Archival Report

Biological Psychiatry: CNNI

Social Health Is Associated With Structural Brain Changes in Older Adults: The Rotterdam Study

Isabelle F. van der Velpen, René J.F. Melis, Marieke Perry, Myrra J.F. Vernooij-Dassen, M. Arfan Ikram, and Meike W. Vernooij

ABSTRACT

BACKGROUND: Social health markers have been linked to the development of dementia. We hypothesize that social health affects brain structure and consequently influences cognitive function. We aim to elucidate the cross-sectional and longitudinal associations between social health markers and structural brain changes in older adults in the general population.

METHODS: Social health markers (loneliness, perceived social support, marital status) were assessed in the Rotterdam Study from 2002 to 2008. Magnetic resonance imaging of the brain was performed repeatedly between 2005 and 2015 for 3737 participants to obtain brain volumetrics, cerebral small vessel disease markers, and white matter microstructural integrity as measures of brain structure. Cross-sectional associations between social health and brain structure were studied using multivariable linear and logistic regression models. Longitudinal associations between baseline social health and changes in brain structure were examined using linear mixed models and generalized estimating equations.

RESULTS: Loneliness was associated with smaller white matter volume at baseline (mean difference = −4.63 mL, 95% CI = −8.46 to −0.81). Better perceived social support was associated with larger total brain volume and gray matter volume at baseline and a less steep decrease in total brain volume over time. Better social support was associated with higher global fractional anisotropy and lower mean diffusivity at baseline. Participants who had never been married had a smaller total brain volume (mean difference = −8.27 mL, 95% CI = −13.16 to −3.39) at baseline than married peers.

CONCLUSIONS: Social health is associated with brain structure. Better perceived social support at baseline was associated with better brain structure over time.

https://doi.org/10.1016/j.bpsc.2021.01.009

With the worldwide aging population, the number of persons living with dementia continues to increase steadily (1). Because treatment options are currently limited to symptom relief without cure, calls for preventive measures have become stronger (1,2). Modifiable lifestyle factors have gained interest as targets for dementia prevention, among which the role of the social environment is increasingly recognized (2,3). The influence of the social environment on health and the competencies of the individual to participate in social interaction are captured in the concept of social health (4–6). Social health covers individuals' needs and perceptions of social life (e.g., social support, intimacy, loneliness). In addition, it includes concepts concerning structural aspects of social interaction, such as social network structure and contact frequency (7).

Social health markers have repeatedly been linked to dementia incidence (8–12), covering factors such as social support (10), marital status (11,12), and loneliness (13) and factors indicating a lack of satisfactory social relationships (8,9,14). Although social withdrawal is known to be an early symptom of cognitive impairment (15), associations of social health as a risk factor for dementia remained robust in studies accounting for reverse causation (13,16,17). A better understanding of the pathophysiology that links social health to dementia would clarify the direction of the association. Although the underlying mechanisms so far have remained unclear, brain structure is a promising candidate to be involved.

Persons with cognitive impairment and dementia have distinct changes in brain structure: markers of neurodegeneration and neuropathology are present many years before the onset of clinical symptoms (18,19). These structural brain changes, such as global and regional brain atrophy (e.g., hippocampal), cerebral small vessel disease, and white matter microstructural integrity, have been linked strongly to cognitive impairment and can be captured by imaging technology in preclinical population-based settings (20,21).

Structural brain changes are increasingly studied in the context of social health (22–25). Loneliness has been associated with smaller gray matter volumes of the amygdala, hippocampus, and entorhinal cortex (22). In another study, loneliness was associated with reduced white matter density in clusters related to social cognition (25). Social engagement modified amyloid-β burden–related cognitive decline in

ISSN: 2451-9022 Biological Psychiatry: Cognitive Neuroscience and Neuroimaging July 2022; 7:659–668 www.sobp.org/BPCNNI

cognitively healthy older adults (24). Age range across the aforementioned studies varied widely, hampering conclusions about effects on the brain in middle and older age, when adults become at risk for dementia. Moreover, studies measured brain structural markers only at a single time point, limiting conclusions on the direction of the associations. Still, their findings together demonstrate associations between social health and brain structure in multiple domains, indicating that a global investigative approach is appropriate.

We hypothesize that worse social health is associated with structural brain changes that relate to dementia, specifically global volume loss, larger burden of small vessel disease, and decreased white matter microstructural integrity. In this study, we aim to elucidate the cross-sectional and longitudinal associations between social health markers and structural brain changes in community-dwelling older adults without dementia.

METHODS AND MATERIALS

Design

This study was conducted within the Rotterdam Study, a prospective population-based cohort study in Rotterdam in The Netherlands that started in 1990 and is ongoing (26,27). Inhabitants of the neighborhood Ommoord aged ≥40 years were invited to participate and were followed up every 3 to 4 years. From 2005 onward, magnetic resonance imaging (MRI) of the brain was performed in all participants as part of the core study protocol. The Rotterdam Study has been approved by the Institutional Review Board of the Erasmus Medical Center and by the Ministry of Health, Welfare and Sports in The Netherlands. All participants gave written informed consent to participate in the study.

Population

Baseline social health markers were collected from January 2002 to November 2008. MRI data were collected from August 2005 to September 2015. Participants with data on social health markers and a baseline MRI scan of the brain with complete structural segmentation were eligible for inclusion in the study (n = 3917). Participants with prevalent dementia (n = 57) or cortical brain infarcts on MRI (n = 101) were excluded. After outlier removal (n = 22) (see Statistical Analysis), a sample of 3737 participants was available for baseline cross-sectional analysis. Participants underwent MRI scanning multiple times during follow-up until 2015, resulting in another 5196 scans with complete structural segmentation data after baseline. To limit potential reverse causation, scans of participants with a diagnosis of dementia at a follow-up MRI scan date (n = 147) were excluded from their diagnosis onward. Another 43 scans of participants with cortical brain infarcts during follow-up were excluded. After removal of 33 scans in quality control (see Statistical Analysis), 8710 scans from 3720 participants were available for longitudinal analyses, which included both baseline and follow-up scans.

Social Health Markers

Available social health markers in the Rotterdam Study were loneliness, perceived social support, and marital status. Loneliness and perceived social support reflect the perception of social life, whereas marital status is a structural aspect of social health. These markers were assessed during a home interview. Loneliness is defined as "the subjective experience of an unpleasant lack of (quality of) social relationships." Loneliness was assessed with a single-item question in the Center for Epidemiological Studies Depression scale. We dichotomized the responses into lonely (feelings of loneliness ≥1 day/week) and not lonely (feelings of loneliness <1 day/week). Perceived social support was assessed with a 5-item questionnaire modified from the Health and Lifestyle Survey. Participants could respond with agree, somewhat agree, or disagree to the questions "I know people, among my family and friends, 1) who do things that make me happy; 2) whom I can always count on; 3) who would make sure that I would get help if I would need it; 4) who give me the feeling that I am important in their lives; and 5) who accept me for who I am." Sum scores range from 0 to 10, where higher scores indicate better perceived social support. Scores were weighted to account for responses with one missing item. Scores with <4 responses were excluded. Marital status was categorized into married/has a partner, widowed/divorced, and never married.

Structural Brain Changes

Brain MRI was performed in all participants over all time points with a single 1.5T MRI unit (General Electric Healthcare, Milwaukee, WI) with an 8-channel head coil; no software or hardware changes were performed over the study period. The scan protocol included T1-weighted, proton density–weighted, fluid-attenuated inversion recovery and T2*-weighted gradient recalled echo sequences for morphological imaging. A detailed protocol of the Rotterdam Scan Study, including quality control, was described previously (28). All scans were visually inspected on scan quality and presence of artifacts. Quantification of brain volumetric measures was obtained by automated brain tissue segmentation based on a k-nearest neighbor algorithm. All segmentations were visually inspected and manually corrected when necessary. Total brain volume was defined as the sum of gray matter, normal-appearing white matter, and white matter hyperintensity (WMH) volume. Hippocampal volume was obtained by processing T1-weighted images with FreeSurfer (version 5.1) (29). Visual evaluation of all scans was performed by trained raters to assess the presence of cortical infarcts, lacunar infarcts, and cerebral microbleeds. Lacunar infarcts were defined as focal lesions of noncortical tissue ≥3 and <15 mm in size, with signal intensity on all sequences similar to cerebrospinal fluid and a hyperintense rim on fluid-attenuated inversion recovery images when supratentorial (28). Cerebral microbleeds were assessed on T2*-weighted gradient recalled echo images and defined as focal areas of very low signal intensity that were not accompanied by signal abnormality on other sequences (28). Diffusion tensor imaging was performed to obtain measures of white matter microstructural integrity. Processing was done with a standardized pipeline and combined with tissue segmentation data to obtain global mean diffusivity (MD) and fractional anisotropy (FA) in normal-appearing white matter. FA represents the degree to which water diffuses in the same direction, whereas MD represents the average amount of water

diffusion. Lower FA values and higher MD values indicate worse white matter microstructural integrity.

For volumetric markers, we used total brain volume, gray matter volume, white matter volume, and hippocampal volume. Cerebral small vessel disease markers comprised WMH volume, presence/absence of lacunar infarcts, and presence/absence of microbleeds. We used global FA and MD as markers of white matter microstructural integrity. Hippocampal volume and global FA and MD were available in a subset of the sample (baseline participants: n = 3711 and n = 2677, respectively, compared with total N = 3737; follow-up scans: n = 8633 and n = 7508, respectively, compared with total n = 8710).

Other Measurements

Covariates were selected for being a potential cause of the exposure (social health markers) or the outcome (brain structure), or both, or for being a potential proxy of unmeasured confounding (30). Age, sex, and intracranial volume were included. Participants ≥45 years at baseline were included, and no age cutoff was used. Education was included for its established relation with social health and brain structure (31,32). Baseline cognitive function was included as a cause of social health (15). Physical health factors (smoking status, alcohol use, body mass index, diet quality, physical activity, multimorbidity) and mental health factors (anxiety and depression scores) were included as potential confounders. A detailed assessment of each covariate is described in the Supplement. All covariates were measured at the same follow-up round as the social health markers, except for diet quality and physical activity, which were assessed one follow-up visit later (median time difference = 6.4 years, interquartile range [IQR] = 6.3–6.5) for a subset of participants (n = 722).

Statistical Analysis

Missing covariate data at baseline (<1.7%) was imputed with fivefold multiple imputation. WMH volume was natural log-transformed to obtain a normal distribution. Extreme outliers at baseline (n = 22) and follow-up (n = 25) were removed, as well as participants with an MRI scan before assessment of their social health markers (n = 8). Outliers were defined as >2 × IQR for total brain, gray matter, white matter, and WMH volumes and >3 × IQR for hippocampal volume and diffusion tensor imaging measures. We used multivariable linear regression models to study cross-sectional associations between social health markers and continuous outcomes. Multivariable logistic regression models were used for cross-sectional associations with dichotomous outcomes.

We performed stepwise adjustment of the models to interpret the change of the effect estimates with each addition of a set of covariates. In model 1, we adjusted for age, sex, intracranial volume, educational level, and Mini-Mental State Examination score. A quadratic term for age at baseline was added to account for a nonlinear effect of age on brain outcomes (33). Models for white matter microstructural integrity were additionally adjusted for normal-appearing white matter, WMH volume, and phase-encoding direction. In model 2, we added smoking status, alcohol consumption, body mass index, and multimorbidity score as covariates. In model 3, we additionally adjusted the model for Center for Epidemiological Studies Depression scale–weighted score and presence of anxiety. A correlation plot of social health markers and covariates is presented in Figure S1.

Next, we performed stratified analyses for sex on the cross-sectional data. To assess interaction effects, we added an interaction term to model 3, which was the product of sex with each of the social health markers.

Longitudinal associations between baseline social health markers and change in brain volumetrics and white matter microstructure were studied using linear mixed models. In the fixed effects structure, we included an interaction term for the product of follow-up time and baseline age, in addition to an interaction term for the product of follow-up time and each of the social health markers. In the random effects structure, we applied random intercepts and random linear slopes with a diagonal covariance matrix.

Longitudinal associations between baseline social health markers and change in the presence of lacunar infarcts and microbleeds were studied using generalized estimating equations. We applied the same fixed effects structure as in the linear mixed model and used a first-order autoregressive correlation matrix.

The longitudinal analyses were adjusted for all covariates that were included in model 3. R-packages nlme and geepack were used to perform the longitudinal analyses (34,35).

We performed six separate sensitivity analyses on the cross-sectional data. A detailed description of these can be found in the Supplement.

RESULTS

Baseline characteristics of the study sample are presented in Table 1. Mean age at baseline was 59.6 years (range = 45.5–92.7), and 54.7% of participants were female. Median follow-up time was 4.1 years (range = 0–13.3), during which 8710 scans were made. A total of 1872 participants (50.1%) had three MRI scans over follow-up. Feelings of loneliness for at least 1 day per week were reported by 12.0% of participants. Perceived social support scores were high, with 81.3% of participants answering positive on all social support items (median and IQR both at maximum score). Most participants were married or had a partner (80.3%), whereas 9.4% were divorced, 5.9% were widowed, and 4.4% had never been married.

Cross-sectional associations between social health markers and brain volumes are presented in Table 2. Loneliness was associated with a smaller white matter volume (mean difference = −4.63 mL, 95% CI = −8.46 to −0.81). Participants with higher social support scores had a larger total brain volume (mean difference = 1.21 mL per point increase, 95% CI = 0.11 to 2.31) and larger gray matter volume (mean difference = 0.99 mL per point increase, 95% CI = 0.01 to 1.97). Never-married participants had an 8.27 mL smaller total brain volume (95% CI = 13.16 to −3.39) than participants who were married or had a partner, most pronounced in smaller gray matter volume (mean difference = −4.75 mL, 95% CI = −9.09 to −0.40). Being widowed or divorced was not associated with any brain volumetric measures at baseline. None of the social health markers were associated with hippocampal volume.

Table 1. Baseline Characteristics of the Study Sample

Characteristics	Overall, *N* = 3737
Age, Years, Mean (SD)	59.6 (8.0)
Sex, Female	2046 (54.7%)
Loneliness	
Not lonely, <1 day during the past week	3289 (88.0%)
Lonely, ≥1 day during the past week	448 (12.0%)
Perceived Social Support, Weighted Score, Median (IQR)	10.0 (10.0–10.0)
Perceived Social Support Categories, Weighted Score	
Low, agree on 0–2 items	113 (3.0%)
Moderate, agree on 3–4 items	584 (15.6%)
High, agree on 5 items	3040 (81.3%)
Marital Status	
Married or has partner	2999 (80.3%)
Never married	165 (4.4%)
Widowed or divorced	573 (15.3%)
Education	
Primary education	306 (8.2%)
Higher vocational education or university	940 (25.2%)
MMSE Score, Median (IQR)	28.0 (27.0–29.0)
Employment Status	
Paid employment	1846 (49.4%)
Unemployed	101 (2.7%)
Homemaker	610 (16.3%)
Retired	1003 (26.8%)
Other	177 (4.8%)
Living Situation	
Independent	3613 (96.7%)
Assisted living	121 (3.2%)
Care home, nursing home, or other	3 (0.1%)
Smoking Status	
Never	1204 (32.2%)
Former	1821 (48.7%)
Current	712 (19.1%)
Alcohol Use	
None	405 (10.8%)
Moderate, 0–1 units per day	2186 (58.5%)
Heavy, >1 unit per day	1146 (30.7%)
Body Mass Index, kg/m^2, Mean (SD)	27.4 (4.6)
MET-Hours, Median (IQR)	44.5 (18.0–80.6)
Diet Quality Score, Mean (SD)	7.0 (1.9)
Multimorbidity Score	
Low, no chronic illness	3029 (81.1%)
Moderate, 1 chronic illness	591 (15.8%)
High, >1 chronic illness	117 (3.1%)
Hypertension	
No hypertension	1695 (45.4%)
Hypertension	2042 (54.6%)
Anxiety	
No anxiety	3460 (92.6%)
Anxiety	277 (7.4%)
CES-D Score, Median (IQR)	3.0 (1.0–7.0)
Depressive Symptoms	
No depressive symptoms, CES-D < 16	3426 (91.7%)
Depressive symptoms, CES-D ≥ 16	311 (8.3%)
Intracranial Volume, mL, Mean (SD)	1140 (115)
Total Brain Volume, mL, Mean (SD)	951 (98.3)
Gray Matter Volume, mL, Mean (SD)	535 (53.3)
White Matter Volume, mL, Mean (SD)	416 (57.6)
Normal-Appearing White Matter, mL, Mean (SD)	412 (58.4)
White Matter Hyperintensity Volume, mL, Median (IQR)	2.4 (1.5–4.3)
Mean Hippocampal Volume, mL, Mean (SD)	4.0 (0.5)
Cerebral Microbleeds	
Absent	3178 (85.0%)
Present	559 (15.0%)
Lacunar Infarcts	
Absent	3558 (95.2%)
Present	179 (4.8%)
Fractional Anisotropy, Mean (SD)	0.343 (0.015)
Mean Diffusivity, 10^{-3} mm^2/s, Mean (SD)	0.730 (0.021)

Values are shown as *n* (%) unless otherwise noted. For the perceived social support score categories, responses of "somewhat agree" were grouped with "disagree."

CES-D, Center for Epidemiological Studies Depression Scale; IQR, interquartile range; MET, metabolic equivalent of task; MMSE, Mini-Mental State Examination.

There were no associations between social health markers and any of the small vessel disease markers at baseline after adjustment for all covariates (Table 3). Social support was associated with higher FA and lower MD, indicating better white matter microstructural integrity (Table 3).

Figure 1 shows the differences in cross-sectional associations between social health markers and brain volumes for male and female participants. Of 1691 male participants, 8.1% reported feelings of loneliness, whereas 15.2% of female participants did (Table S1). Lonely males had smaller white matter volumes than nonlonely males, while this association was not present in female participants (p for interaction = .04). There were no further meaningful interaction effects between sex and loneliness for other brain outcomes or for the other two social health markers and brain outcomes (Figure S2).

Figure 2 shows the longitudinal associations between social health markers and brain volume during follow-up. Participants with an optimal social support score had a less steep decline in total brain volume over time than participants with a lower social support score (Figure 2A, center row) (interaction term time × social support score: mean difference of 0.13 mL per year per point increase in social support, 95% CI = 0.01 to 0.24). There were no significant associations between social health markers and changes in other brain outcomes over time (Figures S3 and S4).

None of the sensitivity analyses changed any of aforementioned results.

Table 2. Cross-Sectional Associations Between Social Health Markers and Brain Volumes

Social Health Markers	Model 1	Model 2	Model 3
	Total Brain Volume, Mean Difference (95% CI), mL		
Loneliness, Yes vs. No	−1.99 (−5.12 to 1.13)	−1.43 (−4.53 to 1.66)	−1.80 (−5.53 to 1.93)
Social Support, Per Point Increase	1.19 (0.09 to 2.29)[a]	1.19 (0.10 to 2.28)[a]	1.21 (0.11 to 2.31)[a]
Marital Status, Never Married vs. Ref	−7.92 (−12.86 to −2.98)[a]	−8.22 (−13.10 to −3.34)[a]	−8.27 (−13.16 to −3.39)[a]
Marital Status, Widowed/Divorced vs. Ref	1.31 (−1.61 to 4.23)	1.53 (−1.36 to 4.42)	1.68 (−1.25 to 4.61)
	Gray Matter Volume, Mean Difference (95% CI), mL		
Loneliness, Yes vs. No	1.35 (−1.40 to 4.10)	1.66 (−1.09 to 4.40)	2.83 (−0.48 to 6.15)
Social Support, Per Point Increase	1.01 (0.04 to 1.98)[a]	1.00 (0.03 to 1.97)[a]	0.99 (0.01 to 1.97)[a]
Marital Status, Never Married vs. Ref	−4.55 (−8.89 to −0.20)[a]	−4.76 (−9.10 to −0.41)[a]	−4.75 (−9.09 to −0.40)[a]
Marital Status, Widowed/Divorced vs. Ref	0.20 (−2.37 to 2.77)	0.50 (−2.07 to 3.08)	0.60 (−2.01 to 3.21)
	White Matter Volume, Mean Difference (95% CI), mL		
Loneliness, Yes vs. No	−3.34 (−6.52 to −0.16)[a]	−3.09 (−6.26 to 0.08)	−4.63 (−8.46 to −0.81)[a]
Social Support, Per Point Increase	0.18 (−0.94 to 1.30)	0.20 (−0.92 to 1.32)	0.21 (−0.92 to 1.35)
Marital Status, Never Married vs. Ref	−3.37 (−8.41 to 1.66)	−3.46 (−8.48 to 1.56)	−3.53 (−8.55 to 1.49)
Marital Status, Widowed/Divorced vs. Ref	1.11 (−1.87 to 4.08)	1.03 (−1.95 to 4.00)	1.08 (−1.93 to 4.09)
	Hippocampus Volume, Mean Difference (95% CI), mL		
Loneliness, Yes vs. No	−0.01 (−0.05 to 0.03)	0.00 (−0.04 to 0.03)	0.02 (−0.03 to 0.06)
Social Support, Per Point Increase	0.00 (−0.02 to 0.01)	0.00 (−0.02 to 0.01)	0.00 (−0.02 to 0.01)
Marital Status, Never Married vs. Ref	−0.01 (−0.07 to 0.05)	−0.01 (−0.07 to 0.05)	−0.01 (−0.07 to 0.05)
Marital Status, Widowed/Divorced vs. Ref	0.00 (−0.04 to 0.03)	0.00 (−0.04 to 0.03)	0.00 (−0.03 to 0.04)

Model 1: adjusted for age, age^2, sex, intracranial volume, education level, and MMSE score; Model 2: Model 1 + adjusted for smoking, alcohol consumption, BMI, and multimorbidity score; Model 3: Model 2 + adjusted for anxiety and CES-D score. Reference category for marital status is being married/having a partner.

BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; MMSE, Mini-Mental State Examination; Ref, reference category.

[a]Statistically significant results.

DISCUSSION

Participants with better perceived social support had larger total brain and gray matter volumes and better white matter microstructural integrity at baseline. They also had a less steep decline in total brain volume over time than those with suboptimal social support. Participants who were never married had smaller brain volumes at baseline than married participants. Loneliness was associated with smaller white matter volumes at baseline, which was more pronounced for male than female participants. We will next discuss each of these findings, starting with social support.

To the best of our knowledge, our study is the first to longitudinally link perceived social support and structural brain changes. Perceived social support has been associated with brain structure cross-sectionally, namely with left amygdala volume and shape in young adults. Another study showed that individuals' social network size was associated with white matter tract structural integrity and demonstrated correlations with gray matter volume in the limbic and temporal lobe regions (36). These studies align with our findings on general measures of brain structure, specifically the associations of social support with global FA and gray matter volume.

Several previously described mechanisms could explain our results. Proposed mechanisms underlying social health and dementia include mediation by mental health and lifestyle factors, stress responses, proinflammatory pathways, and cognitive reserve (13,16,37,38). Good social support generally encourages health-promoting behavior and affects psychological processes involved with mood and feelings of appraisal and control. Social support may have a stress-buffering effect in cardiovascular disease and a beneficial role in neuroendocrine and neuroimmune systems (39). Ultimately, lifestyle, cardiovascular health, and (neuro)inflammation culminate in the brain, where they affect brain structure and function (40). The cognitive reserve hypothesis links brain structure and function and states that cognitive reserve allows individuals to maintain cognitive function despite the presence of neuropathology (41). Social health may stimulate cognitive compensatory networks, driving cognitive reserve (6). Combining this hypothesis with our findings that persons with better social support have better brain structure implies that social support potentially grants individuals double protection from cognitive decline.

Lifestyle behaviors and physical and mental health may be confounders as well as potential mediators of the association between social health and brain structure. To account for the confounding effect, we chose to adjust for these covariates measured at the study baseline. The effects of social health markers on brain structure largely remained stable with adding covariates, indicating that covariates did not substantially confound or drive the effects. Formal causal mediation methods are needed to draw conclusions on which mechanisms drive our findings.

Table 3. Cross-Sectional Associations Between Social Health Markers and Cerebral Small Vessel Disease Markers and White Matter Microstructural Integrity

Social Health Markers	Model 1	Model 2	Model 3
	White Matter Hyperintensity Volume, Log, μL, Mean Difference (95% CI)		
Loneliness, Yes vs. No	0.06 (−0.01 to 0.14)	0.05 (−0.02 to 0.12)	0.03 (−0.05 to 0.12)
Social Support, Per Point Increase	−0.03 (−0.05 to 0.00)	−0.03 (−0.05 to 0.00)	−0.02 (−0.05 to 0.00)
Marital Status, Never Married vs. Ref	0.02 (−0.10 to 0.13)	0.01 (−0.10 to 0.13)	0.01 (−0.11 to 0.12)
Marital Status, Widowed/Divorced vs. Ref	0.04 (−0.03 to 0.11)	0.03 (−0.04 to 0.10)	0.02 (−0.05 to 0.09)
	Microbleeds, Presence, Odds Ratio (95% CI)		
Loneliness, Yes vs. No	1.24 (0.95 to 1.63)	1.23 (0.94 to 1.62)	1.30 (0.94 to 1.80)
Social Support, Per Point Increase	1.00 (0.91 to 1.10)	1.00 (0.91 to 1.09)	1.00 (0.91 to 1.10)
Marital Status, Never Married vs. Ref	1.23 (0.80 to 1.90)	1.26 (0.82 to 1.95)	1.26 (0.82 to 1.95)
Marital Status, Widowed/Divorced vs. Ref	1.11 (0.86 to 1.43)	1.10 (0.85 to 1.42)	1.09 (0.84 to 1.42)
	Lacunar Infarcts, Presence, Odds Ratio (95% CI)		
Loneliness, Yes vs. No	1.19 (0.76 to 1.88)	1.10 (0.70 to 1.74)	0.81 (0.47 to 1.40)
Social Support, Per Point Increase	0.98 (0.85 to 1.14)	0.98 (0.85 to 1.14)	1.01 (0.87 to 1.16)
Marital Status, Never Married vs. Ref	1.14 (0.54 to 2.44)	1.10 (0.51 to 2.36)	1.06 (0.49 to 2.29)
Marital Status, Widowed/Divorced vs. Ref	1.57 (1.05 to 2.34)[a]	1.50 (1.00 to 2.24)	1.41 (0.94 to 2.13)
	Fractional Anisotropy, Standardized Mean Difference (95% CI)		
Loneliness, Yes vs. No	−0.03 (−0.13 to 0.07)	−0.02 (−0.12 to 0.09)	0.00 (−0.13 to 0.12)
Social Support, Per Point Increase	0.05 (0.01 to 0.09)[a]	0.04 (0.00 to 0.08)[a]	0.04 (0.00 to 0.08)[a]
Marital Status, Never Married vs. Ref	0.00 (−0.16 to 0.16)	0.00 (−0.16 to 0.16)	0.00 (−0.16 to 0.16)
Marital Status, Widowed/Divorced vs. Ref	−0.06 (−0.15 to 0.04)	−0.04 (−0.14 to 0.06)	−0.03 (−0.13 to 0.07)
	Mean Diffusivity, Standardized Mean Difference (95% CI), 10^{-3} mm^2/s		
Loneliness, Yes vs. No	0.05 (−0.04 to 0.15)	0.04 (−0.05 to 0.13)	0.04 (−0.08 to 0.15)
Social Support, Per Point Increase	−0.05 (−0.09 to −0.02)[a]	−0.05 (−0.08 to −0.01)[a]	−0.05 (−0.08 to −0.01)[a]
Marital Status, Never Married vs. Ref	0.06 (−0.08 to 0.21)	0.06 (−0.08 to 0.21)	0.06 (−0.08 to 0.21)
Marital Status, Widowed/Divorced vs. Ref	0.06 (−0.03 to 0.15)	0.05 (−0.04 to 0.13)	0.04 (−0.05 to 0.13)

Model 1: adjusted for age, age^2, sex, intracranial volume, education level, and MMSE score. White matter microstructure models were additionally adjusted for normal-appearing white matter volume, white matter hyperintensity volume, and phase-encoding direction; Model 2: Model 1 + adjusted for smoking, alcohol consumption, BMI, and multimorbidity score; Model 3: Model 2 + adjusted for anxiety and CES-D score. Reference category for marital status was being married/having a partner. Standardized mean differences represent mean difference per standard deviation increase in fractional anisotropy or mean diffusivity.

BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; log, natural logarithm; MMSE, Mini-Mental State Examination; Ref, reference category.

[a]Statistically significant results.

Together, our findings show that better perceived social support is associated with better brain structure, both at baseline and over time. While volume differences of 1 mL for changes in social support are small effects on a total brain volume of 1000 mL, they align with observations that subtle changes in brain volumes and white matter microstructure indicate subclinical global brain pathology (42–44). Overall, social support may provide a protective effect on cognitive functioning through reduced microstructural brain pathology.

Marital status was associated with brain structure at baseline, with a striking difference between never-married participants and those who were married or had a partner. The difference in total brain volume between these groups was 8 mL, which compares with 2 years of brain aging, considering the brain shrinks approximately 4 mL per year in normal aging (45,46).

Marital status has been linked to cognitive impairment and dementia extensively, where being married predominantly has a protective effect (11,12,16). Overall, married people tend to be healthier than unmarried peers, potentially by the same mechanisms linking social support to health outcomes. Being married also imposes social and cognitive challenges in everyday life that might add to brain reserve (12). The brain reserve hypothesis states that individual differences in brain structure may increase tolerance to pathology and thus may provide a buffer to cognitive decline with loss of structural integrity of the brain (41). Our finding that participants who were never married have smaller brains may indicate that they have less brain reserve than married peers to withstand the damage of factors leading to cognitive decline.

We found that loneliness was associated with smaller white matter volume at baseline. Structural brain correlates of loneliness have been studied in several neuroimaging studies. A voxel-based morphometry study found smaller gray matter volumes in the amygdala and hippocampus of lonely older adults (22). Loneliness scores were inversely correlated with regional white matter density in young adults (25). We did not find similar associations with white matter microstructure, possibly owing to the macrostructural white matter effects' being more dominant in our study. Similar to social support,

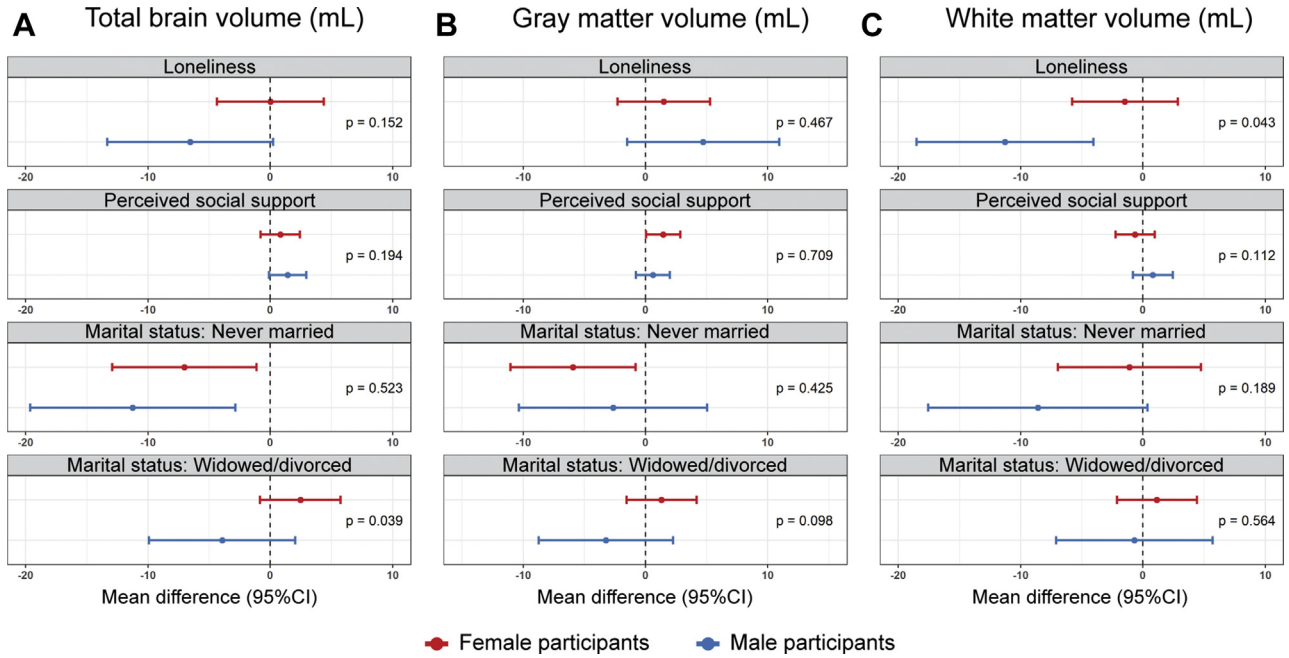

Figure 1. Associations between social health markers and brain volumes, stratified for male and female participants. Cross-sectional associations of social health markers with **(A)** total brain volume, **(B)** gray matter volume, and **(C)** white matter volume, stratified for sex. Associations for female participants are presented in red (n = 2046) and associations for male participants in blue (n = 1691). Points represent mean differences (in mL) of brain volumes per social health marker. Top row: reference category for loneliness is not lonely. Second row: perceived social support represents association per point increase in social support score. Third and fourth rows: reference category for marital status is being married/having a partner. The p values represent p value for the interaction term of the social health marker with sex. All analyses are adjusted for age, age^2, intracranial volume, education level, Mini-Mental State Examination score, smoking status, alcohol consumption, body mass index, multimorbidity score, anxiety, and Center for Epidemiological Studies Depression Scale score.

loneliness has been linked to adverse health behaviors, cardiovascular disease and mortality, depression, poor sleep, increased stress, and inflammation (40,47), all of which may affect brain structure. Further research is needed to study the causal structure underlying our findings.

We did not find a longitudinal relationship between loneliness and white matter volume. This might be a consequence of power in our study. The baseline prevalence of loneliness in our sample was 12%, which is quite low compared with similar population-based studies in older adults (20%–30%) (47–49). Loneliness prevalence is known to depend on the instrument used. A direct question as used in the Center for Epidemiological Studies Depression scale is prone to lead to underreporting because of social stigma on loneliness, as opposed to a question in which the term loneliness is not mentioned (47,50).

Finally, we found an interaction effect of sex for the association between loneliness and white matter volume. The effect for male participants was more pronounced than for female participants, even though the prevalence of loneliness in males was half the prevalence in female participants. Overall, loneliness prevalence among women is higher than among men when confronted with a direct question (51,52), whereas prevalence is equal on indirect measures (53,54). Lonely men are more likely to face social rejection by their peers than lonely women and may thus be less likely to report loneliness on a direct question (50,52). When they do, they might already experience a deeper sense of loneliness or loneliness for a longer duration, resulting in more adverse effects on brain structure. We can conclude from these findings that loneliness is associated with worse brain structure, more prominently in male than in female participants.

We did not find any associations between social health markers and hippocampal volume. This might indicate that the mechanisms through which social health markers affect the brain are less specific for Alzheimer's disease. Similarly, we did not find associations with cerebral small vessel disease markers. The brain changes we found may be more general markers of brain disease reflecting global underlying mechanisms, such as neurodegeneration. Different social health markers may manifest in different areas or temporality of neurodegeneration, reflected by the association of loneliness specifically with white matter loss, whereas marital status was associated with global brain atrophy and perceived social support with gray matter volume and white matter microstructure. Moreover, our sensitivity analyses showed that these effects were independent of the other social health markers. Social health aspects may thus differentially affect brain structure and cognitive function.

This study had several strengths. A large number of multiple time-point MRI scans allowed us to study changes in brain structure over time in a population-based setting. We studied social health aspects that reflect the perception of social life, as well as the structural aspect of marital status. Moreover, we included both a positive (perceived social support) and a

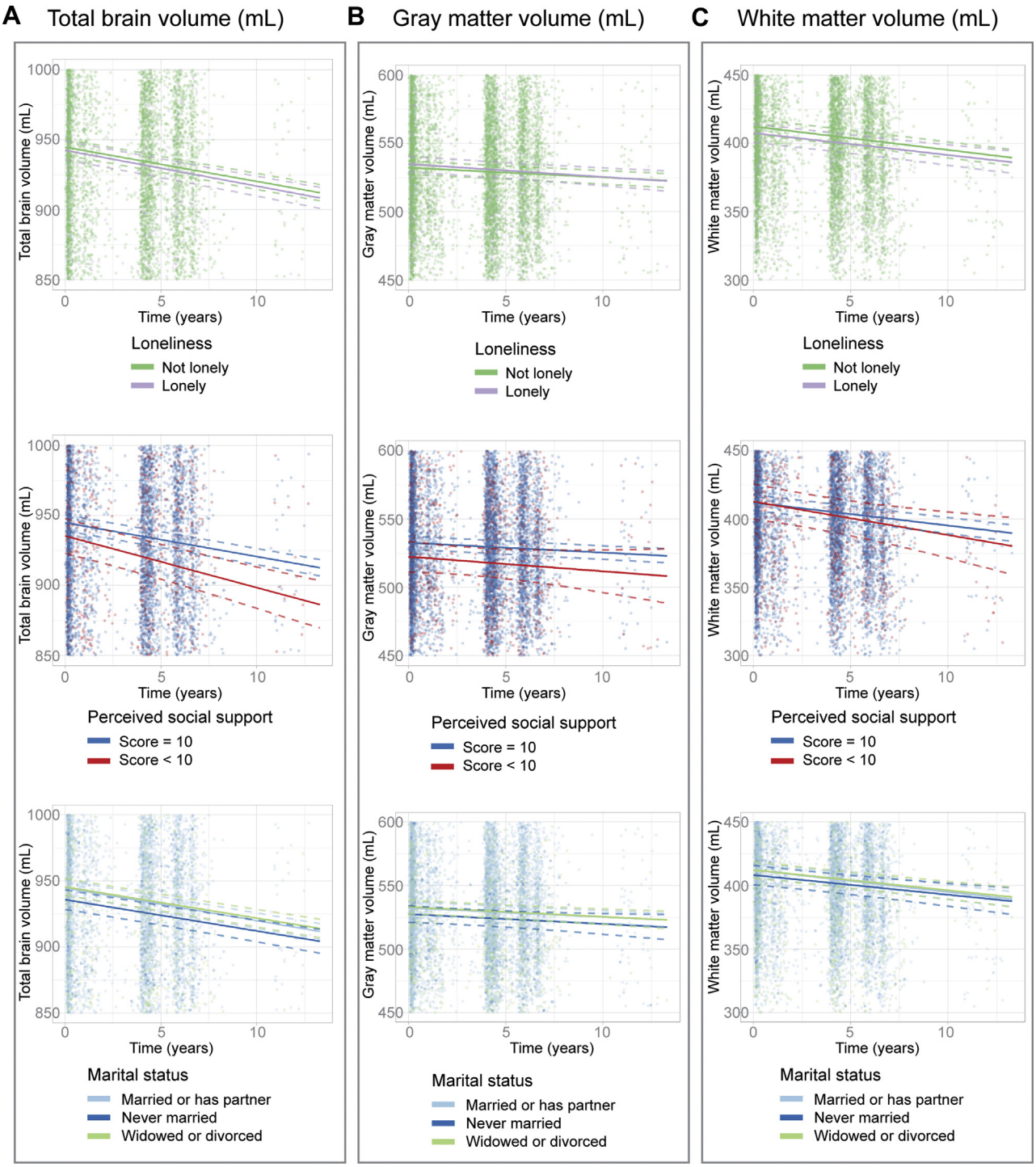

Figure 2. Longitudinal associations between social health markers and brain volumes. Change in **(A)** total brain volume, **(B)** gray matter volume, and **(C)** white matter volume per social health marker (rows) over 13 years of follow-up. Solid lines represent the marginal (group) change in volume over time, and dashed lines represent 95% CIs. Individual data points over follow-up time are presented as dots.

negative (loneliness) dimension of social health. A limitation was that the instrument for perceived social support was not formally validated. In addition, loneliness was measured with a direct question, which may have resulted in information bias that was potentially sex differential. Our study focused on brain structure in a general sense, limiting inference on specific brain regions and functions related to social health. Although we were able to adjust for a large number of confounders, the

possibility of residual confounding remains. We are not able to rule out reverse causation completely. Neurodegeneration in dementia starts many years before symptom onset. Although we excluded participants with a diagnosis of dementia from the study, our follow-up duration might be too short to rule it out fully. An important limitation to any study on social health is potential selection bias in the inclusion of participants. People with the worst social health (i.e., socially isolated, lonely, limited social support) are difficult to reach and less likely to participate in research (50). This could have attenuated the strength of our findings. Potential selection shows in the small proportion of participants with low social support or experiencing loneliness, consequently limiting our statistical power. Finally, societal factors associated with ethnicity matter when studying social factors at the individual level. Because the population of the Rotterdam Study is predominantly white, the generalizability of our results is limited.

Conclusions

In conclusion, participants with better perceived social support had better brain structure, whereas being never married and loneliness were associated with worse brain structure at baseline. Better perceived social support was associated with a less steep decline in brain volume over time. These findings support that social health is associated with brain structure and could in this way affect cognitive function. Pathways underlying the link between social health markers and dementia go beyond psychological mechanisms and even manifest in structural differences in the brain. Good social support appears to have a protective effect on brain structure. In the search for strategies to prevent dementia, improving social health would be a valuable tool to promote brain health.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was funded by a Netherlands Organization for the Health Research and Development (ZonMw) Memorabel grant (project number 733050831). The study received further funding by the EU Joint Programme - Neurodegenerative Diseases (JPND) in the HeSoCare-call for the project Social Health and Reserve in the Dementia patient journey (SHARED) (HESOCARE-329-109) funded through the Deltaplan Dementia by ZonMW (number 733051082) and Alzheimer Nederland. The Rotterdam Study is funded by the Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam.

We are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

Parts of this work were presented at the 2019 Alzheimer Europe conference; no abstract or other information was published previously.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Epidemiology (IFvdV, MAI, MWV) and Department of Radiology and Nuclear Medicine (IFvdV, MWV), Erasmus University Medical Center, Rotterdam; and the Department of Geriatric Medicine (RJFM, MP), Radboudumc Alzheimer Center; and Radboud Institute for Health Sciences (RJFM), Department of Primary and Community Care (MP), and Department of IQ Healthcare (MJFV-D), Radboud University Medical Center, Nijmegen, The Netherlands.

Address correspondence to Meike W. Vernooij, M.D., Ph.D., at m.vernooij@erasmusmc.nl.

Received Nov 23, 2020; revised and accepted Jan 26, 2021.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2021.01.009.

REFERENCES

1. Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT (2016): Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther 8:23.
2. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, *et al.* (2017): Dementia prevention, intervention, and care. Lancet 390:2673–2734.
3. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, *et al.* (2020): Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 396:413–446.
4. Vernooij-Dassen M, Jeon YH (2016): Social health and dementia: The power of human capabilities. Int Psychogeriatr 28:701–703.
5. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, *et al.* (2011): How should we define health? BMJ 343:d4163.
6. Vernooij-Dassen M, Moniz-Cook E, Verhey F, Chattat R, Woods B, Meiland F, *et al.* (2021): Bridging the divide between biomedical and psychosocial approaches in dementia research: The 2019 INTERDEM manifesto. Aging Ment Health 25:206–212.
7. Dröes RM, Chattat R, Diaz A, Gove D, Graff M, Murphy K, *et al.* (2017): Social health and dementia: A European consensus on the operationalization of the concept and directions for research and practice. Aging Ment Health 21:4–17.
8. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, Smidt N (2015): Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev 22:39–57.
9. Penninkilampi R, Casey AN, Singh MF, Brodaty H (2018): The association between social engagement, loneliness, and risk of dementia: A systematic review and meta-analysis. J Alzheimers Dis 66:1619–1633.
10. Murata C, Saito T, Saito M, Kondo K (2019): The association between social support and incident dementia: A 10-year follow-up study in Japan. Int J Environ Res Public Health 16:239.
11. Sundström A, Westerlund O, Mousavi-Nasab H, Adolfsson R, Nilsson LG (2014): The relationship between marital and parental status and the risk of dementia. Int Psychogeriatr 26:749–757.
12. Håkansson K, Rovio S, Helkala EL, Vilska AR, Winblad B, Soininen H, *et al.* (2009): Association between mid-life marital status and cognitive function in later life: Population based cohort study. BMJ 339:b2462.
13. Sutin AR, Stephan Y, Luchetti M, Terracciano A (2020): Loneliness and risk of dementia. J Gerontol *B* Psychol Sci Soc Sci 75:1414–1422.
14. Kuiper JS, Zuidersma M, Zuidema SU, Burgerhof JG, Stolk RP, Oude Voshaar RC, Smidt N (2016): Social relationships and cognitive decline: A systematic review and meta-analysis of longitudinal cohort studies. Int *J* Epidemiol 45:1169–1206.
15. Henry JD, von Hippel W, Thompson C, Pulford P, Sachdev P, Brodaty H (2012): Social behavior in mild cognitive impairment and early dementia. J Clin Exp Neuropsychol 34:806–813.
16. Rafnsson SB, Orrell M, d'Orsi E, Hogervorst E, Steptoe A (2020): Loneliness, social integration, and incident dementia over 6 years: Prospective findings from the English longitudinal study of ageing. J Gerontol *B* Psychol Sci Soc Sci 75:114–124.
17. Sörman DE, Rönnlund M, Sundström A, Adolfsson R, Nilsson LG (2015): Social relationships and risk of dementia: A population-based study. Int Psychogeriatr 27:1391–1399.
18. Frisoni GB, Fox NC, Jack CR Jr, Scheltens P, Thompson PM (2010): The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 6:67–77.

19. Tondelli M, Wilcock GK, Nichelli P, De Jager CA, Jenkinson M, Zamboni G (2012): Structural MRI changes detectable up to ten years before clinical Alzheimer's disease. Neurobiol Aging 33:825.e25–825.e36.
20. Bos D, Wolters FJ, Darweesh SKL, Vernooij MW, de Wolf F, Ikram MA, Hofman A (2018): Cerebral small vessel disease and the risk of dementia: A systematic review and meta-analysis of population-based evidence. Alzheimers Dement 14:1482–1492.
21. Vernooij MW, Ikram MA, Vrooman HA, Wielopolski PA, Krestin GP, Hofman A, *et al.* (2009): White matter microstructural integrity and cognitive function in a general elderly population. Arch Gen Psychiatry 66:545–553.
22. Düzel S, Drewelies J, Gerstorf D, Demuth I, Steinhagen-Thiessen E, Lindenberger U, Kühn S (2019): Structural brain correlates of loneliness among older adults. Sci Rep 9:13569.
23. Sin ELL, Liu HL, Lee SH, Huang CM, Wai YY, Chen YL, *et al.* (2018): The relationships between brain structural changes and perceived loneliness in older adults suffering from late-life depression. Int J Geriatr Psychiatry 33:606–612.
24. Biddle KD, d'Oleire Uquillas F, Jacobs HIL, Zide B, Kirn DR, Rentz DM, *et al.* (2019): Social engagement and amyloid-β-related cognitive decline in cognitively normal older adults. Am J Geriatr Psychiatry 27:1247–1256.
25. Nakagawa S, Takeuchi H, Taki Y, Nouchi R, Sekiguchi A, Kotozaki Y, *et al.* (2015): White matter structures associated with loneliness in young adults. Sci Rep 5:17001.
26. Ikram MA, Brusselle G, Ghanbari M, Goedegebure A, Ikram MK, Kavousi M, *et al.* (2020): Objectives, design and main findings until 2020 from the Rotterdam Study. Eur J Epidemiol 35:483–517.
27. Ikram MA, Brusselle GGO, Murad SD, van Duijn CM, Franco OH, Goedegebure A, *et al.* (2017): The Rotterdam Study: 2018 update on objectives, design and main results. Eur J Epidemiol 32:807–850.
28. Ikram MA, van der Lugt A, Niessen WJ, Koudstaal PJ, Krestin GP, Hofman A, *et al.* (2015): The Rotterdam Scan Study: Design update 2016 and main findings. Eur *J* Epidemiol 30:1299–1315.
29. Fischl B, Salat DH, van der Kouwe AJ, Makris N, Ségonne F, Quinn BT, Dale AM (2004): Sequence-independent segmentation of magnetic resonance images. Neuroimage 23(suppl 1):S69–S84.
30. VanderWeele TJ (2019): Principles of confounder selection. Eur *J* Epidemiol 34:211–219.
31. Coffey CE, Saxton JA, Ratcliff G, Bryan RN, Lucke JF (1999): Relation of education to brain size in normal aging: Implications for the reserve hypothesis. Neurology 53:189–196.
32. Huang J, Maassen van den Brink H, Groot W (2009): A meta-analysis of the effect of education on social capital. Econ Educ Rev 28:454–464.
33. Vinke EJ, de Groot M, Venkatraghavan V, Klein S, Niessen WJ, Ikram MA, Vernooij MW (2018): Trajectories of imaging markers in brain aging: The Rotterdam Study. Neurobiol Aging 71:32–40.
34. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team R Core (2021): nlme: Linear and Nonlinear Mixed Effects Models, R package version 3.1-152.
35. Højsgaard S, Halekoh U, Yan J (2005): The R package geepack for generalized estimating equations. J Stat Softw 15:1–11.
36. Noonan MP, Mars RB, Sallet J, Dunbar RIM, Fellows LK (2018): The structural and functional brain networks that support human social networks. Behav Brain Res 355:12–23.
37. Walker E, Ploubidis G, Fancourt D (2019): Social engagement and loneliness are differentially associated with neuro-immune markers in older age: Time-varying associations from the English Longitudinal Study of Ageing. Brain Behav Immun 82:224–229.
38. Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW (2015): The neuroendocrinology of social isolation. Annu Rev Psychol 66:733–767.
39. Uchino BN (2006): Social support and health: A review of physiological processes potentially underlying links to disease outcomes. J Behav Med 29:377–387.
40. Cacioppo S, Capitanio JP, Cacioppo JT (2014): Toward a neurology of loneliness. Psychol Bull 140:1464–1504.
41. Stern Y (2012): Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 11:1006–1012.
42. Zonneveld HI, Ikram MA, Hofman A, Niessen WJ, van der Lugt A, Krestin GP, *et al.* (2017): N-terminal pro-B-type natriuretic peptide and subclinical brain damage in the general population. Radiology 283:205–214.
43. Sedaghat S, Cremers LG, de Groot M, Hofman A, van der Lugt A, Niessen WJ, *et al.* (2016): Lower microstructural integrity of brain white matter is related to higher mortality. Neurology 87:927–934.
44. Ma Y, Yilmaz P, Bos D, Blacker D, Viswanathan A, Ikram MA, *et al.* (2020): Blood pressure variation and subclinical brain disease. J Am Coll Cardiol 75:2387–2399.
45. Ikram MA, Vrooman HA, Vernooij MW, van der Lijn F, Hofman A, van der Lugt A, *et al.* (2008): Brain tissue volumes in the general elderly population. The Rotterdam Scan Study. Neurobiol Aging 29:882–890.
46. Sigurdsson S, Aspelund T, Forsberg L, Fredriksson J, Kjartansson O, Oskarsdottir B, *et al.* (2012): Brain tissue volumes in the general population of the elderly: The AGES-Reykjavik study. Neuroimage 59:3862–3870.
47. Ong AD, Uchino BN, Wethington E (2016): Loneliness and health in older adults: A mini-review and synthesis. Gerontology 62:443–449.
48. Holwerda TJ, Deeg DJ, Beekman AT, van Tilburg TG, Stek ML, Jonker C, Schoevers RA (2014): Feelings of loneliness, but not social isolation, predict dementia onset: Results from the Amsterdam Study of the Elderly (AMSTEL). J Neurol Neurosurg Psychiatry 85:135–142.
49. Holwerda TJ, van Tilburg TG, Deeg DJ, Schutter N, Van R, Dekker J, *et al.* (2016): Impact of loneliness and depression on mortality: Results from the Longitudinal Ageing Study Amsterdam. Br J Psychiatry 209:127–134.
50. Shiovitz-Ezra S, Ayalon L (2012): Use of direct versus indirect approaches to measure loneliness in later life. Res Aging 34:572–591.
51. Dahlberg L, Andersson L, McKee KJ, Lennartsson C (2015): Predictors of loneliness among older women and men in Sweden: A national longitudinal study. Aging Ment Health 19:409–417.
52. Borys S, Perlman D (1985): Gender differences in loneliness. Pers Soc Psychol Bull 11:63–74.
53. Hackett RA, Hamer M, Endrighi R, Brydon L, Steptoe A (2012): Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. Psychoneuroendocrinology 37:1801–1809.
54. Steptoe A, Shankar A, Demakakos P, Wardle J (2013): Social isolation, loneliness, and all-cause mortality in older men and women. Proc Natl Acad Sci U S A 110:5797–5801.