Social health and subsequent cognitive functioning in people aged 50 years and older: examining the mediating roles of depressive symptoms and inflammatory biomarkers in two European longitudinal studies

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Summary

Background Social health markers, including marital status, contact frequency, network size, and social support, have been shown to be associated with cognition. However, the mechanisms underlying these associations remain poorly understood. We investigated whether depressive symptoms and inflammation mediated associations between social health and subsequent cognition.

Methods In the English Longitudinal Study of Ageing (ELSA), a nationally representative longitudinal study in England, UK, we sampled 7136 individuals aged 50 years or older living in private households without dementia at baseline or at the intermediate mediator assessment timepoint, who had recorded information on at least one social health marker and potential mediator. We used four-way decomposition to examine to what extent depressive symptoms, C-reactive protein, and fibrinogen mediated associations between social health and subsequent standardised cognition (verbal fluency and delayed and immediate recall), including cognitive change, with slopes derived from multilevel models (12-year slope). We examined whether findings were replicated in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), a population-based longitudinal study in Sweden, in a sample of 2604 individuals aged 60 years or older living at home or in institutions in Kungsholmen (central Stockholm) without dementia at baseline or at the intermediate mediator assessment timepoint (6-year slope). Social health exposures were assessed at baseline, potential mediators were assessed at an intermediate timepoint (wave 2 in ELSA and 6-year follow-up in SNAC-K); cognitive outcomes were assessed at a single timepoint (wave 3 in ELSA and 12-year follow-up in SNAC-K), and cognitive change (between waves 3 and 9 in ELSA and between 6-year and 12-year follow-ups in SNAC-K).

Findings The study sample included 7136 participants from ELSA, of whom 3962 (55·5%) were women and 6934 (97·2%) were White; the mean baseline age was 63·8 years (SD 9·4). Replication analyses included 2604 participants from SNAC-K, of whom 1604 (61·6%) were women (SNAC-K did not collect ethnicity data); the mean baseline age was 72·3 years (SD 10·1). In ELSA, we found indirect effects via depressive symptoms of network size, positive support, and less negative support on subsequent verbal fluency, and of positive support on subsequent immediate recall (pure indirect effect [PIE] 0·002 [95% CI 0·001–0·003]). Depressive symptoms also partially mediated associations between less negative support and slower decline in immediate recall (PIE 0·001 [0·000–0·002]) and in delayed recall (PIE 0·001 [0·000–0·002]), and between positive support and slower decline in immediate recall (PIE 0·001 [0·000–0·001]). We did not observe mediation by inflammatory biomarkers. Findings of mediation by depressive symptoms in the association between positive support and verbal fluency and between positive support and change in immediate recall were replicated in SNAC-K.

Interpretation The findings of this study provide new insights into mechanisms linking social health with cognition, suggesting that associations between interactional aspects of social health, especially social support, and cognition are partly underpinned by depressive symptoms.

Funding EU Joint Programme—Neurodegenerative Disease Research (JPND) and Alzheimer's Society.

Introduction

Social health, an umbrella term encompassing aspects of social relationships, ranging from the individual level to wider sociocultural factors,[1] is increasingly recognised as a crucial component of health across the life course but especially in older age. Multiple aspects of social health,

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Research in context

Evidence before this study

Previous studies have shown links between social health markers, including marital status and social support, and subsequent cognition. However, the mechanisms underlying these relationships are underexamined, including the potential roles of depressive symptoms and inflammation. We searched PubMed for studies published from database inception until Oct 19, 2023, using terms pertaining to "social relationships", "cognition", "depression" or "inflammation", and "mediation". We retrieved 507 papers, with eight relevant studies identified. Although several previous studies indicated a possible mediating role of depressive symptoms, these studies were cross-sectional or had relatively short follow-up periods (4–10 years), and few studies examined cognitive change over time. Studies examined a variety of social health markers, including loneliness, friendship, cohabitation, and social support, but all focused on global cognition rather than individual cognitive domains. Few studies examined inflammation as a mediator, and findings of these studies were mixed. Two studies found no evidence of mediation by inflammatory biomarkers in associations between loneliness and cognition, whereas another study found that inflammatory biomarkers mediated the association between social isolation and cognition in men only. To clarify these relationships, further research is needed involving representative samples and longer follow-up periods, including a wider range of social health markers and individual cognitive domains, for which distinct relationships may be present.

Added value of this study

We investigated the mediating role of depressive symptoms and inflammation in associations between social health and subsequent cognition in two cohort studies: the English Longitudinal Study of Ageing and the Swedish National Study on Aging and Care in Kungsholmen. Our findings provide new insights into the mediating roles of depressive symptoms and inflammation in the relationships between multiple structural and interactional social health markers and subsequent cognition. In one of the first longitudinal investigations in this area, we show that depressive symptoms are a pathway through which social health, particularly positive and negative aspects of social support, could influence subsequent cognition, including cognitive trajectories. In contrast, inflammatory biomarkers (C-reactive protein and fibrinogen) were not found to mediate associations between social health and cognition. We examined whether findings were replicated across two longitudinal studies, allowing more robust inference and comparison of findings across settings.

Implications of all the available evidence

Taken together, these findings indicate that interactional aspects of social health, especially social support, may have positive effects on cognition, partly by helping to reduce depressive symptoms. In contrast, our findings do not support inflammation as a mediator, although further research is needed to examine a wider range of inflammatory biomarkers. These insights into underlying mechanisms could contribute to the development of interventions and preventive strategies targeting social health, with potential downstream benefits for mental health and cognitive functioning in older people.

such as marital status, social isolation, and loneliness, have been linked with diverse health-related outcomes, including mental health,[2] cardiovascular disease,[3] and mortality.[4] Distinct markers of social health have also been associated with subsequent cognitive decline and dementia.[5,6] Our previous cross-cohort research revealed that positive aspects of social health were associated with lower risk of dementia[7] and with better subsequent cognitive functioning, including slower cognitive decline, in people without dementia.[8] Structural social health markers, such as marital and cohabitation status, network size and frequency of contact,[6,9] and interactional aspects of social health, such as perceived social support,[5] have been shown to be associated with cognitive outcomes and dementia risk.

However, substantial gaps remain in understanding the mechanisms underpinning the relationships between social health and cognition. Several pathways have been posited to underlie these relationships, including depressive symptoms, given the potential for social relationships to provide feelings of security and emotional support and to buffer against stress.[10] In line with this, social disconnectedness and perceived isolation have been shown to have bidirectional relationships with depression and anxiety in older people,[11] and psychiatric symptoms are, in turn, associated with increased risk of cognitive decline and dementia.[12] Both late-life depression and social isolation were identified as modifiable risk factors in the *Lancet* Commission on dementia prevention, intervention, and care.[13]

Inflammation has also been proposed as a pathway that could underlie associations between social health and cognition. Chronic inflammation has been implicated in a range of age-related health conditions.[14] Berkman and colleagues[15] suggested that physiological pathways, including inflammation, are key mechanisms through which social relationships influence subsequent health outcomes, and that the stress associated with social disconnectedness could lead to accelerated ageing. In addition, the social bonding pathway proposed by Perry and colleagues[16] posits that having a cohesive network of close ties can have downstream benefits for the neuroendocrine system, thereby positively affecting cognitive ageing. Social health markers, such as social

isolation and loneliness, have been associated with inflammatory biomarkers,[17] including with C-reactive protein (CRP), an acute phase protein, and with fibrinogen, a crucial aspect of coagulation, both of which are markers of systemic inflammation and have been implicated in ageing-related processes. Inflammatory biomarkers have, in turn, been linked with increased risk of cognitive decline and implicated in the pathophysiology of dementia.[18]

However, there is sparse evidence to date of the possible mediating roles of depressive symptoms or inflammation in the relationships between social health and cognitive functioning. Although several previous studies have indicated a possible mediating role of depressive symptoms,[19–23] most of these studies were cross-sectional. Previous longitudinal studies have also shown evidence of mediation. For instance, the Irish Longitudinal Study on Ageing[21] found that depressive symptoms, but not anxiety, mediated the association between loneliness and subsequent cognitive functioning, although the direct effect was larger than the indirect effect. A further study using data from the National Social Life, Health and Aging Project[19] also showed that depressive symptoms mediated associations between loneliness and subsequent general cognitive ability. However, these studies had relatively short follow-up periods (4–10 years) and focused on assessments of cognition at a single timepoint, rather than cognitive change. Previous studies also examined a variety of social health markers, including loneliness,[19,21] friendship,[20] cohabitation,[22] and social support,[23] and mainly focused on global cognition rather than individual cognitive domains. As a result, the literature to date does not provide comprehensive insight into whether social health markers are associated with subsequent cognition in general or whether domain-specific effects are present.[24] Researchers have highlighted the importance of examining social health markers in relation to individual cognitive outcomes to allow for a more nuanced understanding of possible pathways through which social relationships may affect cognition,[24,25] and the previous literature has been critiqued for not examining domain-specific effects of social health on cognition.[24] Cognitive processes are typically dependent on the integrity of specific cortical or subcortical regions. Social stimulation might have a global influence on the brain, which would be reflected in global cognition measures, or could benefit specific brain regions, which would be reflected in measures of specific cognitive domains. Therefore, examining global cognition alone might dilute different patterns of association between social health and individual cognitive domains.

Previous studies have shown distinct patterns of association between individual social health markers and cognitive domains.[21,24] For instance, having a larger social network was associated specifically with better executive function and memory in the Sydney Memory and Ageing Study.[26] Nonetheless, the hypothesis that social health markers show distinct relationships with individual cognitive domains requires further research involving corroboration with neuroimaging data. Fewer studies to date have examined inflammation as a mediator, with two studies finding no evidence of inflammation mediating the association between loneliness and cognitive function[19,27] and one study finding a mediating role of inflammation in the association between social isolation and cognition in men only.[28] These studies were cross-sectional or had relatively short follow-up periods and did not examine cognitive trajectories, and one study combined inflammatory biomarkers with other physiological markers.[19] Further research is therefore required to investigate the mediating role of depressive symptoms and inflammation in representative samples using longer follow-up periods, including examination of cognitive trajectories and a range of social health markers and individual cognitive domains. Although depressive symptoms and inflammation could mediate links between social health and cognition, it is also possible that there is interplay between social health, depressive symptoms, and inflammation, whereby relationships between social health and cognition vary according to levels of depressive symptoms or inflammation. Further examination of the potential interplay between these factors is required.

To address these gaps in knowledge, we used the English Longitudinal Study of Ageing (ELSA) to investigate whether and to what extent depressive symptoms and inflammation mediated or modified associations between social health and subsequent cognitive functioning, including cognitive trajectories. We examined whether findings from ELSA were replicated in the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K) to ascertain whether findings are similar across studies and settings, which would thereby enhance confidence in the replicability of findings, or whether findings differ, which would suggest that a more cautious interpretation may be needed.[29] We focused on both structural aspects of social health—including marital and cohabitation status, network size, and frequency of contact—and interactional aspects, such as perceived social support.

Methods

Study design and participants
In this examination of two European national longitudinal studies, we conducted the primary analysis using data from ELSA and the replication analysis using SNAC-K. ELSA is an ongoing nationally representative survey of participants aged 50 years and older living in private households in England, UK. Participants were initially recruited from households that had previously responded to the Health Survey for

England from 1998 to 2001. Baseline data for ELSA were collected between March 1, 2002, and March 1, 2003 (individual response rate 67%), with eight subsequent waves taking place every 2 years. For this study, we included participants without recorded dementia at baseline or at any of the intermediate timepoints at which mediators were assessed (appendix 2 p 28), and who had recorded information on at least one social health marker and potential mediator (inflammation or depressive symptoms) and three assessments of the same cognitive outcome between waves 3 and 9 (with the first assessment at wave 3). Ethical approval for all ELSA waves was granted by the London Multicentre Research Ethics Committee, and all participants provided full informed written consent.

SNAC-K is an ongoing population-based longitudinal study, which recruited people aged 60 years and older living at home or in institutions in Kungsholmen (central Stockholm), Sweden. Baseline data were collected between March 21, 2001, and Aug 30, 2004. 3027 (90·0%) of the sample were born in Sweden, 101 (3·0%) in Finland, 44 (1·3%) in Germany, and 191 (5·7%) in other regions. Younger age cohorts (60 to <78 years) were followed up every 6 years and older age cohorts (≥78 years) were followed up every 3 years. SNAC-K was approved by the Ethical Review Board in Stockholm, and written informed consent was obtained from all participants or from their next of kin. For this study, we included SNAC-K data from baseline and from 3-year, 6-year, 9-year, and 12-year follow-up examinations. Participants with dementia at baseline or at the timepoint of mediator assessment were excluded.

Procedures and outcomes

We used comparable measures across ELSA and SNAC-K wherever possible, although not all variables included in ELSA were available in SNAC-K; hence, the replication analysis is limited to available variables. Full information about social health exposures, mediators, cognitive outcomes, and covariates is provided in appendix 2 (pp 36–42).

Social health markers were assessed at baseline in ELSA and SNAC-K. Structural social health markers included: marital or cohabitation status; network size based on the number of children, family, and friends with whom participants reported having a close relationship (capped at 30 people); and frequency of contact with children, friends, and family members in person, by telephone, or through writing or email (never to every few months, once or twice a month, or at least weekly). Interactional social health markers included perceived positive social support from partners, children, friends, and other family members. For each of these relationship types, participants were asked, "How much do they really understand the way you feel about things?", "How much can you rely on them if you have a serious problem?", and "How much can you open up to them if you need to talk about your worries?", with each item rated as "a lot", "some", "a little", or "not at all". Items were reverse coded and we computed the mean of each question across relationship types. Scores were summed across questions to generate a total score, with higher scores indicating more positive support. To assess negative support across the same relationship types, participants were asked, "How much do they criticise you?", "How much do they let you down when you are counting on them?", and "How much do they get on your nerves?", with each question rated as "a lot", "some", "a little", or "not at all". We computed the mean of each question across relationship types and summed scores to generate a negative support variable, with higher scores indicating less negative support. We also created a composite social health variable, which has been used previously in SNAC-K[30] and is described in appendix 2 (p 38). The composite variable combined information on structural markers and interactional markers to create an overall variable grouped into tertiles based on the distribution (low, moderate, or high social health).

Mediators were assessed at an intermediate timepoint (wave 2 in ELSA and 6-year follow-up in SNAC-K) between social health exposures and cognitive outcomes. Depressive symptoms were measured using the eight-item Center for Epidemiologic Studies Depression Scale (CES-D),[31] and inflammation (CRP [mg/L] and fibrinogen [g/L]) were measured using blood concentrations obtained from fasted blood samples. We log-transformed CRP for analysis (appendix 2 p 42).

We examined cognitive outcomes at a single timepoint (wave 3 in ELSA and 12-year follow-up in SNAC-K), and cognitive change (between waves 3 and 9 in ELSA and between 6-year and 12-year follow-ups in SNAC-K). Cognitive outcomes included verbal fluency and immediate recall in ELSA and SNAC-K, and delayed recall, which was only available in ELSA; tasks are described in appendix 2 (p 36). We selected verbal fluency and recall as cognitive outcomes because these are important and commonly assessed cognitive domains that were available with repeated measurements at multiple timepoints after exposure and mediator measurement in both datasets. Recall and verbal fluency tests are frequently used in neuropsychological assessments of older adults. Impairments in recall and verbal fluency are both features of Alzheimer's disease. Verbal fluency has been found to be predictive of progression from mild cognitive impairment to Alzheimer's-type dementia,[32] and a systematic review and meta-analysis found that recall tests were the most effective tests in detecting mild cognitive impairment from a range of cognitive assessments.[33] We standardised each test across timepoints and within studies on a common SD-based scale, with a mean of 0 and an SD of 1.

Covariates were self-reported and included age (years), sex (male or female), educational attainment (lower than

secondary or none, secondary, or higher education), occupational class (manual or non-manual), total non-pension household wealth quintiles, vascular-related health conditions (0 or ≥1), other comorbidities (including cancer, chronic lung disease, asthma, arthritis, osteoporosis, and Parkinson's disease; 0 or ≥1), basic and instrumental activities of daily living (0 or ≥1), smoking status (never smoked, or previous or current smoker), physical activity (inactive, moderately active, or vigorous), alcohol consumption (not at all in the last year, monthly or less, around weekly, or almost daily), self-reported hearing ability (excellent or very good, good, or poor), baseline cognition (measured using verbal fluency and recall tests), and baseline depressive symptoms measured using the CES-D. Directed acyclic graphs are presented in appendix 2 (pp 29–30).

Statistical analysis

We examined the mediating roles of depressive symptoms and inflammation using a causal mediation approach based on the counterfactual framework.[34] Before completing mediation analysis, we examined associations between exposures, mediators, and outcomes. We only tested for mediation where we observed associations between a given exposure and mediator, and between a given mediator and outcome.[35] We did not require an overall exposure–outcome association, as recent methodological developments have shown that mediation can be examined where there is theoretical interest even when there is no significant total effect.[36]

First, we examined associations between social health markers and potential mediators using linear regression models. Second, we tested associations of social health exposures and mediators with subsequent cognition at a single timepoint, and cognitive trajectories derived from mixed-effects multilevel models. The date of each individual's interview (month and year) at each wave was used as the time metric, centred to date at baseline. To enable inclusion in mediation analyses, we extracted individual-level predicted slopes as indicators of cognitive change over time, expressed as standardised change per decade. Associations between exposures, mediators, and extracted cognitive trajectories were tested using linear regression models before completing mediation analysis. We applied three levels of adjustment: first, for age and sex; second, adding sociodemographic and health-related covariates; and third, further adjusting for baseline cognition and depressive symptoms.

Next, we completed a four-way decomposition of the total effect into the controlled direct effect, the reference interaction effect, the mediated interaction effect, and the pure indirect effect (PIE).[37] The controlled direct effect refers to the portion of the total effect of social health markers on cognitive outcomes that is due to pathways not involving depressive symptoms or inflammatory markers (neither mediation nor interaction). The reference interaction effect is the portion of the total

	ELSA (n=7136)	ELSA weighted (n=7068)	SNAC-K (n=2604)
Baseline age, years	63·8 (9·4)	63·6 (9·7)	72·3 (10·1)
Sex			
Female	3962 (55·5%)	3831 (54·2%)	1604 (61·6%)
Male	3174 (44·5%)	3237 (45·8%)	1000 (38·4%)
Occupational class			
Manual	2702 (37·9%)	2755 (39·0%)	441 (16·9%)
Non-manual	4210 (59·0%)	4065 (57·5%)	2087 (80·2%)
Missing	224 (3·1%)	248 (3·5%)	76 (2·9%)
Education			
Lower or none	2605 (36·5%)	2604 (36·8%)	359 (13·8%)
Secondary	2053 (28·8%)	2038 (28·8%)	1282 (49·2%)
Higher	1841 (25·8%)	1806 (25·6%)	963 (37·0%)
Other	634 (8·9%)	617 (8·7%)	..
Missing	<10 (<0·5%)	<10 (<0·5%)	..
Wealth quintile			
1 (lowest)	1095 (15·3%)	1105 (15·6%)	..
2	1298 (18·2%)	1286 (18·2%)	..
3	1439 (20·2%)	1437 (20·3%)	..
4	1537 (21·5%)	1526 (21·6%)	..
5 (highest)	1659 (23·3%)	1609 (22·8%)	..
Missing	108 (1·5%)	107 (1·5%)	..
Basic and instrumental activities of daily living			
None	3121 (43·7%)	3150 (44·6%)	2189 (84·1%)
At least one	4015 (56·3%)	3918 (55·4%)	338 (13·0%)
Missing	..	..	77 (3·0%)
Cardiovascular disease			
No	6340 (88·9%)	6294 (89·0%)	1971 (75·7%)
Yes	795 (11·1%)	773 (10·9%)	633 (24·3%)
Missing	<10 (<0·5%)	<10 (<0·5%)	..
Depression symptoms at baseline (binary)			
No depression	6085 (85·3%)	6032 (85·4%)	2159 (82·9%)
Depression	1043 (14·6%)	1026 (14·5%)	370 (14·2%)
Missing	<10 (<0·5%)	<10 (<0·5%)	75 (2·9%)
Smoking status			
Never smoked	2636 (36·9%)	2607 (36·9%)	1171 (45·0%)
Previous or current smoker	4500 (63·1%)	4461 (63·1%)	1420 (54·5%)
Missing	..	..	13 (0·5%)
Alcohol intake			
Monthly or less (ELSA), no or occasional (SNAC-K)	2101 (29·4%)	2084 (29·5%)	800 (30·7%)
Around weekly (ELSA), light-to-moderate (SNAC-K)	2276 (31·9%)	2261 (32·0%)	1356 (52·1%)
Almost daily (ELSA), heavy drinking (SNAC-K)	2064 (28·9%)	2035 (28·8%)	440 (16·9%)
Not at all in last 12 months (ELSA)	694 (9·7%)	686 (9·7%)	..
Missing	<10 (<0·5%)	<10 (<0·5%)	<10 (<0·5%)
Physical activity			
Vigorous activity at least once a week	2198 (30·8%)	2174 (30·8%)	680 (26·1%)
Moderate activity at least once a week	3479 (48·8%)	3445 (48·7%)	1321 (50·7%)
Inactive (no moderate or vigorous activity)	1456 (20·4%)	1445 (20·5%)	603 (23·2%)
Missing	<10 (<0·5%)	<10 (<0·5%)	..

(Table 1 continues on next page)

	ELSA (N=7136)	ELSA weighted (N=7068)	SNAC-K (N=2604)
(Continued from previous page)			
Hearing ability			
Excellent or very good	3551 (49·8)	3519 (49·8%)	..
Good	2159 (30·3)	2140 (30·3%)	..
Fair or poor	1424 (20·0%)	1407 (19·9%)	..
Missing	<10 (<0·5%)	<10 (<0·5%)	..
Additional comorbidities			
None	3824 (53·6%)	3852 (54·5%)	..
One or more	3311 (46·4%)	3214 (45·5%)	..
Missing	<10 (<0·5%)	<10 (<0·5%)	..
Marital or cohabitation status			
Unmarried and alone	1494 (20·9%)	1458 (20·6%)	1297 (49·8%)
Married or cohabiting	5642 (79·1%)	5610 (79·4%)	1304 (50·1%)
Missing	..	..	<10 (<0·5%)
Contact frequency with family and friends			
Never to every few months	3347 (46·9%)	3322 (47·0%)	312 (12·0%)
Once or twice a month	2555 (35·8%)	2519 (35·7%)	1117 (42·9%)
One to three or more times per week	907 (12·7%)	889 (12·6%)	1047 (40·2%)
Missing	327 (4·6%)	338 (4·8%)	128 (4·9%)
Social network size (continuous)			
Range	0–30	0–30	..
Mean	7 (5·3)	7 (5·3)	..
Missing	370 (5·2%)	380 (5·4%)	..
Social network size (categorical)			
None	165 (2·3%)	169 (2·4%)	37 (1·4%)
1–2 people	814 (11·4%)	811 (11·5%)	404 (15·5%)
3–6 people	2832 (39·7%)	2785 (39·4%)	1098 (42·2%)
>6 people	2955 (41·4%)	2922 (41·4%)	876 (33·6%)
Missing	370 (5·2%)	380 (5·4%)	189 (7·3%)
Positive support (higher scores indicate more positive support)			
Range	0–9	0–9	0–6
Mean	6·8 (1·6)	6·8 (1·6)	5·3 (1·4)
Missing	337 (4·7%)	347 (4·9%)	172 (6·6%)
Negative support (higher scores indicate less negative support)			
Range	0–9	0–9	..
Mean	7·1 (1·4)	7·1 (1·4)	..
Missing	346 (4·9%)	355 (5·0%)	..
Overall social support tertiles			
Lowest tertile	2218 (31·1%)	2179 (30·8%)	719 (27·6%)
Middle tertile	2235 (31·3%)	2218 (31·4%)	867 (33·3%)
Highest tertile	2133 (29·9%)	2114 (29·9%)	915 (35·1%)
Missing	550 (7·7%)	557 (7·9%)	103 (4·0%)
Verbal fluency*			
Range	0–50	0–50	1–50
Mean	20·1 (6·2)	20·2 (6·2)	21·3 (6·5)
Missing	<10 (<0·5%)	<10 (<0·5%)	<10 (<0·5%)
Rate of decline β†	–0·016 (–0·018 to –0·013)	..	–0·057 (–0·065 to –0·049)

(Table 1 continues on next page)

effect that is due to interaction, but not mediation, and the mediated interaction effect is the portion due to both interaction and mediation. PIE is the effect only due to mediation that does not involve interaction.

Associations between exposures, mediators, and outcomes, and mediation analyses are presented overall and stratified by sex, given the potential for different relationships in men and women. We completed the first sensitivity analysis in both datasets, and further sensitivity analyses in ELSA only. First, we assessed associations with depression as a binary variable in associations indicating high levels of depressive symptoms (cutoff scores 4 or above in CES-D in ELSA, and higher than 6 in the Montgomery–Åsberg Depression Rating Scale in SNAC-K) using logistic regression. Second, in ELSA, we examined associations after excluding participants with CRP levels higher than 10 mg/L, which may indicate an acute infection or serious illness. Finally, we assessed associations after survey design weights were applied in ELSA. Replication in SNAC-K was examined by qualitative comparison of effect estimates and 95% CIs.

We completed all analyses in Stata version 17.0, using the Med4way package for four-way decomposition.

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results
Baseline characteristics of eligible participants from ELSA are presented in table 1 and appendix 2 (p 2). In ELSA, of the 11 391 participants aged 50 years and older at baseline, 4155 were excluded due to missing data on social health markers, mediators, or cognitive outcomes and 100 participants were excluded due to having recorded dementia at baseline or at any intermediate timepoints (appendix 2 p 3). This resulted in a final sample of 7136 participants included in the analysis. 3962 (55·5%) were women, 6934 (97·2%) were White, and the mean baseline age was 63·8 years (SD 9·4). The median follow-up time from assessment of social health exposures to assessment of cognitive outcomes was 14·4 years (IQR 8·5–16·3). Participants included in the analysis differed on socioeconomic and health-related factors from those excluded; for instance, those excluded were more likely to have lower education, to be in the lower wealth quintile group, to have comorbidities, and to have negative health behaviours.

Before conducting mediation analyses, we examined associations between social health and cognition in ELSA (tables 2, 3). After partial adjustment, all social health markers were associated with cognition across most domains; most associations were attenuated and no longer significant after full adjustment. However, less negative support remained associated with higher verbal

fluency (β=0·02 [95% CI 0·00–0·03]) and with slower decline in immediate recall (β=0·005 [0·000–0·009]), higher contact frequency was associated with slower decline in immediate recall (β=0·014 [0·001–0·026]), and positive support was associated with slower decline in delayed recall (β=0·007 [0·002–0·012]).

Depressive symptoms were associated with all social health markers after full adjustment, except for contact frequency (appendix 2 p 5), and with lower cognitive scores and faster decline across domains (appendix 2 pp 6–7). Therefore, depressive symptoms were tested as potential mediators.

Inflammatory biomarkers were not tested as mediators due to their weak association with exposures and outcomes.

Mediation analyses were first done with cognitive outcomes assessed at a single timepoint. In fully adjusted models in ELSA, we found a total effect of network size on subsequent standardised verbal fluency of 0·01 (0·00–0·03), indicating an overall positive effect of larger network size on verbal fluency. There was also an indirect effect via depressive symptoms of 0·001 (0·000–0·001), showing the effect of network size on verbal fluency due to mediation but not interaction. The proportion mediated was small (0·04; figure 1, appendix 2 pp 8–9). We found indirect effects of positive support via depressive symptoms on verbal fluency and immediate recall of 0·002 (0·001–0·003, proportion mediated 0·14). Negative support had a total effect on verbal fluency of 0·02 (0·00–0·03), and an indirect effect via depressive symptoms of 0·002 (0·00–0·01, proportion mediated 0·10). Associations between high overall social health (relative to low or middle tertiles) and subsequent verbal fluency and immediate recall were partly mediated by depressive symptoms (PIE=0·01 [0·00–0·01], proportion mediated 0·02). Mediation of associations between network size and negative support with recall outcomes, and of marital or cohabitation status on cognition in all domains, were not observed.

We then did mediation analyses with cognitive trajectories as outcomes. We found indirect effects of positive support on change in immediate recall via depressive symptoms of 0·001 (0·000 to 0·001, proportion mediated 0·39; figure 2, appendix 2 pp 10–11), a total effect of positive support on change in delayed recall of 0·005 (0·001 to 0·009), and a controlled direct effect of positive support on change in delayed recall of 0·005 (0·001 to 0·009). There was no evidence of mediation in the association between positive support and change in delayed recall. Less negative support had a total effect on change in immediate recall of 0·006 (0·001 to 0·011), with an indirect effect via depressive symptoms of 0·001 (0·000 to 0·002, proportion mediated 0·12) that was also observed for delayed recall. Associations between high overall social health, relative to low or middle tertiles, and subsequent change in delayed recall were partly mediated by depressive

	ELSA (N=7136)	ELSA weighted (N=7068)	SNAC-K (N=2604)
(Continued from previous page)			
Immediate recall*			
Range	0–10	0–10	0–16
Mean	5·7 (1·7)	5·7 (1·7)	7·1 (2·4)
Missing	<10 (<0·5%)	<10 (<0·5%)	40 (1·5%)
Rate of decline β†	−0·028 (−0·031 to −0·026)	..	−0·057 (−0·066 to −0·047)
Delayed recall*			
Range	0–10	0–10	..
Mean	4·3 (2·0)	4·3 (2·0)	..
Missing	<10 (<0·5%)	<10 (<0·5%)	..
Rate of decline β†	−0·036 (−0·038 to −0·034)	..	..

Data are n (%), mean (SD), range, or β (95% CI). ELSA=English Longitudinal Study of Ageing. SNAC-K=Swedish National Study on Aging and Care in Kungsholmen. *Raw cognitive scores are presented for baseline descriptives. Standardised outcomes are used in the main analysis. †Rate of decline from linear mixed models.

Table 1: Baseline characteristics of ELSA and SNAC-K

symptoms (PIE=0·002 [0·000 to 0·003]; proportion mediated 0·05). We found reference interactions indicating combined effects of network size and depressive symptoms on change in immediate (−0·001 [−0·003 to −0·000]) and delayed recall (−0·002 [−0·003 to 0·000]), although no total effects were found.

Sensitivity analyses showed that social health remained associated with lower depressive symptoms as a binary variable (appendix 2 p 12), and binary depression remained associated with lower cognitive scores and faster decline for all domains in relation to cognitive change (appendix 2 pp 6–7). Similar patterns of association were observed between CRP, social health exposures, and cognitive outcomes when excluding participants with CRP levels greater than 10 mg/L (appendix 2 pp 6–7, 13). Associations between exposures, mediators, and outcomes were similar when survey design weights were applied (appendix 2 pp 14–16).

Sex-stratified associations between exposures, mediators, and outcomes in ELSA are reported in appendix 2 (p 17). In men but not in women, depressive symptoms mediated associations of positive and negative support with subsequent verbal fluency and immediate recall. Depressive symptoms also mediated associations between marital or cohabitation status and verbal fluency, and between high social health with verbal fluency and immediate recall in men (eg, negative support–verbal fluency PIE=0·01 [0·00–0·01]) but not in women (appendix 2 pp 24–25).

For women only, depressive symptoms mediated associations between negative support and delayed recall trajectories (PIE=0·002 [0·000–0·003]; appendix 2 pp 26–27). Total effects of negative support on immediate and delayed recall trajectories (0·011 [0·002–0·021]) with no mediation were found in men only. The relationships between positive support and overall social health with

	Verbal fluency*						Immediate recall*						Delayed recall*		
	ELSA Adj1	ELSA Adj2	ELSA Adj3	SNAC-K Adj1	SNAC-K Adj2	SNAC-K Adj3	ELSA Adj1	ELSA Adj2	ELSA Adj3	SNAC-K Adj1	SNAC-K Adj2	SNAC-K Adj3	ELSA Adj1	ELSA Adj2	ELSA Adj3
Married or cohabiting (reference: unmarried and alone)	0·11 (0·06 to 0·16)†	0·05 (–0·01 to 0·10)	0·02 (–0·03 to 0·06)	0·14 (0·02 to 0·26)†	0·06 (–0·06 to 0·17)	0·01 (–0·10 to 0·11)	0·09 (0·04 to 0·15)†	0·01 (–0·05 to 0·06)	0·01 (–0·04 to 0·06)	0·15 (0·03 to 0·27)†	0·10 (–0·03 to 0·22)	0·10 (–0·02 to 0·22)	0·09 (0·03 to 0·14)†	0·00 (–0·05 to 0·06)	0·00 (–0·05 to 0·05)
Contact frequency (reference: never to every few months)															
Once or twice per month	0·08 (0·03 to 0·12)†	0·05 (0·01 to 0·10)†	0·02 (–0·02 to 0·06)	0·26 (0·06 to 0·46)†	0·19 (–0·01 to 0·38)	0·12 (–0·05 to 0·29)	0·05 (0·00 to 0·10)†	0·02 (–0·03 to 0·06)	0·01 (–0·03 to 0·06)	0·13 (–0·08 to 0·34)	0·09 (–0·12 to 0·30)	0·06 (–0·14 to 0·25)	0·03 (–0·01 to 0·08)	0·01 (–0·03 to 0·06)	0·01 (–0·04 to 0·05)
Once to three or more times per week	0·00 (–0·07 to 0·07)	0·04 (–0·03 to 0·01)	0·01 (–0·05 to 0·07)	0·19 (–0·02 to 0·39)	0·13 (–0·07 to 0·34)	0·11 (–0·07 to 0·29)	–0·03 (–0·10 to 0·04)	0·03 (–0·04 to 0·09)	0·03 (–0·03 to 0·09)	0·16 (–0·06 to 0·37)	0·14 (–0·07 to 0·36)	0·13 (–0·07 to 0·33)	–0·07 (–0·13 to 0·00)	–0·02 (–0·08 to 0·05)	0·01 (–0·06 to 0·07)
Network size	0·01 (0·00 to 0·01)†	0·01 (0·00 to 0·01)†	0·00 (0·00 to 0·01)	0·07 (0·01 to 0·13)†	0·01 (–0·05 to 0·07)	–0·01 (–0·06 to 0·04)	0·01 (0·00 to 0·01)†	0·01 (0·00 to 0·01)†	0·00 (0·00 to 0·01)	0·10 (0·04 to 0·16)†	0·06 (0·00 to 0·12)	0·05 (–0·01 to 0·11)	0·01 (0·00 to 0·01)†	0·00 (0·00 to 0·01)	0·00 (0·00 to 0·01)
Positive social support	0·01 (0·00 to 0·03)	0·00 (–0·01 to 0·02)	0·00 (–0·02 to 0·01)	0·04 (–0·01 to 0·10)	0·01 (–0·05 to 0·07)	0·01 (–0·04 to 0·06)	0·02 (0·01 to 0·04)†	0·01 (0·00 to 0·03)†	0·01 (0·00 to 0·03)	0·05 (–0·02 to 0·11)	0·01 (–0·05 to 0·07)	0·01 (–0·06 to 0·07)	0·02 (0·00 to 0·03)†	0·01 (–0·01 to 0·02)	0·00 (–0·01 to 0·02)
Less negative social support	0·04 (0·02 to 0·05)†	0·02 (0·01 to 0·04)†	0·02 (0·00 to 0·03)†	..	..	..	0·03 (0·02 to 0·05)†	0·01 (0·00 to 0·03)	0·01 (–0·01 to 0·02)	..	..	..	0·04 (0·02 to 0·06)†	0·02 (0·01 to 0·04)†	0·01 (0·00 to 0·03)
Social health (reference: lowest tertile)															
Middle tertile	0·09 (0·04 to 0·14)†	0·05 (0·00 to 0·10)	0·03 (–0·02 to 0·08)	0·08 (–0·09 to 0·24)	0·03 (–0·13 to 0·20)	0·07 (–0·07 to 0·22)	0·07 (0·01 to 0·12)†	0·02 (–0·03 to 0·07)	0·02 (–0·03 to 0·07)	0·07 (–0·10 to 0·25)	0·04 (–0·13 to 0·22)	0·02 (–0·15 to 0·19)	0·10 (0·05 to 0·15)†	0·06 (0·01 to 0·11)†	0·03 (–0·02 to 0·08)
Highest tertile	0·04 (–0·01 to 0·09)	0·01 (–0·04 to 0·06)	0·01 (–0·04 to 0·05)	0·25 (0·10 to 0·41)†	0·12 (–0·05 to 0·28)	0·05 (–0·10 to 0·19)	0·06 (0·01 to 0·12)†	0·02 (–0·04 to 0·07)	0·02 (–0·03 to 0·07)	0·31 (0·15 to 0·48)†	0·22 (0·05 to 0·39)†	0·15 (–0·02 to 0·32)	0·08 (0·02 to 0·13)†	0·03 (–0·02 to 0·08)	0·02 (–0·03 to –0·07)

Data are β (95% CI). ELSA=English Longitudinal Study of Ageing (primary sample). SNAC-K=Swedish National Study on Aging and Care in Kungsholmen (replication sample). Adj1=adjustment for age and sex. Adj2=adjustment for age, sex, education, occupational class, cardiovascular disease, basic and instrumental activities of daily living, wealth quintiles (ELSA only), smoking status, alcohol intake, and physical activity. Adj3=adjustment for age, sex, education, occupational class, cardiovascular disease, basic and instrumental activities of daily living, wealth quintiles (ELSA only), smoking status, alcohol intake, physical activity, baseline depression and cognition, hearing ability, and additional comorbidities (ELSA only). *Standardised cognitive outcomes assessed in wave 3 of ELSA and 12-year follow-up of SNAC-K. †p<0·05.

Table 2: Associations between social health markers and subsequent cognition (single timepoint)

immediate recall trajectories (PIE=0·002 [0·000–0·004]) were mediated by depressive symptoms in men only.

Baseline characteristics of participants in SNAC-K (n=2604) are provided in table 1 and appendix 2 (p 2). Compared with ELSA, the SNAC-K cohort was older at baseline (72·3 years [SD 10·1] *vs* 63·8 years [9·4]), had a greater proportion of women (1604 [61·6%] *vs* 3962 [55·5%] of 7136), and had a greater proportion of participants with non-manual occupations (2087 [80·2%] *vs* 4210 [59·0%] of 7136). Associations between exposures, mediators, and outcomes in SNAC-K are reported in tables 2 and 3 and appendix 2 (pp 5–7).

The indirect effects of positive support on verbal fluency, measured at a single timepoint, via depressive symptoms observed in ELSA were replicated in SNAC-K (PIE=0·003 [95% CI 0·00–0·01]; appendix 2 pp 8–9, 31). In contrast, indirect effects of positive support on immediate recall and of network size on verbal fluency via depressive symptoms found in ELSA were not replicated in SNAC-K. In SNAC-K, there was an indirect effect of marital or cohabitation status on verbal fluency via depressive symptoms (PIE=0·02 [0·00–0·04]), which was not found in ELSA. It was not possible to examine replication of associations relating to negative support or delayed recall because these were not available in SNAC-K.

The indirect effect of positive support on change in immediate recall via depressive symptoms that was observed in ELSA was replicated in SNAC-K (PIE=0·0003 [0·000–0·001]; appendix 2 pp 10–11, 32). We also found indirect effects of positive support on verbal fluency change via depressive symptoms (PIE=0·001 [0·000–0·001]; appendix 2 pp 10–11) and of marital or cohabitation status on verbal fluency change (PIE=0·005 [0·001–0·012]), which were not found in ELSA. Mediation by depressive symptoms of associations of marital and cohabitation status, positive support, and high social health with verbal fluency (both assessed at a single timepoint and as cognitive trajectories) was stronger for women than for men in SNAC-K.

Discussion

Although positive social health markers have been posited to protect against cognitive decline, the pathways underpinning these associations are underexamined. We investigated the mediating roles of depressive symptoms and inflammation in associations between

	Verbal fluency*						Immediate recall*						Delayed recall*		
	ELSA Adj1	ELSA Adj2	ELSA Adj3	SNAC-K Adj1	SNAC-K Adj2	SNAC-K Adj3	ELSA Adj1	ELSA Adj2	ELSA Adj3	SNAC-K Adj1	SNAC-K Adj2	SNAC-K Adj3	ELSA Adj1	ELSA Adj2	ELSA Adj3
Married or cohabiting (reference: unmarried and alone)	0·000 (−0·020 to 0·020)	−0·011 (−0·031 to 0·010)	−0·012 (−0·033 to 0·008)	0·011 (−0·016 to 0·037)	−0·001 (−0·028 to 0·026)	−0·008 (−0·035 to 0·019)	0·010 (−0·005 to 0·026)	−0·004 (−0·019 to 0·012)	−0·004 (−0·019 to 0·012)	0·023 (0·006 to 0·041)†	0·015 (−0·002 to 0·033)	0·012 (−0·005 to 0·029)	0·007 (−0·011 to 0·026)	−0·005 (−0·024 to 0·014)	−0·006 (−0·025 to 0·013)
Contact frequency (reference: never to every few months)															
Once or twice per month	0·017 (−0·001 to 0·034)	0·009 (−0·008 to 0·027)	0·009 (−0·009 to 0·026)	0·041 (−0·003 to 0·086)	0·031 (−0·015 to 0·076)	0·018 (−0·026 to 0·062)	0·021 (0·009 to 0·034)†	0·014 (0·002 to 0·027)†	0·014 (0·001 to 0·026)†	0·021 (−0·008 to 0·050)	0·013 (−0·016 to 0·043)	0·005 (−0·022 to 0·033)	0·019 (−0·004 to 0·035)	0·012 (−0·003 to 0·028)	0·012 (−0·004 to 0·028)
Once to three or more times per week	−0·005 (−0·032 to 0·022)	−0·003 (−0·030 to 0·025)	−0·003 (−0·030 to 0·025)	0·039 (−0·006 to 0·085)	0·032 (−0·015 to 0·076)	0·023 (−0·022 to 0·068)	0·001 (−0·017 to 0·020)	0·003 (−0·016 to 0·022)	0·002 (−0·016 to 0·021)	0·023 (−0·007 to 0·052)	0·018 (−0·012 to 0·049)	0·014 (−0·014 to 0·042)	−0·009 (−0·032 to 0·015)	−0·008 (−0·032 to 0·015)	−0·007 (−0·031 to 0·016)
Network size	0·002 (0·000 to 0·004)†	0·001 (−0·001 to 0·003)	0·001 (−0·001 to 0·003)	0·006 (−0·007 to 0·018)	−0·004 (−0·017 to 0·009)	−0·005 (−0·018 to 0·007)	0·001 (0·000 to 0·002)	0·000 (−0·001 to 0·002)	0·000 (−0·001 to 0·002)	0·014 (0·006 to 0·022)†	0·007 (−0·001 to 0·016)	0·006 (−0·002 to 0·014)	0·001 (−0·001 to 0·002)	0·000 (−0·001 to 0·002)	0·000 (−0·001 to 0·002)
Positive social support	0·008 (0·003 to 0·013)†	0·006 (0·001 to 0·011)†	0·005 (0·000 to 0·010)	0·008 (−0·004 to 0·021)	0·003 (−0·010 to 0·016)	0·001 (−0·012 to 0·014)	0·005 (0·001 to 0·009)†	0·003 (−0·001 to 0·007)	0·002 (−0·002 to 0·006)	0·008 (0·000 to 0·016)†	0·003 (−0·006 to 0·011)	0·001 (−0·007 to 0·009)	0·009 (0·005 to 0·014)†	0·007 (0·002 to 0·012)†	0·007 (0·002 to 0·012)†
Less negative social support	0·009 (0·003 to 0·014)†	0·005 (−0·001 to 0·011)	0·004 (−0·003 to 0·010)	..	..	..	0·009 (0·005 to 0·014)†	0·006 (0·002 to 0·011)†	0·005 (0·000 to 0·009)†	..	..	..	0·008 (0·003 to 0·014)†	0·005 (0·000 to 0·011)	0·005 (−0·001 to 0·010)
Social health (reference: lowest tertile)															
Middle tertile	0·011 (−0·010 to 0·031)	0·007 (−0·014 to 0·028)	0·005 (−0·016 to 0·026)	0·006 (−0·029 to 0·041)	−0·001 (−0·038 to 0·035)	0·003 (−0·033 to 0·039)	0·017 (0·003 to 0·032)†	0·011 (−0·003 to 0·026)	0·011 (−0·004 to 0·025)	0·022 (−0·001 to 0·045)	0·014 (−0·009 to 0·038)	0·012 (−0·011 to 0·034)	0·014 (−0·004 to 0·032)	0·007 (−0·012 to 0·025)	0·004 (−0·014 to 0·022)
Highest tertile	0·018 (−0·002 to 0·038)	0·010 (−0·011 to 0·030)	0·007 (−0·014 to 0·027)	0·034 (0·000 to 0·068)†	0·011 (−0·024 to 0·047)	0·002 (−0·033 to 0·038)	0·005 (−0·009 to 0·019)	−0·002 (−0·016 to 0·013)	0·002 (−0·017 to 0·012)	0·053 (0·031 to 0·076)†	0·037 (0·014 to 0·060)†	0·027 (0·004 to 0·049)†	0·022 (0·005 to 0·040)†	0·016 (−0·002 to 0·034)	0·015 (−0·003 to 0·033)

Data are β (95% CI). ELSA=English Longitudinal Study of Ageing (primary sample). SNAC-K=Swedish National Study on Aging and Care in Kungsholmen (replication sample). Adj1=adjustment for age and sex. Adj2=adjustment for age, sex, education, occupational class, cardiovascular disease, basic and instrumental activities of daily living, wealth quintiles (ELSA only), smoking status, alcohol intake, and physical activity. Adj3=adjustment for age, sex, education, occupational class, cardiovascular disease, basic and instrumental activities of daily living, wealth quintiles (ELSA only), smoking status, alcohol intake, physical activity, baseline depression and cognition, hearing ability, and additional comorbidities (ELSA only). *Standardised cognitive outcomes. Individual predicted slopes for cognitive change between waves 3 and 9 (ELSA) and between 6-year and 12-year follow-ups (SNAC-K) extracted from mixed-effects models. Therefore, a positive coefficient indicates slower decline in cognition for those with higher levels of social health markers. †p<0·05.

Table 3: Associations between social health markers and subsequent cognitive change

social health and subsequent cognition in ELSA and examined whether findings were replicated in SNAC-K. Using causal mediation analysis, we found indirect effects via depressive symptoms of network size and of positive and negative support on subsequent verbal fluency, and of positive support on immediate recall. The mediation by depressive symptoms of the association between positive support and verbal fluency was replicated in SNAC-K, whereas the other relationships were not replicated or could not be tested. In SNAC-K, depressive symptoms mediated associations between marital or cohabitation status and verbal fluency, both measured at a single timepoint and trajectories, which was not observed in ELSA.

In ELSA, depressive symptoms also partially mediated the effects of positive and negative support on immediate recall trajectories, and of negative support on delayed recall trajectories. Although we observed total and controlled direct effects of positive support on delayed recall trajectories, we did not observe mediation, suggesting that this relationship is not underpinned by depressive symptoms. The finding of mediation by depressive symptoms of positive support on immediate recall trajectories was replicated in SNAC-K, whereas, because delayed recall and negative support variables were not available in SNAC-K, it was not possible to test for associations or mediation in relation to these variables in SNAC-K. Different relationships observed across cognitive domains and social health markers highlight the importance of examining associations individually.[24]

The proportion mediated by depressive symptoms for associations between social health and cognition at a single timepoint varied widely, from 4% to 89%, whereas the proportion mediated for associations with cognitive trajectories ranged from 12% to 64%. Mediation by depressive symptoms was observed for both men and women, with variation by social health marker and cognitive domain. In ELSA, mediation by depressive symptoms of associations between social health and cognition at a single timepoint was generally stronger in men, whereas this mediation was stronger in women in SNAC-K. These findings could reflect sex differences in the psychological effects of social relationships and the
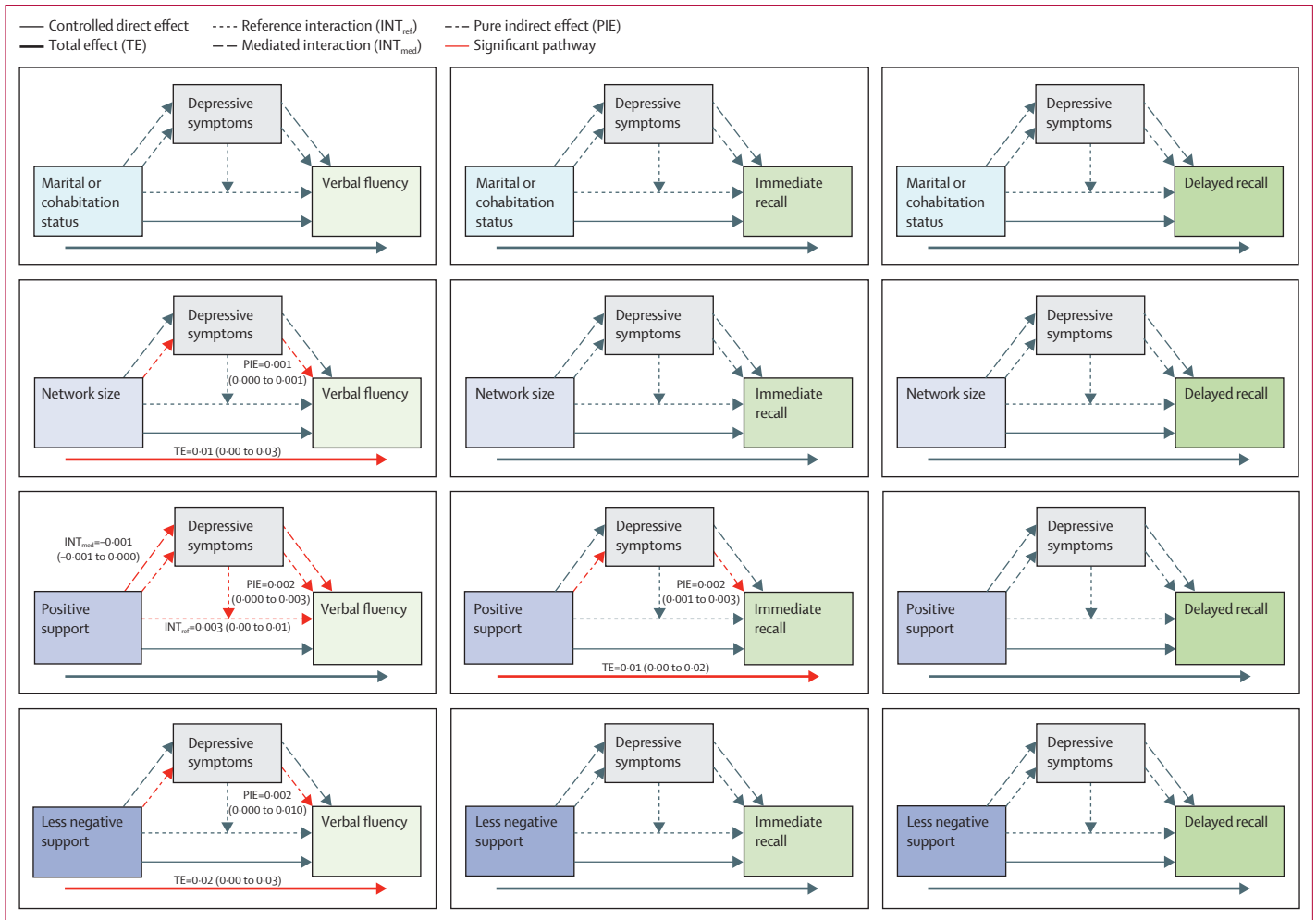
***Figure 1:* Four-way decomposition of total effects of social health on subsequent cognition (single timepoint) in ELSA—role of depressive symptoms**
ELSA=English Longitudinal Study of Ageing.

pathways through which social health markers relate to subsequent cognition. However, sex-stratified results differed between datasets, suggesting that the sociocultural context may further modulate these sex-specific pathways.

Our findings correspond with a previous study,[21] which found that depressive symptoms, but not anxiety, mediated the association between loneliness and subsequent cognitive functioning in participants from the Irish Longitudinal Study on Ageing, although the indirect effect was small relative to the direct effect. Similarly, using data from the National Social Life, Health and Aging study,[19] a longitudinal study found that depressive symptoms, among other factors such as functional ability, mediated associations between loneliness and general cognitive ability 10 years later.

Our results provide new insights into potential mechanisms linking social health with cognition, suggesting that interactional aspects of social health in particular, including more positive and less negative

social support, may help to buffer against cognitive decline partly by lowering depressive symptoms. This supports the social bonding theory, which posits that closer social connections can affect health, including cognitive outcomes, by providing psychological benefits, which then positively affect cognition.[16]

Establishing mechanisms linking social health and cognition is crucial for identifying possible targets for interventions to mitigate cognitive decline, which is a high priority for public health. Despite the modest effect sizes observed in this study, our findings could have notable implications at a population level,[38] particularly given the high prevalence of depression and cognitive impairment in the population. Given that depressive symptoms did not fully mediate associations between social support and cognition, and given the mixed findings regarding structural social health markers, further research is needed to examine other potential pathways through which social health could affect cognition.
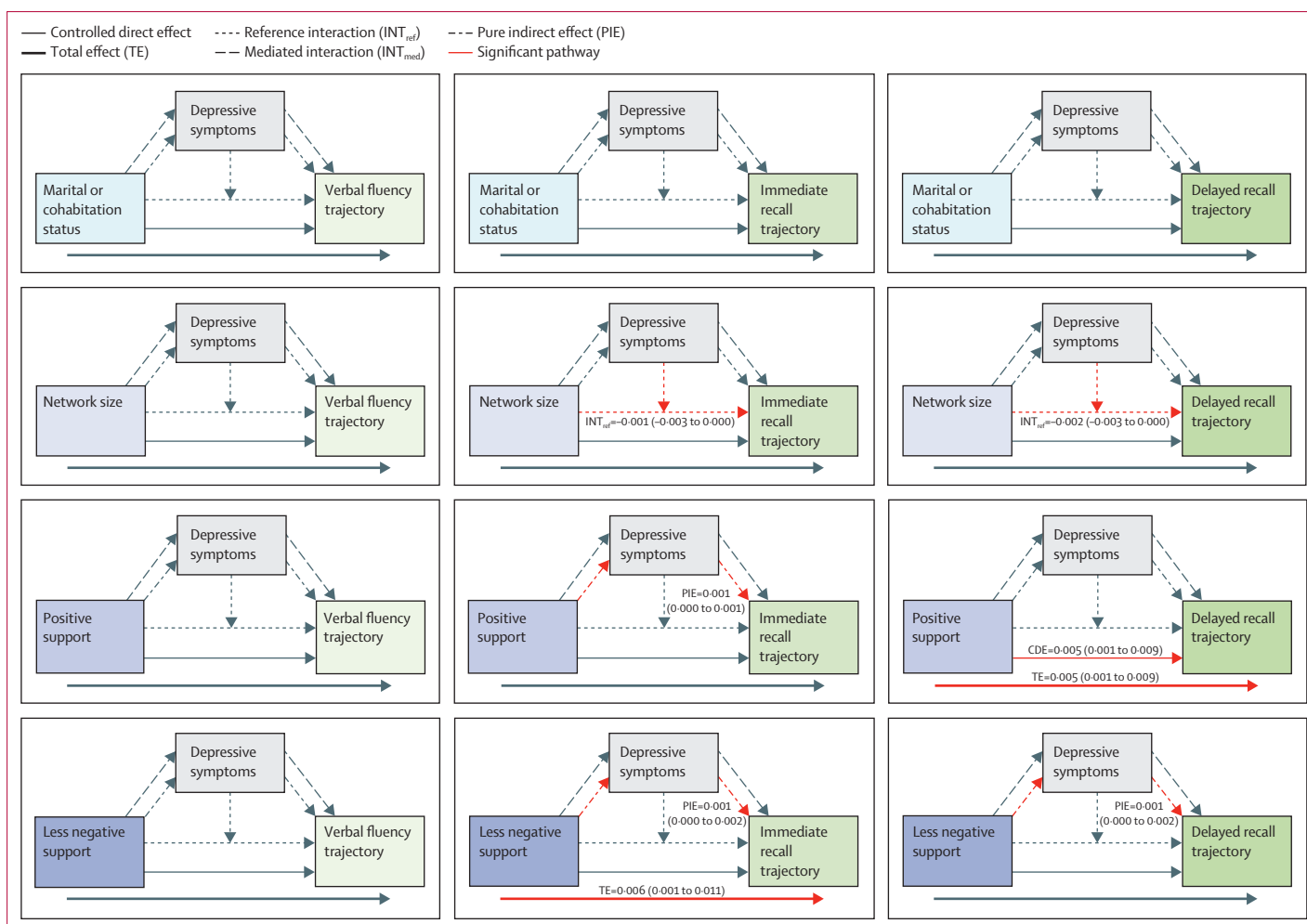
Figure 2: Four-way decomposition of total effects of social health on cognitive change in ELSA—role of depressive symptoms
ELSA=English Longitudinal Study of Ageing.

Several key findings observed in ELSA were replicated in SNAC-K, particularly in relation to mediation by depressive symptoms of associations between positive support and cognition. This replication suggests consistency in depressive symptoms as a mechanism linking social support, an interactional social health marker, and cognition across two settings, adding robustness to the role of depressive symptoms in this relationship. However, findings differed between samples regarding mediation of associations between structural social health markers (marital or cohabitation status and network size) and cognition. These discrepancies could reflect differences across settings in relationships between social health, depression symptoms, and cognition. For instance, it is possible that the perception of the value, function, and meaning ascribed to relationship structures, and the perceived adequacy of structures such as network size, are interpreted and experienced differently across countries, thereby altering downstream relationships with subsequent depression

and cognition. Findings could also be influenced by different social policies across countries, which could affect structural social health markers, such as network size, and their effect on people's mental health and subsequent cognition. The observed discrepancies suggest the importance of considering distinct sociocultural contexts when examining the mechanisms linking structural markers with cognition across different settings. However, discrepant findings could also reflect methodological differences between SNAC-K and ELSA, as described below.

We found no evidence of mediation by inflammatory biomarkers. These results align with two previous studies,[19,27] which did not find a mediating role of inflammatory biomarkers in associations between loneliness and global cognition. An additional study[28] involving older people in the USA found that CRP and fibrinogen partially mediated the association between social isolation and cognition in men only. These findings contrast with our hypothesis and diverge from conceptual

models, such as the social bonding theory and Berkman and colleagues' model,[15] which posit that physiological pathways such as inflammation are a key mechanism underpinning links between social relationships and health. Further research is needed to investigate a wider range of inflammatory biomarkers and other possible physiological mechanisms, particularly those that may be influenced by the stress-buffering qualities of social relationships, such as hypothalamic–pituitary–adrenal axis abnormalities.[16]

Strengths of the study include the use of data from two large, representative longitudinal cohorts, which allowed examination of prospective associations and replication across samples. Few previous studies have investigated mediators of longitudinal associations between social health and cognition, despite long-standing hypotheses about mechanisms including mental health and physiological markers.

We applied causal mediation analysis to overcome some of the limitations of traditional mediation approaches, such as the assumed absence of exposure–mediator interaction. We investigated a range of structural and interactional social health exposures, and multiple cognitive domains. In contrast to most previous studies in this area, we examined mediation in relation to cognitive trajectories, in addition to cognition measured at a single timepoint. ELSA and SNAC-K included rich sociodemographic and health-related data, which enabled adjustment for a range of potential confounders, and had relatively long follow-up periods, which mitigates the risk of reverse causality.

Nonetheless, we note several limitations. First, some measurements were not available in both samples. SNAC-K had a lower sensitivity measure of CRP than ELSA and did not include measures of the fibrinogen mediator, the negative support exposure, the delayed recall outcome, or the wealth quintiles covariate. Although we sought to include comparable exposure, mediator, and outcome measures across studies, it is possible that differences in results observed between ELSA and SNAC-K reflect variation in measurement between studies. Participants in SNAC-K were also older at baseline, compared to participants in ELSA, and durations between assessment of exposures, mediators, and outcomes differed between samples. Differences in participants excluded from analysis on sociodemographic and health-related characteristics, and our use of complete case analysis—despite the relatively low proportion of missing data (generally ≤5%)—could have introduced bias into our results. Further, given that we investigated multiple social health markers and cognitive outcomes, it remains possible that some of the observed differences between studies arose due to chance.

In addition, causal mediation analysis relies on assumptions about identification of and adjustment for confounders in the association between exposures, mediators, and outcomes. Although we adjusted for a range of important sociodemographic and health-related confounders, we were not able to account for other potential confounders, such as traumatic brain injury, and we cannot exclude the possibility of unmeasured confounders resulting in biased estimates. Further, we did not adjust for other potentially relevant variables, such as personality traits (eg, neuroticism), which were only measured in ELSA after social health marker, mediator, and cognitive assessments. Personality traits such as neuroticism have been found to be associated with depressive and anxiety symptoms[39] as well as with cognitive decline,[40] and future studies could consider including these traits as covariates. We also made several assumptions about the temporal order of associations between social health markers and inflammation and depressive symptoms, as set out in our directed acyclic graphs. In addition, despite relatively long follow-up periods and adjustment for baseline depression and cognition, reverse causality remains a potential issue, whereby depressive symptoms, inflammation, and changes in social health could reflect early signs, rather than causes, of cognitive decline.

Although we investigated a range of social health and cognitive domains, further research is needed to examine other outcomes, such as executive functioning, and other social health markers, including loneliness (which was not available at baseline in the present study). Although our replication analysis was a strength, we were only able to compare results qualitatively due to a lack of available methods to quantitatively assess replication across the two studies. Further examination of replication is required across a wider range of settings, including in non-European cohorts.

Our findings indicate that depressive symptoms are a pathway through which social health, particularly positive and negative aspects of social support, can influence subsequent cognitive outcomes, including cognitive decline. These insights into underlying mechanisms could contribute to the development of interventions and preventive strategies targeting social health, with potential downstream benefits for both mental health and cognitive functioning in older people.

References
1 Vernooij-Dassen M, Verspoor E, Samtani S, et al. Conceptual advancement: social health as a facilitator in the use of cognitive reserve. *medRxiv* 2022; published online June 7. https://doi.org/10.1101/2022.06.07.22276079 (preprint).
2 Santini ZI, Koyanagi A, Tyrovolas S, Mason C, Haro JM. The association between social relationships and depression: a systematic review. *J Affect Disord* 2015; 175: 53–65.
3 Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart* 2016; 102: 1009–16.
4 Holt-Lunstad J, Smith TB, Layton JB. Social relationships and mortality risk: a meta-analytic review. *PLoS Med* 2010; 7: e100316.
5 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.
6 Samtani S, Mahalingam G, Lam BCP, et al. Associations between social connections and cognition: a global collaborative individual participant data meta-analysis. *Lancet Healthy Longev* 2022; 3: e740–53.
7 Mahalingam G, Samtani S, Lam BCP, et al. Social connections and risk of incident mild cognitive impairment, dementia, and mortality in 13 longitudinal cohort studies of ageing. *Alzheimers Dement* 2023; 19: 5114–28.
8 Maddock J, Gallo F, Wolters FJ, et al. Social health and change in cognitive capability among older adults: findings from four European longitudinal studies. *Gerontology* 2023; 69: 1330–46.
9 Wang S, Molassiotis A, Guo C, Leung ISH, Leung AYM. Association between social integration and risk of dementia: a systematic review and meta-analysis of longitudinal studies. *J Am Geriatr Soc* 2023; 71: 632–45.
10 Cohen S, Gottlieb BH, Underwood LG. Social relationships and health: challenges for measurement and intervention. *Adv Mind Body Med* 2001; 17: 129–41.
11 Santini ZI, Nielsen L, Hinrichsen C, et al. Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. *Lancet Public Health* 2020; 5: e62–70.
12 Stafford J, Chung WT, Sommerlad A, Kirkbride JB, Howard R. Psychiatric disorders and risk of subsequent dementia: systematic review and meta-analysis of longitudinal studies. *Int J Geriatr Psychiatry* 2022; published online April 11. https://doi.org/10.1002/gps.5711.
13 Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *Lancet* 2020; 396: 413–46.
14 Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018; 15: 505–22.
15 Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. *Soc Sci Med* 2000; 51: 843–57.
16 Perry BL, McConnell WR, Coleman ME, Roth AR, Peng S, 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.
17 Smith KJ, Gavey S, RIddell NE, Kontari P, Victor C. The association between loneliness, social isolation and inflammation: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2020; 112: 519–41.
18 Peila R, Launer LJ. Inflammation and dementia: epidemiologic evidence. *Acta Neurol Scand* 2006; 114: 102–06.
19 Kim AJ, Beam CR, Greenberg NE, Burke SL. Health factors as potential mediators of the longitudinal effect of loneliness on general cognitive ability. *Am J Geriatr Psychiatry* 2020; 28: 1272–83.
20 Peng C, Hayman LL, Mutchler JE, Burr JA. Friendship and cognitive functioning among married and widowed Chinese older adults. *J Gerontol B Psychol Sci Soc Sci* 2022; 77: 567–76.
21 McHugh Power J, Tang J, Kenny RA, Lawlor BA, Kee F. Mediating the relationship between loneliness and cognitive function: the role of depressive and anxiety symptoms. *Aging Ment Health* 2020; 24: 1071–8.
22 Wang H, Yang C, Yao Y. Familial factors, depression and cognitive decline: a longitudinal mediation analysis based on latent growth modeling (LGM). *Int J Methods Psychiatr Res* 2022; 31: e1913.
23 Peng C, Burr JA, Han SH. Cognitive function and cognitive decline among older rural Chinese adults: the roles of social support, pension benefits, and medical insurance. *Aging Ment Health* 2023; 27: 771–79.
24 Gow AJ, Corley J, Starr JM, Deary IJ. Which social network or support factors are associated with cognitive abilities in old age? *Gerontology* 2013; 59: 454–63.
25 Marioni RE, Proust-Lima C, Amieva H, et al. Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study. *BMC Public Health* 2015; 15: 1089.
26 Casey ANS, 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.
27 Yu K, Siang Ng TK. Investigating biological pathways underpinning the longitudinal association between loneliness and cognitive impairment. *J Gerontol A Biol Sci Med Sci* 2023; 78: 1417–26.
28 Qi X, Ng TKS, Wu B. Sex differences in the mediating role of chronic inflammation on the association between social isolation and cognitive functioning among older adults in the United States. *Psychoneuroendocrinology* 2023; 149: 106023.
29 O'Connor M, Spry E, Patton G, et al. Better together: advancing life course research through multi-cohort analytic approaches. *Adv Life Course Res* 2022; 53: 100499.
30 Marseglia A, Wang HX, Rizzuto D, Fratiglioni L, Xu W. Participating in mental, social, and physical leisure activities and having a rich social network reduce the incidence of diabetes-related dementia in a cohort of Swedish older adults. *Diabetes Care* 2019; 42: 232–39.
31 Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977; 1: 385–401.
32 Nutter-Upham KE, Saykin AJ, Rabin LA, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. *Arch Clin Neuropsychol* 2008; 23: 229–41.
33 Tsoi KKF, Chan JYC, Hirai HW, et al. Recall tests are effective to detect mild cognitive impairment: a systematic review and meta-analysis of 108 diagnostic studies. *J Am Med Dir Assoc* 2017; 18: 807.e17–29.
34 Vanderweele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. *Stat Interface* 2009; 2: 457–68.

35   Valeri L, VanderWeele TJ. Mediation analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS Macro. *Psychol Methods* 2013; **18:** 137–50.

36   O'Rourke HP, MacKinnon DPM. Reasons for testing mediation in the absence of an intervention effect: a research imperative in prevention and intervention research. *J Stud Alcohol Drugs* 2018; **79:** 71–81.

37   Discacciati A, Bellavia A, Lee JJ, Mazumdar M, Valeri L. Med4way: a Stata command to investigate mediating and interactive mechanisms using the four-way effect decomposition. *Int J Epidemiol* 2019; **48:** 15–20.

38   Carey EG, Ridler I, Ford TJ, Stringaris A. Editorial perspective: when is a "small effect" actually large and impactful? *J Child Psychol Psychiatry* 2023; **64:** 1643–47.

39   Kotov R, Gamez W, Schmidt F, Watson D. Linking "big" personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychol Bull* 2010; **136:** 768–821.

40   Luchetti M, Terracciano A, Stephan Y, Sutin AR. Personality and cognitive decline in older adults: data from a longitudinal sample and meta-analysis. *J Gerontol B Psychol Sci Soc Sci* 2016; **71:** 591–601.