores. We also conducted exploratory analyses on the sex differences in the association between social connection function or quality and cognitive decline.

### Statistical analysis

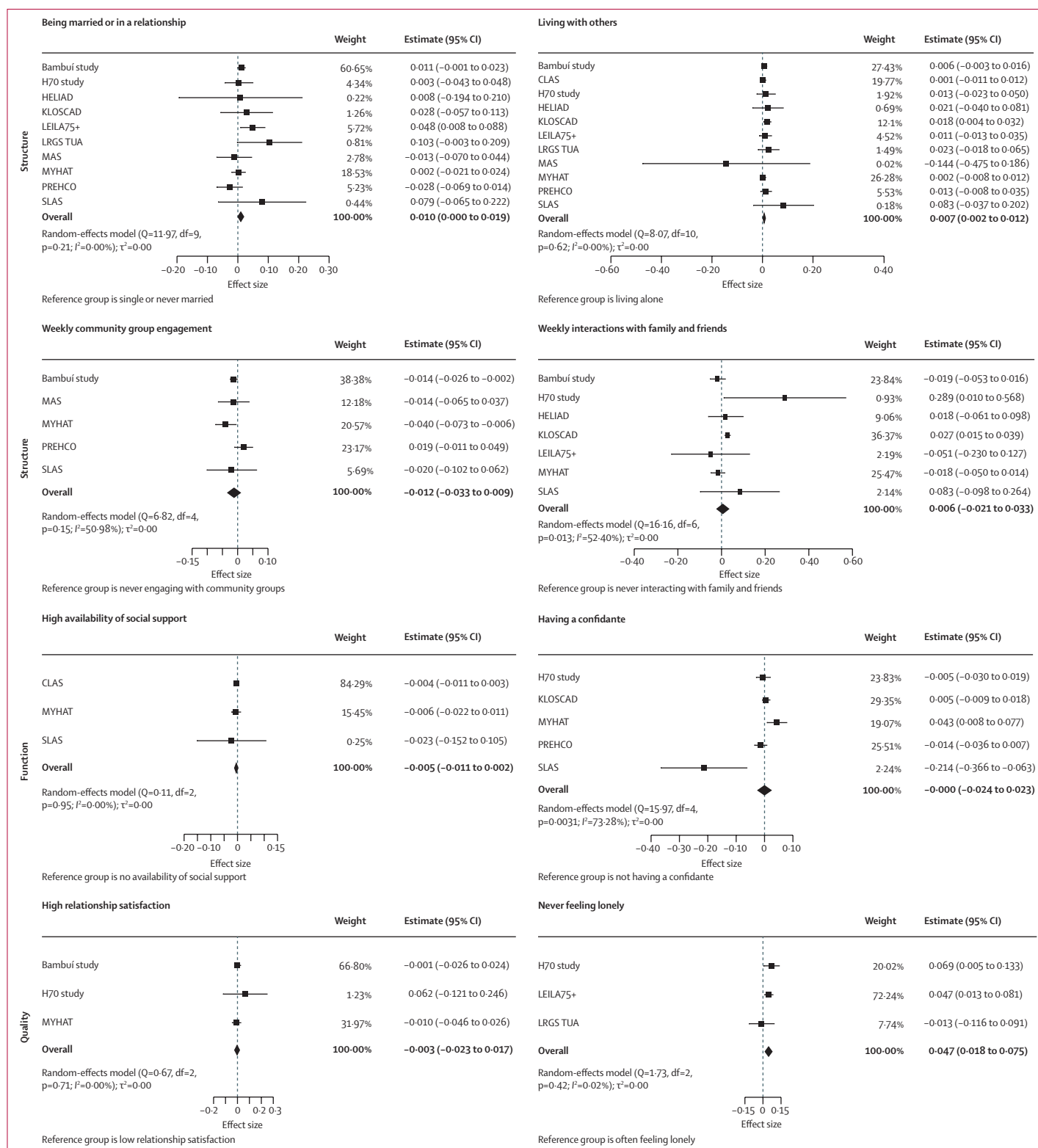
We used a two-stage individual participant data meta-analysis to pool effects across studies,<sup>34</sup> which enables controlling for the same covariates across studies rather than relying on aggregate data that is adjusted for different sets of covariates. Furthermore, variables can be defined consistently across studies, thereby reducing methodological heterogeneity. The first stage used linear mixed modelling to estimate the association between social connections and cognitive outcomes within each

study. We specified random intercept for participant and fixed effect for time in study (coded as years since baseline). First, we examined the overall linear effect of time in study (unstandardised regression coefficient [ $b$ ]=−0.015, 95% CI −0.048 to 0.018) on cognitive function (ie, global cognition and the cognitive domains) and the quadratic effect of time in study ( $b$ =−0.013, 95% CI −0.032 to 0.005) on cognitive function. As the quadratic time-in-study effect was not significant, we used a linear effect in all analyses involving social connection markers. Model assumptions for linear mixed regression were checked and satisfied by GM. We ran each social connection marker–cognitive outcome model separately because of differences in the availability of social connection markers and cognitive variables across cohort studies. In these models, a significant interaction between a social connection marker at baseline and time in study indicates that the social connection marker was associated with annual rate of cognitive decline.

The second stage pooled the effects across studies by use of random-effects meta-analysis with a restricted maximum likelihood estimator, which is a relatively unbiased and efficient estimator of between-study variance.<sup>35</sup> We examined heterogeneity using the  $I^2$  and  $\tau^2$  statistics<sup>36</sup> and bias using Egger’s test (appendix pp 26–27) and funnel plots (appendix pp 28–31).<sup>37</sup> To examine sex differences in the associations between social connection markers and change in cognition over time, we repeated the analysis with additional terms for the interactions between sex, time in study, and social connection markers and then pooled the interaction effects in the meta-analysis. We present  $b$  in the meta-analyses results and forest plots. Unstandardised coefficients from the linear mixed models represent differences in the annual rate of change in cognitive Z scores comparing the target category of the social connection marker with the reference category. A negative  $b$  indicates that the predictor is associated with faster decline in cognition, whereas a positive  $b$  indicates that the predictor is associated with slower decline in cognition. We conducted sensitivity analyses with complete cases to determine whether the results obtained from multiple imputation for missing data were robust.

Missing data ranged from 0.00% to 43.36% for covariates and 0.00% to 35.08% for social connection markers. We visually inspected data to examine whether our observed variables were related to the pattern of missingness and used auxiliary variables (ie, data from predictors and covariates) in the multiple imputation to reduce the effect of non-random missing data on the pattern of results.

Multiple imputation with the Markov Chain Monte Carlo method was used to impute missing data for the demographics, covariates, and social connection markers with less than 50% missing data, incorporating information from auxiliary variables and generating



**Figure 1: Associations between social connection markers and global cognition**  
Markers are categorised by structure, function, and quality. Data presented are for main (partially adjusted) models.

20 imputed datasets in each study.<sup>38</sup> Estimates computed from each imputed dataset were then pooled by use of Rubin's rules.<sup>39</sup> Although multiple imputation is effective with up to 50% missingness,<sup>39</sup> we conducted additional sensitivity analyses to compare the major findings when only complete cases (ie, 0% missing) were used.

We used R studio software version 4.1.2 and R packages mice for multiple imputation, lme4 for linear mixed modelling, and metafor for meta-analyses.

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

### Results

Of the 40006 people in the 13 cohorts, we excluded 1392 people living with dementia at baseline (ranging from no participants to 289 participants per study; appendix p 7) and 38614 participants were included in the analyses. Sample descriptive statistics for age, sex, education, and study timepoints are presented in appendix p 4, for covariates in appendix p 22, and for social connection markers in appendix pp 23–25. Recruitment dates (baseline and final follow-up year) for individual cohorts are provided in the appendix (p 4).

Follow-up periods ranged from 2 years to 15 years across cohorts, and the time in study for participants ranged from 0 years to 15 years, with a median of 3 years (IQR 2–6). Participants were community dwelling in all cohorts, apart from 50 (4.8%) of 1045 participants from the LEILA75+ study, who resided in assisted living facilities (50 [0.1%] of 38614 of the overall sample).

The sample included in the main analyses (13 cohorts,  $n=38614$ ) was similar in age at baseline (mean 70.50 years, SD 8.67; female mean age 70.63 years [SD 8.87 vs male mean age 70.32 [8.38]) compared with the sample for the fully adjusted models (ten cohorts,  $n=29718$ , mean 70.49 years, SD 8.65,  $t=-0.13$ ,  $df=58282$ ,  $p=0.90$ ; female mean age 70.72 years [8.90] vs male mean age 70.19 years [8.30]). In the main models, married men were slightly older (mean 69.79 [SD 7.83]) than married women (67.36 [7.59]). Furthermore, the sample for the main analyses had a similar proportion of women (22556 [58.4%] of 38614 vs 17145 [57.7%] of 29728;  $\chi^2=3.50$ ,  $df=1$ ,  $p=0.060$ ) to and fewer years of education (mean 8.48 years [SD 4.88] vs 9.12 years [4.61];  $df=58282$ ,  $p<0.0001$ ) than did the sample for the fully adjusted models.

Longitudinal associations between social connection markers and each of the four cognitive outcomes for the main models are shown in figures 1–4 (detailed results of the main and fully adjusted models are shown in the appendix pp 26–27). Here, we report the results for the main models that were replicated in the fully adjusted models. Being married or in a relationship was associated with slower global cognitive decline than

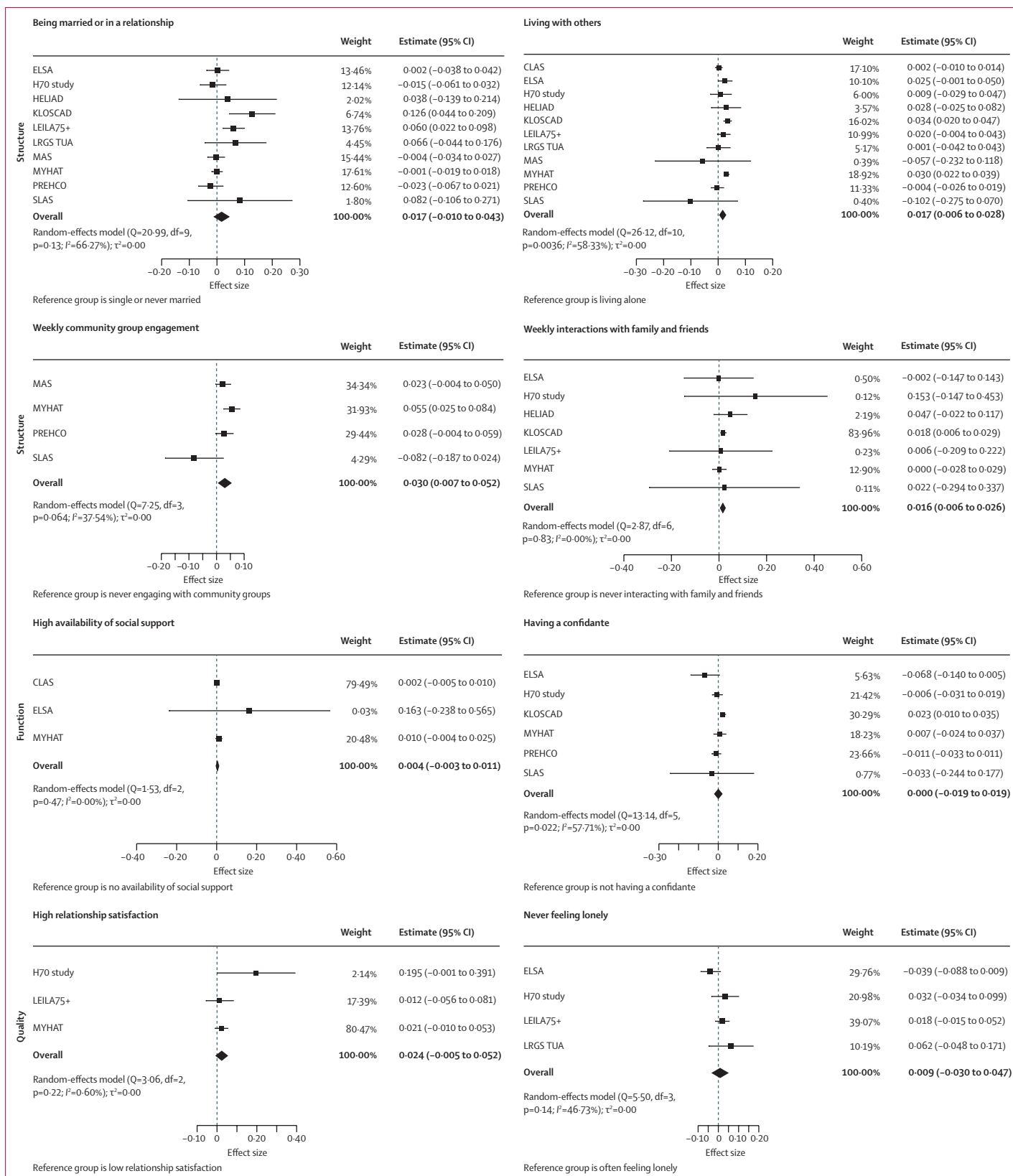
was being single or never married. Living with others was associated with slower global cognitive, memory, and language decline than was living alone. Yearly, monthly, or weekly engagement in a community group was associated with slower annual memory decline than was never engaging with community groups. Additionally, monthly or weekly interactions with family and friends were associated with slower memory decline than was never interacting (appendix pp 26–27). Never feeling lonely was associated with slower annual decline in global cognition and executive function than was often feeling lonely. Heterogeneity estimates for the results reported here for the main models were low ( $I^2=0.00-15.11\%$ ), indicating that the findings were largely consistent across studies. The exceptions were for the association between memory and living situation ( $I^2=58.33\%$ ), for which only the North American and South Korean cohorts showed significant results, and for the association between memory and community group engagement ( $I^2=37.54-72.19\%$ ), which might reflect the different activities assessed in different cohorts. These findings were all replicated in the fully adjusted models (ie, in ten of 13 cohorts).

Several findings were inconsistent between the main and fully adjusted models. In the fully adjusted models, monthly engagement in a community group was significantly associated with faster global cognitive decline than was never engaging with community groups. In the main models, yearly interactions with family and friends were associated with slower annual decline in global cognition than was never interacting, but this association was not replicated in the fully adjusted models (appendix pp 26–27). Sensitivity analyses using complete cases for the main models suggested that the overall pattern of findings was consistent (appendix pp 38–39).

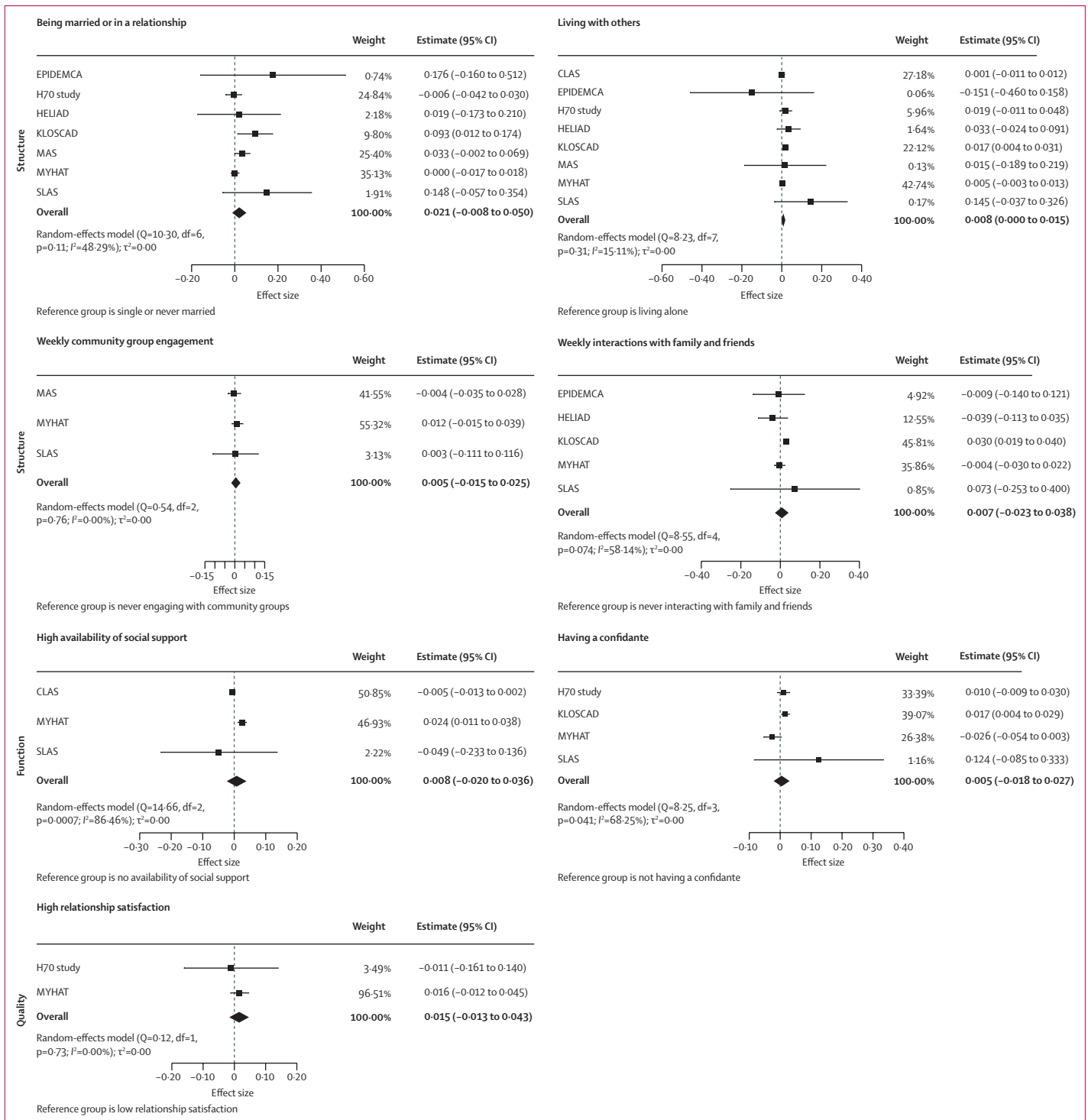
In terms of sex differences, examining the pooled interaction effects of social connection markers with sex across cohorts (table) identified a few sex differences in the associations between social connection markers and cognitive function. Men, but not women, who were in a relationship or were married had faster cognitive decline in global cognition than those not in a relationship or married. Women, but not men, who were in a relationship or were married had slower decline in memory than those not in a relationship or married.

When examining the whole sample, there was a significant sex interaction for living with others and being in a relationship or married, with both factors predicting slower decline in executive function than living alone or being single or never married. Sex differences in the association between social connection markers and annual rate of change in cognition for

**Figure 2: Associations between social connection markers and memory**  
Markers are categorised by structure, function, and quality. Data presented are for main (partially adjusted) models.







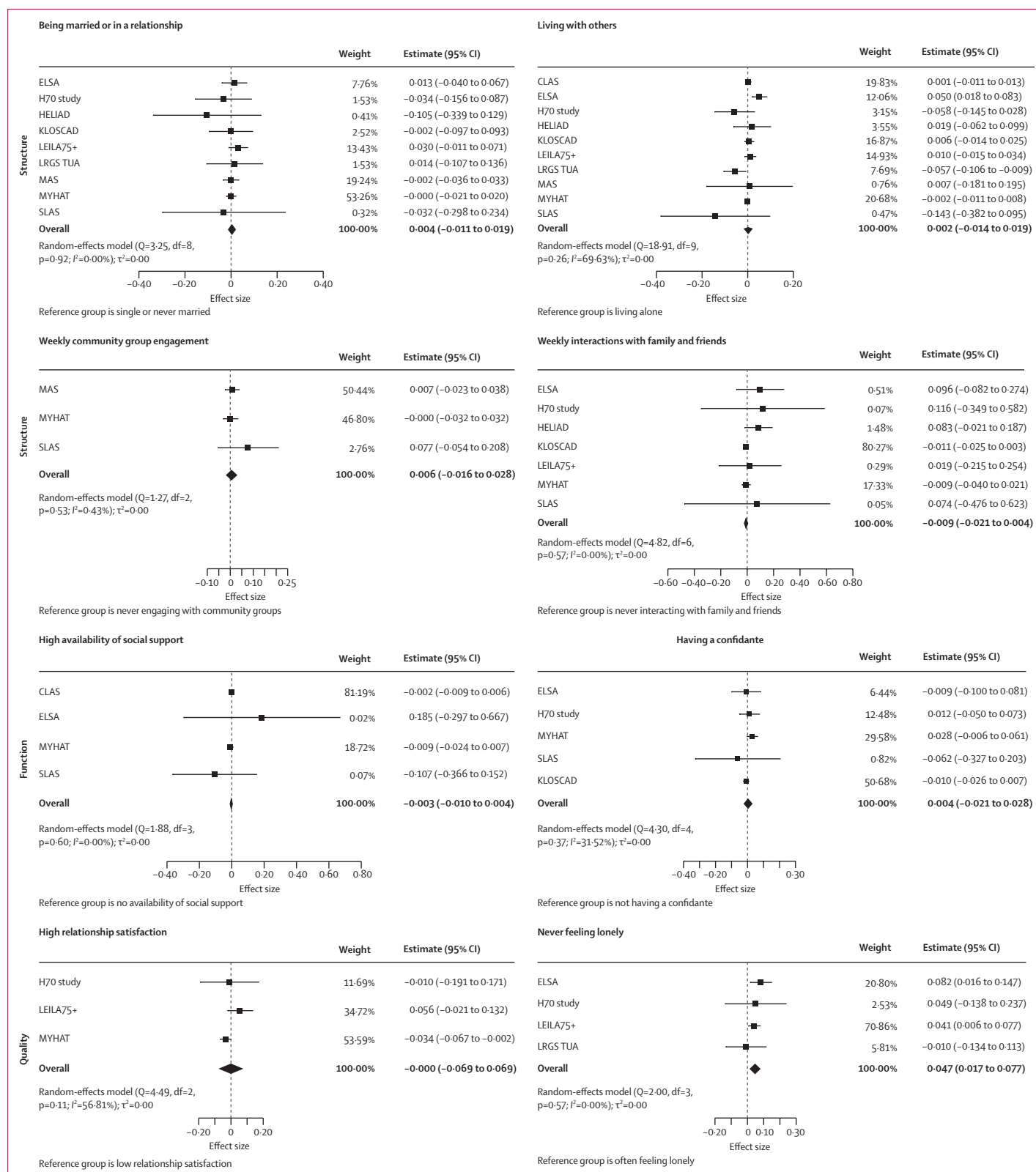
**Figure 3: Associations between social connection markers and language**

Markers are categorised by structure, function, and quality. Data presented are for main (partially adjusted) models. The meta-analytic model for the association between loneliness and language could not be run because data were available for only the H70 study.<sup>23</sup>

individual cohorts are shown in the appendix (pp 32–37). Sensitivity analyses using complete cases replicated the pattern of results (appendix pp 40–41).

## Discussion

In line with our hypothesis that good social connections would be associated with slower cognitive decline over



**Figure 4: Associations between social connection markers and executive function**  
 Markers are categorised by structure, function, and quality. Data presented are for main (partially adjusted) models.

	I <sup>2</sup> (%)	τ <sup>2</sup>	Interaction effect of social connection marker, sex, and time in study, b (95% CI)	Egger's test, Z score (p value)	Simple main effects for men and women (when b is significant; 95% CI)
<b>Global cognition</b>					
Structure					
Being married or in a relationship	0.00%	0.00	0.033 (0.009 to 0.578)	-0.42 (p=0.68)	-0.023 (-0.045 to -0.002) for men; 0.010 (-0.001 to 0.021) for women
Living with others	14.96%	0.00	0.004 (-0.011 to 0.018)	-0.82 (p=0.41)	..
Yearly engagement in community group	0.69%	0.00	0.013 (-0.015 to 0.042)	-0.39 (p=0.70)	..
Monthly engagement in community group	15.53%	0.00	-0.009 (-0.038 to 0.019)	0.03 (p=0.97)	..
Weekly engagement in community group	0.00%	0.00	0.010 (-0.013 to 0.034)	-0.30 (p=0.77)	..
Yearly interactions with family and friends	0.00%	0.00	0.039 (-0.028 to 0.107)	0.44 (p=0.66)	..
Monthly interactions with family and friends	0.00%	0.00	0.006 (-0.019 to 0.031)	-0.08 (p=0.94)	..
Weekly interactions with family and friends	0.00%	0.00	0.004 (-0.017 to 0.026)	0.11 (p=0.91)	..
Function					
High availability of social support	0.45%	0.00	0.002 (-0.013 to 0.014)	-1.66 (p=0.10)	..
Having a confidante	0.00%	0.00	-0.002 (-0.023 to 0.018)	0.10 (p=0.92)	..
Quality					
High relationship satisfaction	0.00%	0.00	-0.036 (-0.078 to 0.006)	-0.27 (p=0.80)	..
Never feeling lonely	0.00%	0.00	-0.057 (-0.140 to 0.027)	0.45 (p=0.66)	..
<b>Memory</b>					
Structure					
Being married or in a relationship	7.14%	0.00	0.042 (0.010 to 0.074)	0.01 (p=0.99)	-0.023 (-0.047 to 0.001) for men; 0.024 (0.001 to 0.048) for women
Living with others	42.70%	0.00	0.009 (-0.012 to 0.031)	0.94 (p=0.35)	..
Yearly engagement in community group	8.33%	0.00	0.001 (-0.035 to 0.054)	NR*	..
Monthly engagement in community group	0.00%	0.00	0.006 (-0.025 to 0.037)	0.10 (p=0.92)	..
Weekly engagement in community group	0.00%	0.00	0.017 (-0.017 to 0.051)	0.86 (p=0.39)	..
Yearly interactions with family and friends	57.32%	0.05	-0.076 (-0.389 to 0.235)	-0.14 (p=0.89)	..

(Table continues on next page)

time than would poor social connections, we identified that being married or in a relationship, living with one or more person, and never feeling lonely were associated with slower annual decline in global cognition than were being single or never married, living alone, and often feeling lonely. Our findings regarding relationship status are consistent with a previous meta-analysis, which showed that being married is protective against dementia due to slower cognitive decline.<sup>8</sup> We also identified an association between never feeling lonely and a slower rate of cognitive decline, similar to previous findings.<sup>11</sup> Overall, our findings support previous research and suggest that improved social connection structures (eg, relationship status, living situation, and interaction frequency), quality (eg, loneliness), but not necessarily function (eg, social support), are associated with decreased rates of cognitive decline. Social connections and cognitive function can also have a bidirectional relationship, where each promotes the other, such that having social connections promotes cognitive skills and vice versa.<sup>40</sup> Declining cognition can also limit social connections and vice versa. Our results support both the bridging (ie, cognitive stimulation via doing activities with loose ties) and bonding (ie, stress buffering via close relationships) pathways that have been proposed to lead from social connections to cognitive health.<sup>4</sup>

In terms of cognitive domains, our hypothesis that good social connection structure markers are associated with slow decline across all cognitive domains was partly supported. Living with others was associated with slower decline in memory and language, but not executive function, than was living alone. We also identified that yearly, monthly, and weekly engagement in a community group and monthly and weekly interactions with family and friends were associated with slower memory decline than were no engagement or interactions, although the association of yearly interactions with family and friends and memory was not replicated in fully adjusted models. Our results are in line with another meta-analysis that identified that social connection structure was linked specifically with memory, although the previous meta-analysis did find associations with executive function, which we did not.<sup>8</sup> We also identified an association between social health structure and language, a relationship that was not examined in the previous meta-analysis.<sup>8</sup> Living with others and interacting regularly with the community and with family and friends could provide frequent opportunities to use memory or language skills.<sup>41</sup> Our hypothesis was good social connection function and quality markers are associated with slower decline in memory was not supported. However, never feeling lonely was associated with slower executive function decline than was often feeling lonely. We identified that good social connections structure (ie, being in a relationship and living with others) and quality (ie, never feeling lonely) were associated with slower global cognitive decline than were being single or never

married, living alone, and feeling lonely. Importantly, associations between specific social connection markers and specific cognitive domains might be overlooked by focusing solely on global cognition. Feeling connected to others (*vs* feeling lonely) might increase cognitive reserve by reducing stress and slowing down memory and executive function decline, whereas interactions with family and friends and community members might provide cognitive stimulation and additional opportunities to practise a variety of cognitive functions, such as memory and language, which is in line with the theorised bridging and bonding pathways and other previous findings.<sup>4,8</sup>

As per our hypothesis, we identified a few sex differences in the associations between social connection markers and cognition, but we did not identify support for our hypothesis that good social health structure markers are associated with a decreased rate of cognitive decline only for men. We identified slower rates of cognitive decline (ie, global cognition and memory) over time for women who were in a relationship or married than for women who were single. These findings are contrary to previous research showing that being in a relationship or married is associated with slower cognitive decline for men only.<sup>18</sup> Although older women might have few social interactions beyond their spouse due to increased household responsibilities, interactions with family and friends outside of the home can provide opportunities for cognitive stimulation.<sup>15</sup> Additionally, women in a relationship or who are married might have greater financial stability and better general and cognitive function. Across the 13 cohorts in our study, the mean age of married men in the main models was 2.43 years greater than was the mean age of married women. This difference in age might explain slower rates of cognitive decline for married women than for men, as married men are older and might have cognitive decline during marriage, whereas married women might have cognitive decline later in life during widowhood. Sex differences in the association between social connection and cognitive decline are inconclusive; some previous studies have reported no differences,<sup>7</sup> whereas others have reported evidence for women benefiting from interactions with family and friends more than men do when newly diagnosed with dementia.<sup>42</sup> Our exploratory analyses on the sex differences between social connection function and quality markers and cognitive decline showed no significant results.

Poor social connections have been proposed to affect cognitive function via multiple pathways. Strong social ties promote cognitive health via cognitive stimulation and affect the function of the neuroendocrine system and activation of the hypothalamic–pituitary–adrenal axis via psychosocial processes (eg, stress buffering).<sup>4</sup> Being in a relationship or married, living with others, and frequent social interactions might provide opportunities for cognitive stimulation and reduce cognitive decline via the stress buffering pathway.

Although our effect sizes represented a 1–2% reduction in the rate of cognitive decline per year, these results might accumulate over decades. Nevertheless, having

	<i>I</i> <sup>2</sup> (%)	$\tau^2$	Interaction effect of social connection marker, sex, and time in study, <i>b</i> (95% CI)	Egger's test, Z score (p value)	Simple main effects for men and women (when <i>b</i> is significant; 95% CI)
(Continued from previous page)					
Monthly interactions with family and friends	0.00%	0.00	0.011 (-0.014 to 0.036)	-1.42 (p=0.16)	..
Weekly interactions with family and friends	52.73%	0.00	0.002 (-0.064 to 0.068)	-1.90 (p=0.057)	..
<b>Function</b>					
High availability of social support	33.13%	0.00	0.008 (-0.019 to 0.035)	0.20 (p=0.84)	..
Having a confidante	0.00%	0.00	-0.005 (-0.025 to 0.015)	-0.14 (p=0.89)	..
<b>Quality</b>					
High relationship satisfaction	0.00%	0.00	-0.029 (-0.087 to 0.028)	-0.42 (p=0.67)	..
Never feeling lonely	0.00%	0.00	-0.039 (-0.102 to 0.024)	-0.38 (p=0.71)	..
<b>Language</b>					
<b>Structure</b>					
Being married or in a relationship	0.00%	0.00	0.010 (-0.024 to 0.043)	-1.76 (p=0.079)	..
Living with others	0.13%	0.00	0.007 (-0.007 to 0.022)	0.87 (p=0.39)	..
Yearly engagement in community group	77.24%†	0.00	-0.001 (-0.094 to 0.092)	NR*	..
Monthly engagement in community group	90.58%†	0.02	0.018 (-0.135 to 0.171)	2.61 (p=0.0069)	..
Weekly engagement in community group	47.96%	0.00	-0.011 (-0.077 to 0.055)	-0.06 (p=0.95)	..
Yearly interactions with family and friends	39.08%	0.03	-0.072 (-0.343 to 0.198)	-0.43 (p=0.67)	..
Monthly interactions with family and friends	0.00%	0.00	-0.006 (-0.030 to 0.018)	-0.29 (p=0.80)	..
Weekly interactions with family and friends	0.00%	0.00	0.004 (-0.017 to 0.024)	-0.60 (p=0.55)	..
<b>Function</b>					
High availability of social support	0.00%	0.00	0.002 (-0.011 to 0.016)	0.65 (p=0.52)	..
Having a confidante	0.00%	0.00	-0.001 (-0.022 to 0.019)	0.25 (p=0.81)	..
<b>Quality</b>					
High relationship satisfaction	0.00%	0.00	-0.000 (-0.057 to 0.056)	NR*	..
Never feeling lonely	NR‡	NR‡	NR‡	NR*	..

(Table continues on next page)

	$I^2$ (%)	$\tau^2$	Interaction effect of social connection marker, sex, and time in study, $b$ (95% CI)	Egger's test, Z score (p value)	Simple main effects for men and women (when $b$ is significant; 95% CI)
(Continued from previous page)					
<b>Executive function</b>					
<b>Structure</b>					
Being married or in a relationship	0.00%	0.00	0.046 (0.011 to 0.082)	-0.38 (p=0.71)	-0.027 (-0.054 to 0.000) for men; 0.017 (-0.002 to 0.036) for women
Living with others	0.00%	0.00	0.016 (0.001 to 0.031)	0.25 (p=0.80)	-0.009 (-0.022 to 0.003) for men; 0.005 (-0.002 to 0.013) for women
Yearly engagement in community group	61.34%	0.00	-0.033 (-0.110 to 0.045)	NR*	..
Monthly engagement in community group	73.11%†	0.01	-0.034 (-0.138 to 0.070)	-1.59 (p=0.11)	..
Weekly engagement in community group	0.00%	0.00	-0.035 (-0.079 to 0.010)	-0.76 (p=0.45)	..
Yearly interactions with family and friends	57.15%	0.06	0.133 (-0.246 to 0.513)	-0.11 (p=0.91)	..
Monthly interactions with family and friends	0.01%	0.00	0.008 (-0.022 to 0.038)	-0.08 (p=0.93)	..
Weekly interactions with family and friends	0.00%	0.00	0.023 (-0.002 to 0.049)	-0.39 (p=0.70)	..
<b>Function</b>					
High availability of social support	0.00%	0.00	0.005 (-0.008 to 0.019)	0.54 (p=0.59)	..
Having a confidante	0.00%	0.00	-0.024 (-0.081 to 0.033)	0.23 (p=0.82)	..
<b>Quality</b>					
High relationship satisfaction	11.29%	0.00	-0.014 (-0.093 to 0.065)	1.37 (p=0.17)	..
Never feeling lonely	42.24%	0.00	0.042 (-0.078 to 0.162)	0.81 (p=0.42)	..

The model results reflect the annual change in cognition ( $b$  [95% CI]) for women compared with men and are controlled for age at baseline, education, and sex. Positive interaction effect  $b$  indicates slower annual decline in cognition for women than for men; negative interaction effect  $b$  indicates slower annual decline in cognition for men than for women. For sex-stratified analyses, simple main effects positive  $b$  indicates slower annual decline in cognition than for the reference group for the specific social connection marker. NR=not reported. \*Some models had less than three cohort studies, and we could not compute Egger's test for them. † $p < 0.05$ . ‡Not enough data points to run analysis.

**Table:** Sex differences in the association between social health markers and annual change in cognition by domain in the main analysis

poor social connections is one contributing factor for cognitive decline and should be considered alongside other risk factors when trying to reduce the risk of cognitive decline.

Our study had several strengths. Previous meta-analyses or collaborative studies have relied on data from North America and Europe, used combined or conflated

social connection markers, used aggregated statistics from studies with diverse sets of covariates, and focused solely on global cognition as the outcome. We harmonised data from 13 longitudinal cohorts, including culturally diverse and low-income and middle-income countries (ie, Brazil, China, and Central African Republic). Our sample was well powered and more representative than were many previous studies examining social connections and cognitive outcomes in older adults. Using an individual participant data meta-analysis, we controlled for the same covariates across studies. Additionally, harmonisation allowed us to examine multiple markers of social connections as risk factors for cognitive decline. We have strictly delineated between structural, functional, and quality markers of social connections.<sup>3</sup> Previous studies have emphasised the need to measure and assess distinct markers of social connections as they might have varying effects on different cognitive domains.<sup>8</sup> We went beyond previous studies by examining associations with memory, executive function, and language, rather than only global cognition. We also examined previously underinvestigated sex differences across multiple social connection markers and change in cognitive function for global cognition and specific cognitive domains.

There were some limitations to our study. Harmonising data from multiple studies entailed a loss of granularity and precluded analyses involving detailed categories of social connection markers. Our results might have been affected by the contributing cohort studies not using validated measures of social connections. For instance, most cohort studies used single questions for concepts such as loneliness instead of validated scales. Few studies provided data for relationship satisfaction (ie, four studies) or loneliness frequency (ie, three studies), emphasising the need for improved quality of data for social connection quality. Disparities in the number of social connection markers between cohort studies meant that we could not compute composite scores for social connection domains (ie, structure, quality, and function) or control for other social connection markers when examining the association between specific social connection markers and cognitive outcomes. It is possible that other social connection markers (eg, loneliness) might confound the relationship between a specific social connection marker and a cognitive outcome (eg, being in a relationship and global cognition). In our study, the meta-analyses models had to be run with different groupings of studies for each social connection predictor–cognitive outcome pair. Future research should investigate the interaction of social connection markers with each other and cognitive outcomes by use of data from studies that included the same set of social connection markers. Reverse causality might affect our results, as cognitive skills are required to maintain social connections, although we excluded people living with dementia at baseline to minimise the risk. Finally, due to the absence of data for social connection markers at follow-up, we examined only baseline

differences in social connection markers and were unable to examine changes in social connection markers over time. Future research could investigate if changes in social connections affect the rate of cognitive decline over the course of dementia. The biopsychosocial pathways leading from having good social connection structure and function to stable cognition function (or vice versa) have not been explored.

Although most cohort studies include measures of only social connections, social health has been expanded to include the individual's ability to adapt to and manage challenges that influence their social participation and activities.<sup>43</sup> More theory and measures of this ability to adapt are needed to get an understanding of the dynamic nature of social health.

To summarise, harmonised individual participant data from 13 longitudinal cohort studies of ageing were meta-analysed at the participant level to examine the association between social connections and risk of cognitive decline. Better social connection structure (eg, relationship status, living situation, and interaction frequency) and quality (eg, never lonely), but not function (eg, social support and having a confidante), were associated with slower rates of cognitive decline. Additionally, being in a relationship or married was associated with slower decline in memory, but only for women.

#### Contributors

SSa was responsible for conceptualisation, data curation, formal analysis, investigation, methodology, project administration, validation, and writing the original draft. GM was responsible for data curation, investigation, formal analysis, methodology, project administration, validation, visualisation, and writing the original draft. BCPL was responsible for methodology and writing the original draft. DML was responsible for conceptualisation, data curation, and methodology. HB, PSS, and Y-HJ were responsible for conceptualisation, funding acquisition, investigation, methodology, and supervision. MFL-C, EC-C, XS, MGu, P-MP, IS, NS, K-WK, SR-H, SSh, MGa, MC, and TPN were responsible for conceptualisation, data curation, and investigation. SLB, AG, JN, TRS, SR, AP, EJ, TFH, and KN were responsible for data curation and investigation. RM, DS, and MV-D were responsible for conceptualisation, funding acquisition, and investigation. All authors were responsible for reviewing and editing the manuscript. SSa and GM accessed and verified the data. SSa and GM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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#### Data sharing

All aggregate participant data are presented either in the manuscript or appendix. Individual participant data cannot be made publicly available because they are protected by a confidentiality agreement. Data were provided by the contributing studies to COSMIC on the understanding and proviso that the relevant study leaders be contacted for further use of their data and additional formal data sharing agreements be made. Researchers can apply to use COSMIC data by completing a COSMIC Research Proposal Form available from <https://cheba.unsw.edu.au/consortia/cosmic/research-proposals>.

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## References

- Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *Lancet* 2020; **396**: 413–46.
- Huber M, Knottnerus JA, Green L, et al. How should we define health? *BMJ* 2011; **343**: d4163.
- Holt-Lunstad J, Steptoe A. Social isolation: an underappreciated determinant of physical health. *Curr Opin Psychol* 2022; **43**: 232–37.
- Perry BL, McConnell WR, Coleman ME, Roth AR, Peng SY, Apostolova LG. Why the cognitive ‘fountain of youth’ may be upstream: pathways to dementia risk and resilience through social connectedness. *Alzheimers Dement* 2022; **18**: 934–41.
- Vernooij-Dassen M, Moniz-Cook E, Verhey F, et al. Bridging the divide between biomedical and psychosocial approaches in dementia research: the 2019 INTERDEM manifesto. *Aging Ment Health* 2021; **25**: 206–12.
- Stern Y. Cognitive reserve in ageing and Alzheimer’s disease. *Lancet Neurol* 2012; **11**: 1006–12.
- Kuiper JS, Zuidersma M, Zuidema SU, et al. Social relationships and cognitive decline: a systematic review and meta-analysis of longitudinal cohort studies. *Int J Epidemiol* 2016; **45**: 1169–206.
- Kelly ME, Duff H, Kelly S, et al. The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: a systematic review. *Syst Rev* 2017; **6**: 259.
- Boyle PA, Buchman AS, Barnes LL, Bennett DA. Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. *Arch Gen Psychiatry* 2010; **67**: 304–10.
- Bosma H, van Boxtel MPJ, Ponds RWHM, et al. Engaged lifestyle and cognitive function in middle and old-aged, non-demented persons: a reciprocal association? *Z Gerontol Geriatr* 2002; **35**: 575–81.
- Freak-Poli R, Wagemaker N, Wang R, et al. Loneliness, not social support, is associated with cognitive decline and dementia across two longitudinal population-based cohorts. *J Alzheimers Dis* 2022; **85**: 295–308.
- Levine DA, Gross AL, Briceño EM, et al. Sex differences in cognitive decline among US adults. *JAMA Netw Open* 2021; **4**: e210169.
- Read S, Comas-Herrera A, Grundy E. Social isolation and memory decline in later-life. *J Gerontol B Psychol Sci Soc Sci* 2020; **75**: 367–76.
- Lee Y, Jean Yeung W-J. Gender matters: productive social engagement and the subsequent cognitive changes among older adults. *Soc Sci Med* 2019; **229**: 87–95.
- Liao J, Scholes S. Association of social support and cognitive aging modified by sex and relationship type: a prospective investigation in the English Longitudinal Study of Ageing. *Am J Epidemiol* 2017; **186**: 787–95.
- Zhou Z, Mao F, Zhang W, Towne SD Jr, Wang P, Fang Y. The association between loneliness and cognitive impairment among older men and women in China: a nationwide longitudinal study. *Int J Environ Res Public Health* 2019; **16**: 16.
- Anstey KJ, Peters R, Mortby ME, et al. Association of sex differences in dementia risk factors with sex differences in memory decline in a population-based cohort spanning 20–76 years. *Sci Rep* 2021; **11**: 7710.
- Murata C, Saito T, Saito M, Kondo K. The association between social support and incident dementia: a 10-year follow-up study in Japan. *Int J Environ Res Public Health* 2019; **16**: 239.
- Lima-Costa MF, Firmo JOA, Uchoa E. Cohort profile: the Bambuí (Brazil) Cohort Study of Ageing. *Int J Epidemiol* 2011; **40**: 862–67.
- Xiao S, Li J, Tang M, et al. Methodology of China’s national study on the evaluation, early recognition, and treatment of psychological problems in the elderly: the China Longitudinal Aging Study (CLAS). *Shanghai Arch Psychiatry* 2013; **25**: 91–98.
- Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English Longitudinal Study of Ageing. *Int J Epidemiol* 2013; **42**: 1640–48.
- Guerchet M, Mbelesso P, Ndamba-Bandzouzi B, et al. Epidemiology of Dementia in Central Africa (EPIDEMCA): protocol for a multicentre population-based study in rural and urban areas of the Central African Republic and the Republic of Congo. *Springerplus* 2014; **3**: 1044.
- Thorvaldsson V, Karlsson P, Skoog J, Skoog I, Johansson B. Better cognition in new birth cohorts of 70 year olds, but greater decline thereafter. *J Gerontol B Psychol Sci Soc Sci* 2017; **72**: 16–24.
- Dardiotis E, Kosmidis MH, Yannakoulia M, Hadjigeorgiou GM, Scarmeas N. The Hellenic Longitudinal Investigation of Aging and Diet (HELIAID): rationale, study design, and cohort description. *Neuroepidemiology* 2014; **43**: 9–14.
- Han JW, Kim TH, Kwak KP, et al. Overview of the Korean Longitudinal Study on Cognitive Aging and Dementia. *Psychiatry Investig* 2018; **15**: 767.
- Riedel-Heller SG, Busse A, Aurich C, Matschinger H, Angermeyer MC. Prevalence of dementia according to DSM-III-R and ICD-10: results of the Leipzig Longitudinal Study of the Aged (LEILA75+) part 1. *Br J Psychiatry* 2001; **179**: 250–54.
- Shahar S, Omar A, Vanoh D, et al. Approaches in methodology for population-based longitudinal study on Neuroprotective Model for Healthy Longevity (TUA) among Malaysian Older Adults. *Aging Clin Exp Res* 2016; **28**: 1089–104.
- Sachdev PS, Brodaty H, Reppermund S, et al. The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70–90 years. *Int Psychogeriatr* 2010; **22**: 1248–64.
- Ganguli M, Snitz B, Vander Bilt J, Chang CH. How much do depressive symptoms affect cognition at the population level? The Monongahela–Youghiogheny Healthy Aging Team (MYHAT) study. *Int J Geriatr Psychiatry* 2009; **24**: 1277–84.
- Bell T, Dávila AL, Clay O, Markides KS, Andel R, Crowe M. The association between cognitive decline and incident depressive symptoms in a sample of older Puerto Rican adults with diabetes. *Int Psychogeriatr* 2017; **29**: 1317–25.
- Niti M, Yap K-B, Kua E-H, Tan C-H, Ng T-P. Physical, social and productive leisure activities, cognitive decline and interaction with APOE-epsilon 4 genotype in Chinese older adults. *Int Psychogeriatr* 2008; **20**: 237–51.
- Lipnicki DM, Crawford JD, Dutta R, et al. Age-related cognitive decline and associations with sex, education and apolipoprotein E genotype across ethnocultural groups and geographic regions: a collaborative cohort study. *PLoS Med* 2017; **14**: e1002261.
- Hughes ME, Waite LJ, Hawkey LC, Cacioppo JT. A short scale for measuring loneliness in large surveys: results from two population-based studies. *Res Aging* 2004; **26**: 655–72.
- Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ* 2010; **340**: c221.
- Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005; **30**: 261–93.
- Jackson D, White IR, Riley RD. Quantifying the impact of between-study heterogeneity in multivariate meta-analyses. *Stat Med* 2012; **31**: 3805–20.
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.
- Little RJA, Rubin DB. *Statistical analysis with missing data*. Hoboken, NJ: John Wiley & Sons, 2019.
- Schafer JL, Graham JW. Missing data: our view of the state of the art. *Psychol Methods* 2002; **7**: 147–77.
- Casey A-NS, Liu Z, Kochan NA, Sachdev PS, Brodaty H. Cross-lagged modeling of cognition and social network size in the Sydney Memory and Ageing Study. *J Gerontol B Psychol Sci Soc Sci* 2021; **76**: 1716–25.
- Ybarra O, Burnstein E, Winkelman P, et al. Mental exercising through simple socializing: social interaction promotes general cognitive functioning. *Pers Soc Psychol Bull* 2008; **34**: 248–59.
- Donato KM, León-Pérez G, Wallston KA, Kripalani S. Something old, something new: when gender matters in the relationship between social support and health. *J Health Soc Behav* 2018; **59**: 352–70.
- Vernooij-Dassen M, Jeon Y-H. Social health and dementia: the power of human capabilities. *Int Psychogeriatr* 2016; **28**: 701–03.