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Sex-differences in the association of social health and marital status with blood-based immune and neurodegeneration markers in a cohort of community-dwelling older adults

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ABSTRACT

Background: The immune system has been proposed to play a role in the link between social health and all-cause dementia risk. We explored cross-sectional and longitudinal associations between social health, immune system balance and plasma neurodegeneration markers in community-dwelling older adults, and explored whether the balance between innate and adaptive immunity mediates associations between social health and both cognition and total brain volume.

Methods: Social health markers (social support, marital status, loneliness) were measured in the Rotterdam Study between 2002–2008. Immune system cell counts and balance were assessed repeatedly from 2002 to 2016 using white blood-cell-based indices and individual counts (granulocyte-to-lymphocyte ratio (GLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII)). Plasma neurodegeneration biomarkers (amyloid-β40, amyloid-β42, total tau and neurofilament light chain) were measured once from blood samples collected between 2002–2008. Global cognitive function and total brain volume (MRI) were measured at the follow-up visit between 2009–2014. We used linear mixed models to study longitudinal associations and performed causal mediation analyses.

Results: In 8374 adults (mean age 65.7, 57 % female), never married participants (n = 394) had higher GLR, PLR and SII compared to married peers at baseline and during follow-up, indicating imbalance towards innate immunity. Being never married was associated with higher plasma amyloid-β40, and being widowed or divorced with higher plasma total tau levels at baseline. Widowed or divorced males, but not females, had higher GLR, PLR and SII at baseline. Higher social support was associated with lower PLR in females, but higher PLR in males. Loneliness was not associated with any of the immune system balance ratios. Never married males had higher levels of all plasma neurodegeneration markers at baseline. Immune system balance did not mediate associations between social health and cognition or total brain volume, but does interact with marital status.

Conclusion: This study indicates that marital status is associated with blood-based immune system markers toward innate immunity and higher levels of plasma neurodegeneration markers. This is particularly evident for never married or previously married male older adults compared to married or female peers.

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1. Introduction

Social health is associated with numerous health outcomes, including dementia. Social health has been defined as a reciprocal relational concept in which well-being is defined by how an individual and their social environment relate to each other (Vernooij-Dassen et al., 2022). Social health markers such as loneliness (Holt-Lunstad et al., 2010; Kuiper et al., 2015), insufficient social support and being single have consistently been linked to higher all-cause dementia risk, while engagement in social activities appears to decrease all-cause dementia risk (Penninkilampi et al., 2018). Although mechanisms underlying these associations remain to be elucidated, the immune system is hypothesized to play a key role.

Several studies have focused on the link between social relationships and inflammatory responses, suggesting that worse social health is associated with a pro-inflammatory response (Kiecolt-Glaser et al., 2010 ; Uchino, 2006; Hackett et al., 2012 ; Steptoe et al., 2004; Walker et al., 2019; Eisenberger et al., 2017; Yang et al., 2014). To date, the immune response has predominantly been studied through pro-inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF)-α, which in turn have all been associated with all-cause dementia (Lai et al., 2017). An emerging alternative approach is to study the balance between the innate and adaptive immune system, which can easily be quantified using measures that are available in routine blood tests, such as lymphocytes, neutrophils and platelets. Neutrophils are a subset of granulocytes and are involved in clearance of pathogens and immune system homeostasis as a part of the innate immune system (Rosales, 2018). Platelets play a role in the innate immune system as detectors of endothelial injury and microbial pathogens when these invade tissues or blood, to which they are able to release inflammatory molecules (Ali et al., 2015). Lymphocytes reflect the adaptive immune system: T and B lymphocytes respond to antigens and produce antibodies in response to a pathogen after activation of the innate immune system (Iwasaki and Medzhitov, 2010).

An imbalance in these systems reflects low-grade chronic inflammation, for which white blood-cell-based inflammatory indices can serve as proxy regardless of immune activation stage of these cells: the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR) and the systemic immune-inflammation index (SII) (Fest et al., 2018).

With aging, the balance between innate and adaptive immune systems tend to shift towards a more pro-inflammatory profile (Sanada et al., 2018). Recently, these markers for the balance between innate and adaptive immune system have been linked to all-cause dementia risk in the general population, where an imbalance towards innate immunity was associated with a higher risk of all-cause dementia, independent of age (van der Willik et al., 2019). In addition, higher levels of innate immunity have been associated with plasma biomarkers of neurodegeneration, i.e. with higher plasma amyloid-β42 and amyloid-β40, lower amyloidβ-42/40 ratio, lower total-tau, and higher neurofilament light chain (NfL) (Fani et al., 2021). In the general population, plasma amyloid-β42 and NfL at baseline were associated with risk of incident all-cause dementia in older adults (de Wolf et al., 2020). Other studies have demonstrated that in cognitively healthy adults, low social engagement and widowhood were associated with accelerated cognitive decline related to neocortical amyloid-β accumulation (Biddle et al., 2019; Biddle et al., 2020), and that loneliness was associated with regional tau pathology (d'Oleire Uquillas et al., 2018). Thus far, the relation between social health and plasma markers of neurodegeneration has not been studied.

Plasma markers of immunity and neurodegeneration both provide tools to study subclinical disease processes in healthy older adults prior to the clinical onset of all-cause dementia. The availability of plasma neurodegeneration biomarkers has enabled research on subclinical disease without the need for a lumbar puncture to obtain cerebrospinal fluid levels of neurodegeneration markers or a PET-CT to establish tissue neurodegeneration depositions in the brain. With additional magnetic resonance imaging (MRI) data of the brain and cognitive assessments, we can determine whether these immunity markers mediate relationships between social health and brain health. In this study, we aimed to explore associations between social health, immune system balance and neurodegeneration in community-dwelling older adults using a three-step approach: first, we described cross-sectional and longitudinal associations between social health and blood-based immune system cell counts and their relative balance; second, we determined cross-sectional associations between social health and plasma neurodegeneration markers; and third, we performed a causal mediation analysis of immune system balance for associations between social health and both cognition and total brain volume.

2. Methods

2.1. Study design and population

This study was carried out within the Rotterdam Study, a prospective population-based cohort study of middle-aged and older inhabitants from Ommoord (a neighborhood in Rotterdam), the Netherlands. The study started in 1990 and is still ongoing. Participants aged ≥ 40 years are invited to participate and followed-up in person every 3–4 years (Ikram et al., 2024 Feb). A detailed protocol of the Rotterdam Study design and recent updates has been published elsewhere (Ikram et al., 2024 Feb). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272–159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; https://apps.who.int/trialsearch/) under shared catalogue number NL6645 / NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

A flowchart of the study population is presented in Supplemental Fig. 1. All participants with complete data on social health markers and immune system balance were included. Social health markers were collected at baseline, from January 2002 to November 2008, and were complete for 9721 participants. Blood-based immune ratios to reflect immune system balance were collected repeatedly during two to three follow-up rounds from April 2002 to May 2016. At baseline, 8519 participants had complete data on both social health markers and immune system balance. Participants with prevalent all-cause dementia (N = 48) or insufficient information for a dementia diagnosis (N = 96) at baseline were excluded from the sample. One participant was removed from the sample because of outlying white blood cell counts during follow-up. This resulted in a baseline sample of 8374 participants, with a total of 25,122 measurements of immune system balance during follow-up, including baseline measurements. Plasma neurodegeneration biomarkers were available in a subset of participants (N = 4430) and were collected at baseline from April 2002 to December 2008. Biomarker samples of insufficient quality were removed (N = 331) (quality control has been described elsewhere (de Wolf et al., 2020; Ikram et al., 2024 Feb), resulting in a baseline study sample of 4099 participants with complete information on social health markers and plasma neurodegeneration biomarkers. Causal mediation analyses were performed in a subset of overall study sample of participants with information on cognitive function (N = 4516) or total brain volume on MRI (N = 3600, after removal of 233 scans of insufficient quality and 144 scans with cortical infarcts) during the first follow-up visit after baseline (February 2009 to July 2014).

2.2. Social health markers

Loneliness, marital status and perceived social support were collected as markers of social health and were assessed during a home interview. Loneliness was measured on the Center for Epidemiological Studies Depression scale (CES-D) with a single-item direct question (Radloff, 1977). Responses were dichotomized into lonely (feelings of loneliness $\geq$ 1 day/week) and not lonely (feelings of loneliness $<$ 1 day/week). Marital status was categorized as "married/has a current partner", "widowed/divorced" or "never married". Perceived social support was measured using a 5-item questionnaire adapted from the Health and Lifestyle Survey (Cox et al., 1987). Participants were asked whether they agreed, somewhat agreed or disagreed to the following items: "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; 5) who accept me for who I am." Reponses for each item were summed, resulting in a score ranging from 0 to 10, with higher scores indicating better perceived social support (For scoring, see Supplemental Table 1). Scores with more than one missing item were excluded. To account for responses with only one missing item, the remaining scores were weighted. Cronbach's alpha for the weighted perceived social support score was 0.74 (95 %CI 0.73–0.74).

2.3. Blood-based immune markers

Differential blood counts were assessed directly after fasting venous blood draw using the COULTER AcT diff2 Hematology Analyzer (Beckman Coulter, San Diego, CA, USA) or the Sysmex XS-800 Hematology analyzer (Sysmex, Norderstedt, Germany) (for the latest follow-up visit only). Flow cytometry was not attainable in this research setting. Counts included lymphocytes, granulocytes, leucocytes, monocytes and platelets in 10^9/L. Subsets of lymphocytes (B cells, T cells, CD4 T cells, CD8 T cells) were not differentiated. Since neutrophil counts were not available in our study and granulocytes are the most abundant subtype of neutrophils, we used granulocyte counts as a proxy measure for neutrophil counts (Fest et al., 2018). The granulocyte-to-lymphocyte (GLR) ratio was calculated as the granulocyte count divided by lymphocyte count. The platelet-to-lymphocyte ratio (PLR) was calculated as the platelet count divided by the lymphocyte count. The systemic immune-inflammation index (SII) was defined as the GLR times the platelet count. Higher ratios indicate an imbalance towards innate immunity, whereas lower ratios indicate imbalance towards adaptive immunity.

2.4. Plasma markers of neurodegeneration, cognition and brain volume

Measurements of plasma neurodegeneration markers were performed in a subset of the Rotterdam Study. Blood was sampled in EDTA-treated containers and centrifuged. Next, plasma was aliquoted and frozen at − 80 °C following standard procedures. The Simoa Human Neurology 3-Plex A assay (N3PA) was used to measure plasma amyloid-β40, amyloid-β42 and total tau concentrations (Chang et al., 2017). The NF-light advantage kit was used to measure plasma levels of NfL (Rohrer et al., 2016). All measurements were performed at Quanterix (Lexington, MA, USA) on a single molecule array (Simoa) HD-1 analyzer platform (Rissin et al., 2011). Samples were tested in duplicate and two quality control samples were run for each analyte on each plate. Further quality control criteria have been described in detail elsewhere (de Wolf et al., 2020). General cognitive function was assessed using the g-factor, which represents the first unrotated component of a principal component analysis (explained variance: 49.2 %) including the Stroop Interference test, delayed recall score of the 15-Word Verbal Learning Test, Letter-Digit Substitution Test, Purdue Pegboard Test, and Word Fluency Test (Hoogendam et al., 2014 Feb).

Total brain volume was measured through brain magnetic resonance imaging (MRI). All eligible participants in the Rotterdam Study are invited for a brain MRI during follow-up. Brain MRI was performed with a single 1.5 T MRI unit (General Electric Healthcare, Milwaukee, USA) with an 8-channel head coil. A detailed description of the Rotterdam Study scan protocol, including quality control, can be found elsewhere (Ikram et al., 2015). All scans were visually inspected on scan quality. Automated brain tissue segmentation was based on a k-nearest neighbor algorithm on T1-weighted, proton density-weighted and fluid attenuated inversion recovery (FLAIR) images (Vrooman et al., 2007). Total brain volume was defined as the sum of gray matter volume, normal-appearing white matter volume and white matter hyperintensity volume. Tissue segmentations were visually inspected and manually corrected if needed. To keep the number of statistical comparisons as low as possible, we did not include other brain regions of interests here.

2.5. Other measurements

All covariables were assessed at baseline. Data collection for covariables is described in the Supplemental Methods. Covariables were selected based on their potential role as confounders in the associations between social health and immunity, or social health and neurodegeneration markers. We defined confounders as potential cause of the exposure (social health), a potential cause of the outcome (immunity or neurodegeneration markers), or of both (VanderWeele, 2019). A directed acyclic graph of the proposed causal structure is presented in Supplemental Fig. 2.

2.6. Statistical analyses

Missingness in the overall study sample was $<$ 3.0 % for all covariates, except for diabetes mellitus type 2 diagnosis (23.6 %). Missing data were imputed with fivefold multiple imputation. The distribution of covariates in the population before and after imputation was comparable (for DM type 2 prevalence was 9.8 % pre-imputation and 13.2 % post-imputation). Immune cell counts, ratios and plasma neurodegeneration markers were natural log-transformed to obtain a normal distribution. Monocyte count was square root-transformed since natural log-transformation introduced infinite values. Alpha for statistical tests was set at 0.05. Multivariable linear regression models were used to study cross-sectional associations between social health markers and continuous outcomes (mutually adjusted white blood cell counts, immune system balance and plasma neurodegeneration markers). Monocyte counts were not mutually adjusted since they were not part of immune system balance ratios. We performed stepwise adjustment of the models to observe the change of effect estimates after addition of each set of covariates. In model 1, we adjusted for age, sex, cohort (assay batch) and education. In model 2, we additionally adjusted for smoking status, alcohol consumption, BMI, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus type 2, stroke, coronary heart disease and *APOE-ε4* carrier status. In model 3, we added MMSE score, depressive symptoms score, and presence of anxiety disorders. Model 1 to 3 were applied on both immune system balance outcomes and plasma neurodegeneration marker outcomes. For immune system balance, a final model 4 was applied, were we further adjusted for medication use (systemic corticosteroids, antineoplastic agents, immunosuppressants or anti-inflammatory and antirheumatic products) and lymphocyte count. For the amyloid-β42/40 ratio, we mutually adjusted amyloid-β42 and amyloid-β40 in separate models (Supplementary Table 2).

We stratified the fully adjusted models for all immune system balance and plasma neurodegeneration markers on sex. We assessed additive interaction by adding an interaction term to the final models (model 3 for plasma neurodegeneration markers, model 4 for immune ratios), which was the product of sex with each social health marker. For plasma neurodegeneration markers, models were also stratified on *APOE-ε4* carrier status. Additive interaction was assessed by a product term consisting of *APOE-ε4* carrier status and each of the social health

markers.

We performed two sensitivity analyses on the cross-sectional models. First, we repeated the analyses after excluding participants with clinically relevant depressive symptoms at baseline (N = 867), because of the potential of clinically relevant depressive symptoms acting as a substantial confounder of the association between social health and the immune system. Second, we mutually adjusted the fully adjusted models for all social health markers.

Next, we studied longitudinal associations between baseline social health markers and change in immune system balance over follow-up. Follow-up time in years was calculated as the difference between the interview date and the date of center visit with blood draw at follow-up. We used linear mixed models with an unstructured covariance matrix. In the fixed effects structure, we included interaction terms for the product of follow-up time with both baseline age and each social health marker. All covariates from cross-sectional model 4 were included in the fixed effects structure as their baseline values. R-package *nlme* was used to perform the longitudinal analyses (Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC. nlme: Linear and Nonlinear Mixed Effects Models., 2020).

To explore whether associations between social health and both cognition and total brain volume are mediated by immune system balance, we performed a causal mediation analysis. The exposure (social health) and mediator (immune system balance) were measured at baseline, the outcomes (g-factor and total brain volume) were measured at the first follow-up visit after baseline. Previous research from our group has already reported on associations between social health markers, cognitive function and brain structure using these same exposures and outcomes (Freak-Poli et al., 2022; van der Velpen et al., 2022). Since plasma neurodegeneration markers were only available at baseline, we did not use these markers as outcomes in the mediation analysis. We applied two different approaches to deal with confounding in the associations between social health markers (exposure), immune system balance (mediator) and g-factor or total brain volumes (outcomes). First, we performed a regression-based approach only including covariables that affect determinant, mediator and outcomes, where the confounder theoretically precedes the exposure and mediator-outcome confounders are not affected by the exposure (age, sex, cohort, education, *APOE-ε4* carrier status and medication). All models were additionally adjusted for lymphocyte count. Total brain volume models were additionally adjusted for intracranial volume. All confounders were assessed at study baseline. Second, we applied a model to additionally deal with mediator-outcome confounders that are potentially affected by the exposure (smoking status, alcohol consumption, BMI, systolic blood pressure, total cholesterol, HDL cholesterol, diabetes mellitus type 2, stroke, coronary heart disease, MMSE score, depressive symptoms score, presence of anxiety disorders). Since a regular regression-based approach is not appropriate to estimate the final CMA model that also involved mediator-outcome confounders that are potentially affected by the exposure, we applied the *g*-formula approach, in which causal effects are estimated through direct counterfactual imputation estimation (1000 bootstraps). Causal mediation analyses were performed using R-package *CMAverse* (Shi et al., 2021). Directed acyclic graphs for both approaches are presented in Supplementary Fig. 2.

3. Results

Mean age was 65.7 ± 10.3 years (57.2 % female) in the overall sample (N = 8375) (Table 1). Participants in the plasma neurodegeneration subset (n = 4099) were slightly older (71.5 ± 7.3 years, 57.0 % female). Comparing the overall sample with the plasma neurodegeneration subset, loneliness prevalence was lower in the overall sample (14.9 % versus 15.9 %), the proportion of married participants was higher (71.7 % versus 67.9 %), and the perceived social support was comparable to the neurodegeneration markers subset (median 10.0, the maximum score). Sample characteristics for male and female participants separately are presented in Supplementary Table 3. Median

Table 1
Baseline characteristics.

	Overall(N = 8375)	**Plasma Neurodegeneration subset (N = 4099)**
Age (years), Mean (SD)	65.7 (10.3)	71.5 (7.3)
Sex (female), N (%)	4790 (57.2 %)	2337 (57.0 %)
Cohort, N (%)		
RS-I	2822 (33.7 %)	2301 (56.1 %)
RS-II	2120 (25.3 %)	1798 (43.9 %)
RS-III	3433 (41.0 %)	0 (0 %)
Loneliness, N (%)	1250 (14.9 %)	650 (15.9 %)
Perceived social support, weighted score, Median [Q1 − Q3]	10.0 [10.0–10.0]	10.0 [9.00–10.0]
Perceived social support categories, weighted score, N (%)		
Low (agree on 0–2 items)	422 (5.0 %)	264 (6.4 %)
Moderate (agree on 3–4 items)	1654 (19.7 %)	1001 (24.4 %)
High (agree on 5 items)	6299 (75.2 %)	2834 (69.1 %)
Marital status, N (%)		
Married or has partner	6003 (71.7 %)	2783 (67.9 %)
Never married	394 (4.7 %)	199 (4.9 %)
Widowed or divorced	1978 (23.6 %)	1117 (27.3 %)
Education, N (%)		
Primary education	903 (10.8 %)	432 (10.5 %)
Lower/intermediate general education or lower vocational education	3372 (40.3 %)	1776 (43.3 %)
Intermediate vocational education or higher general education	2427 (29.0 %)	1245 (30.4 %)
Higher vocational education or university	1598 (19.1 %)	584 (14.2 %)
MMSE score, Median [Q1 − Q3]	28.0 [27.0–29.0]	28.0 [27.0–29.0]
CES-D score, Median [Q1 − Q3]	3.0 [1.0–8.0]	3.0 [1.0–8.0]
Depression (CES-D ≥ 16), N (%)	867 (10.4 %)	422 (10.3 %)
Anxiety disorder (yes), N (%)	666 (8.0 %)	321 (7.8 %)
Smoking status, N (%)		
Never	2664 (31.8 %)	1266 (30.9 %)
Former	4271 (51.0 %)	2267 (55.3 %)
Current	1438 (17.2 %)	565 (13.8 %)
Alcohol use, N (%)		
None	1204 (14.4 %)	679 (16.6 %)
Moderate (0–1 units per day)	4277 (51.1 %)	1701 (41.5 %)
Heavy (>1 unit per day)	2885 (34.4 %)	1718 (41.9 %)
Body mass index (kg/m^2), Mean (SD)	27.7 (4.3)	27.6 (4.1)
Systolic blood pressure (mmHg), Mean (SD)	142 (21.9)	149 (20.8)
Total cholesterol (mmol/L), Mean (SD)	5.6 (1.0)	5.6 (1.0)
HDL cholesterol (mmol/L), Mean (SD)	1.4 (0.4)	1.5 (0.4)
History of Diabetes mellitus type 2, N (%)	822 (9.8 %)	439 (10.7 %)
History of coronary heart disease, N (%)	599 (7.2 %)	381 (9.3 %)
History of stroke, N (%)	299 (3.6 %)	170 (4.1 %)
***APOE*-ε4 carriership**, N (%)		

(*continued on next page*)

Table 1 (*continued*)

	Overall(N = 8375)	Plasma Neurodegeneration subset (N = 4099)
Noncarrier	6097 (72.8 %)	3035 (74.0 %)
Heterozygote	2105 (25.1 %)	994 (24.2 %)
Homozygote	173 (2.1 %)	70 (1.7 %)
Systemic corticosteroids (yes), N (%)	108 (1.3 %)	69 (1.7 %)
Antineoplastic agents (yes), N (%)	33 (0.4 %)	23 (0.6 %)
Immunomodulating agents (yes), N (%)	2 (0.0 %)	0 (0 %)
Immunosuppressive agents (yes), N (%)	45 (0.5 %)	7 (0.2 %)
Anti-inflammatory and antirheumatic products (yes), N (%)	1071 (12.8 %)	476 (11.6 %)
Immune system biomarkers		
Granulocyte-to-lymphocyte ratio, Mean (SD)	1.9 (0.8)	2.0 (0.9)
Platelet-to-lymphocyte ratio, Mean (SD)	128 (46.7)	129 (49.3)
Systemic immune-inflammation index, Mean (SD)	512 (273)	517 (283)
Lymphocyte count (*10^3/microL), Mean (SD)	2.3 (1.2)	2.2 (1.4)
Granulocyte count (*10^3/microL), Mean (SD)	4.0 (1.4)	4.0 (1.4)
Platelet count (*10^3/microL), Mean (SD)	269 (66.8)	258 (65.2)
Plasma neurodegeneration biomarkers		
Total-tau (pg/mL), Mean (SD)		2.6 (2.3)
Neurofilament light chain (pg/mL), Mean (SD)		15.4 (11.4)
Amyloid-β40 (pg/mL), Mean (SD)		264 (54.2)
Amyloid-β42 (pg/mL), Mean (SD)		10.6 (3.0)
Amyloid-β42/40 ratio, Mean (SD)		0.04 (0.01)

follow-up time was 6.5 years (range: 0–14.2 years). In total, 4034 participants (48.2 %) had two immunity marker measurements over follow-up, whereas 22.7 % had three follow-up measurements.

3.1. Immune system balance

Cross-sectional associations between social health markers and white blood cell counts are presented in Table 2. Being never or previously married was associated with higher granulocyte counts, higher monocyte counts and lower lymphocyte counts. Being widowed/divorced was associated with higher granulocyte counts and higher monocyte counts. Better perceived social support was associated with higher lymphocyte counts. Cross-sectional associations between social health markers and immune system balance ratios are presented in Table 3. Compared to being married/having a partner, being never married was associated with higher ln(GLR) in the fully adjusted model (mean difference: 0.052 (95 % confidence interval (CI) 0.017; 0.086), p = 0.003), as well as with higher ln(PLR) (mean difference: 0.036 (95 %CI 0.007; 0.065), p = 0.014) and higher ln(SII) (mean difference: 0.072 (95 %CI 0.027; 0.117), p = 0.002). Being widowed/divorced was associated with a higher ln(GLR) only in model 4, and with higher ln(SII). Higher perceived social support was associated with lower ln(GLR) in model 1 and 2, but not in model 3 (mean difference per point increase in social support score: −0.007 (95 %CI −0.013; 0.000), p = 0.062), and after adjusting for medication and lymphocyte count. Higher perceived social support was associated with lower ln(SII) only in model 1 and 2. Loneliness was not associated with any of the immune system balance ratios at baseline. Sex-stratified associations are presented in Fig. 1. For male participants, being widowed/divorced was associated with higher

Table 2
Associations between social health markers and immune system cell counts.

	Ln(Granulocyte count), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	**0.027 (0.008; 0.046)**	0.012 (−0.006; 0.030)	0.002 (−0.019; 0.023)	0.003 (−0.018; 0.024)
Marital status, never married vs. ref.	**0.037 (0.005; 0.069)**	**0.031 (0.001; 0.061)**	**0.030 (0.000; 0.060)**	0.028 (−0.002; 0.058)
Marital status, widowed/ divorced vs. ref.	**0.039 (0.022; 0.056)**	**0.023 (0.007; 0.039)**	**0.021 (0.005; 0.037)**	**0.020 (0.003; 0.036)**
Social support, per point increase	**−0.008 (−0.013; −0.002)**	−0.004 (−0.009; 0.001)	−0.003 (−0.008; 0.003)	−0.002 (−0.008; 0.003)
	Ln(Platelet count), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	0.003 (−0.011; 0.017)	0.004 (−0.010; 0.018)	−0.003 (−0.020; 0.014)	−0.003 (−0.020; 0.014)
Marital status, never married vs. ref.	0.017 (−0.007; 0.041)	0.014 (−0.010; 0.037)	0.013 (−0.011; 0.037)	0.013 (−0.011; 0.037)
Marital status, widowed/ divorced vs. ref.	0.012 (0.000; 0.025)	0.012 (−0.001; 0.024)	0.010 (−0.002; 0.023)	0.011 (−0.002; 0.024)
Social support, per point increase	0.002 (−0.002; 0.006)	0.001 (−0.003; 0.006)	0.002 (−0.002; 0.006)	0.002 (−0.002; 0.006)
	Ln(Lymphocyte count), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	0.009 (−0.009; 0.027)	0.002 (−0.016; 0.020)	0.021 (0.001; 0.042)	0.020 (−0.001; 0.041)
Marital status, never married vs. ref.	**−0.040 (−0.070; −0.009)**	**−0.040 (−0.070; −0.010)**	**−0.039 (−0.069; −0.009)**	**−0.039 (−0.068; −0.009)**
Marital status, widowed/ divorced vs. ref.	**0.019 (0.003; 0.035)**	0.010 (−0.006; 0.026)	0.013 (−0.003; 0.029)	0.013 (−0.004; 0.029)
Social support, per point increase	**0.006 (0.001; 0.011)**	**0.006 (0.001; 0.012)**	**0.005 (0.000; 0.010)**	**0.005 (0.000; 0.011)**
	Sqrt(Monocyte count), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	0.004 (−0.005; 0.012)	0.000 (−0.009; 0.009)	0.005 (−0.006; 0.015)	0.004 (−0.006; 0.015)
Marital status, never married vs. ref.	**0.016 (0.001; 0.031)**	0.015 (0.000; 0.029)	**0.015 (0.000; 0.030)**	**0.015 (0.000; 0.030)**
Marital status, widowed/ divorced vs. ref.	**0.011 (0.003; 0.019)**	0.008 (0.000; 0.016)	**0.009 (0.001; 0.017)**	**0.009 (0.001; 0.017)**
Social support, per point increase	−0.002 (−0.004; 0.001)	−0.001 (−0.004; 0.001)	−0.002 (−0.004; 0.001)	−0.002 (−0.004; 0.001)

Marital status reference (ref): married/current partner. Statistically significant results at p < 0.05 in bold. CI: confidence interval. Monocyte counts were not mutually adjusted. Model 1: Age, sex, education, assay batch number, mutually adjusted for immune system cell counts (except monocytes).
Model 2: model 1 + smoking, alcohol consumption, BMI, systolic blood pressure, total and HDL cholesterol, diabetes mellitus, stroke, coronary heart disease, *APOE-ε4* carrier status.

Model 3: model 2 + MMSE, depressive symptoms score, anxiety.
Model 4: model 3 + medication (anti-inflammatory/immune-modulating).

Table 3
Associations between social health markers and immune system balance at baseline.

	Ln(GLR), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	0.018 (−0.005; 0.042)	0.012 (−0.012; 0.035)	−0.017 (−0.044; 0.011)	0.008 (−0.016; 0.032)
Marital status, never married vs. ref.	**0.070 (0.030; 0.110)**	**0.068 (0.028; 0.107)**	**0.066 (0.026; 0.105)**	**0.052 (0.017; 0.086)**
Marital status, widowed/ divorced vs. ref.	0.019 (−0.002; 0.040)	0.015 (−0.006; 0.036)	0.010 (−0.012; 0.031)	**0.018 (0.000; 0.037)**
Social support, per point increase	**−0.011 (−0.018; −0.005)**	**−0.009 (−0.016; −0.002)**	−0.007 (−0.013; 0.000)	−0.003 (−0.009; 0.003)
	Ln(PLR), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	−0.008 (−0.030; 0.013)	0.001 (−0.020; 0.023)	−0.024 (−0.049; 0.002)	0.003 (−0.017; 0.024)
Marital status, never married vs. ref.	**0.051 (0.015; 0.088)**	**0.052 (0.015; 0.088)**	**0.050 (0.014; 0.086)**	**0.036 (0.007; 0.065)**
Marital status, widowed/ divorced vs. ref.	−0.011 (−0.031; 0.009)	0.001 (−0.018; 0.020)	−0.003 (−0.023; 0.016)	0.008 (−0.007; 0.024)
Social support, per point increase	−0.004 (−0.010; 0.002)	−0.005 (−0.011; 0.001)	−0.003 (−0.010; 0.003)	0.000 (−0.005; 0.005)
	Ln(SII), mean difference (95 % CI)			
	Model 1	Model 2	Model 3	Model 4
Loneliness, yes vs. no	0.028 (−0.001; 0.057)	0.020 (−0.009; 0.048)	−0.017 (−0.051; 0.016)	0.007 (−0.024; 0.038)
Marital status, never married vs. ref.	**0.095 (0.046; 0.143)**	**0.088 (0.040; 0.137)**	**0.085 (0.037; 0.134)**	**0.072 (0.027; 0.117)**
Marital status, widowed/ divorced vs. ref.	**0.040 (0.014; 0.066)**	**0.032 (0.006; 0.058)**	0.025 (−0.001; 0.051)	**0.033 (0.009; 0.057)**
Social support, per point increase	**−0.011 (−0.020; −0.003)**	**−0.008 (−0.017; 0.000)**	−0.005 (−0.014; 0.003)	−0.002 (−0.010; 0.006)

Marital status reference (ref): married/current partner.
Model 1: Age, sex, education, assay batch number.
Model 2: model 1 + smoking, alcohol consumption, BMI, systolic blood pressure, total and HDL cholesterol, diabetes mellitus, stroke, coronary heart disease, *APOE-ε4* carrier status.
Model 3: model 2 + MMSE, depressive symptoms score, anxiety.
Model 4: model 3 + medication (anti-inflammatory/immune-modulating) and lymphocyte count.
Statistically significant results at $p < 0.05$ in bold.
CI: confidence interval; GLR: granulocyte-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index.

ln(PLR) and ln(SII) compared to married peers. This association was less pronounced or absent for female participants. Higher perceived social support was associated with lower ln(PLR) in female participants, but with higher ln(PLR) male participants (p for interaction = 0.02). Sensitivity analyses did not change the interpretation of the results (Supplementary Tables 4-5). Longitudinal associations between social health and immune ratios are presented in Fig. 2. Over 14 years of follow-up, at baseline never married participants had higher GLR, PLR and SII than at baseline married and widowed/divorced peers. There were no differences in immune system balance over time for other social health markers.

3.2. Plasma neurodegeneration markers

Cross-sectional associations between social health and plasma neurodegeneration markers are presented in Table 4. Supplementary Table 2 shows mutually adjusted models for amyloid-β42 and amyloid-β40. Being never married was associated with higher plasma ln(amyloid-β40) levels (mean difference: 0.032 (95 %CI 0.005; 0.059), p = 0.019) compared to married peers. Being widowed/divorced was associated with higher plasma ln(total tau) levels (mean difference: 0.034 (95 %CI 0.009; 0.059), p = 0.008) compared to married peers. Loneliness and social support were not associated with plasma neurodegeneration biomarkers. Sex-stratified analyses showed that compared to married peers, being never married was associated with higher ln (amyloid-β40), ln(amyloid- β42), ln(Total tau) and ln(NfL) levels only in male participants (Fig. 1). *APOE-ε4* carrier status did not modify the associations (data not shown). None of the sensitivity analyses changed the interpretation of the results (Supplementary Tables 6–7).

3.3. Causal mediation analyses

Baseline characteristics of the mediation subsamples are presented in Supplementary Table 8. There were no indirect effects through any of the immune ratios in the associations between social health and g-factor or total brain volume (Supplementary Tables 9–16). With both the regression-based approach and *g*-formula, we found controlled and natural direct effects of loneliness on g-factor (Supplementary Table 9). Direct effects of perceived social support and being widowed/divorced on g-factor using the regression-based approach disappeared when adjusting for post-exposure confounding using the *g*-formula (Supplementary Table 13 and Supplementary Table 15). We found negative direct effects of being never married on total brain volume with both the regression-based approach and the *g*-formula (Supplementary Table 12). There was a reference interaction between being never married and SII on total brain volume, indicating a smaller total brain volume when individuals were never married and had an imbalance towards innate immunity.

4. Discussion

In this study, being never married and being widowed or divorced were associated with an immune system imbalance towards innate immunity (higher GLR, PLR and SII), and with plasma biomarkers of neurodegeneration, i.e. higher plasma amyloid-β40 and higher plasma total tau. This was particularly true for males. In addition, never married males had higher levels of plasma amyloid-β40, amyloid-β42, NfL and tau. Better perceived social support was associated with an imbalance towards innate immunity in male participants, but adaptive immunity in female participants. Loneliness was not associated with immune system balance or plasma neurodegeneration markers. Immune system balance did not mediate associations between social health and cognition or total brain volume.

Our results suggest that being without a partner at older age is associated with worse health indicators (i.e., imbalance towards innate immunity and higher levels of plasma neurodegeneration markers), especially for males. These findings align with existing literature on inflammation markers and marital status and emphasize the existence of sex differences in this association, as well as in the novel association with plasma neurodegeneration markers. In a US population, being never or previously married has been associated with higher NLR values compared to being married (Howard et al., 2019), suggesting an

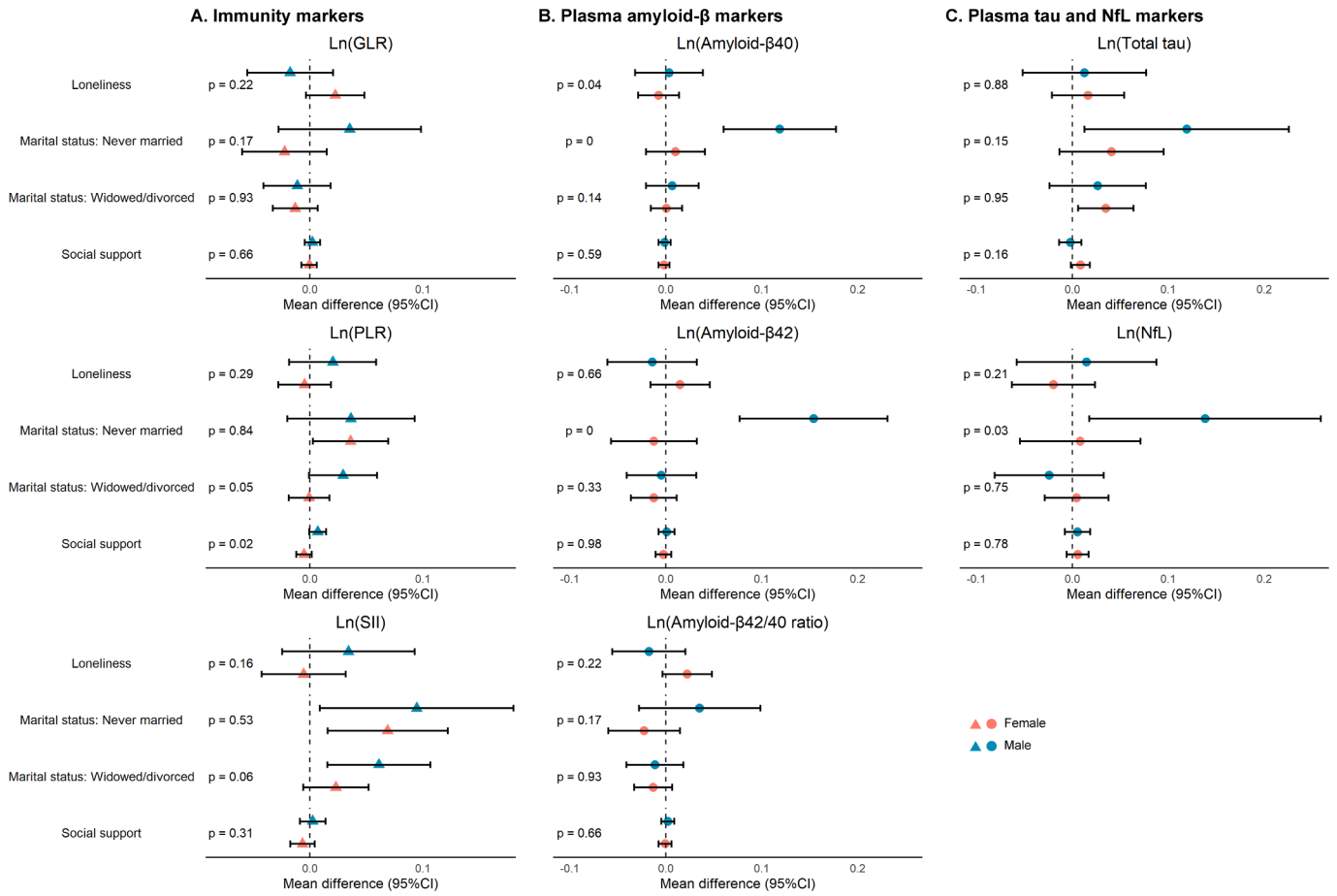

Fig. 1. Cross-sectional associations stratified for male and female participants Associations between social health and immune system balance (A, triangles) and social health and plasma neurodegeneration markers (B and C, dots), stratified on sex. Red (female) and blue (male) colors represent mean differences in natural log-transformed outcome measures. P represents p-value for the interaction term of sex and each social health marker. All analyses are adjusted for age, sex, education, assay batch number, smoking, alcohol consumption, BMI, systolic blood pressure, total and HDL cholesterol, diabetes mellitus, stroke, coronary heart disease, *APOE-ε4* carrier status, MMSE, depressive symptoms score and anxiety. Models for immunity were further adjusted for medication (anti-inflammatory/immune-modulating) and lymphocyte count. Abbreviations: CI: confidence interval; GLR: granulocyte-to-lymphocyte ratio; Ln: natural logarithm; NfL: neurofilament light chain; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

imbalance towards innate immunity. Divorced individuals had higher CRP levels than married individuals in an Irish population (Salinger and Whisman, 2021), suggesting increased innate immunity. Previous research on sex-differences and immunity suggests that the immune system of males responds more strongly to marital dissolution than that of females. For instance, accumulated number of breakups or years lived alone was associated with low-grade inflammation in men, but not in women (Davidsen et al., 2022; Nilsson et al., 2020). Conversely, remaining married in older age was protective against CRP elevations, specifically in men (Sbarra, 2009). In study samples with only male participants, divorced males were more distressed and lonely, reported more recent illness, and had lower antibody titers to herpesviruses than married males (Kiecolt-Glaser et al., 1988). Women are known to be more susceptible to marital distress and marital discord (Kiecolt-Glaser, 2018), which may lead to more stress-related immune activation and may lessen differences in stress-related immune system imbalance between married and unmarried women. The consistent finding that marriage is more protective for men than for women may in part be explained by higher susceptibility to marital distress for women, more varied social integration outside the partner relationship among married women, and greater social control on the partner's health behaviors exerted by women compared to men (Kiecolt-Glaser and Newton, 2001). Through the same logic, being unmarried is more harmful for men than it is for women in heterosexual marriages. Biological aspects of sex (e.g. sex hormones) and societal aspects of gender and accompanying roles in marriage likely both play their respective roles in these associations. Further research is needed to identify which aspects of sex and gender affect associations between social and physical health.

The finding that better perceived social support was associated with an imbalance towards innate immunity in males, but adaptive immunity in females could indicate that receiving social support for males may indicate underlying health issues that warrant increased perceived social support. This may be linked with a higher PLR reflecting underlying health issues. For females, better perceived social support may be linked to a lower PLR, without reflecting an increased need for health-related perceived social support.

Our findings on the association between being unmarried (including previously married) and innate immunity may be explained in different ways. First, social threats (e.g. suboptimal social health) promote innate immunity through the conserved transcriptional response to adversity (CTRA) pathway (Cole, 2014). This pathway is characterized by an increased expression of pro-inflammatory genes (e.g. *IL6, IL8, IL1B, TNF*) and down-regulation of anti-inflammatory genes (e.g. Type I interferon innate antiviral responses (*IFI-, MX- and OAS*-family genes) and genes involved in IgG antibody synthesis)). Second, increased activity of the innate immune system may be the result of a general stress

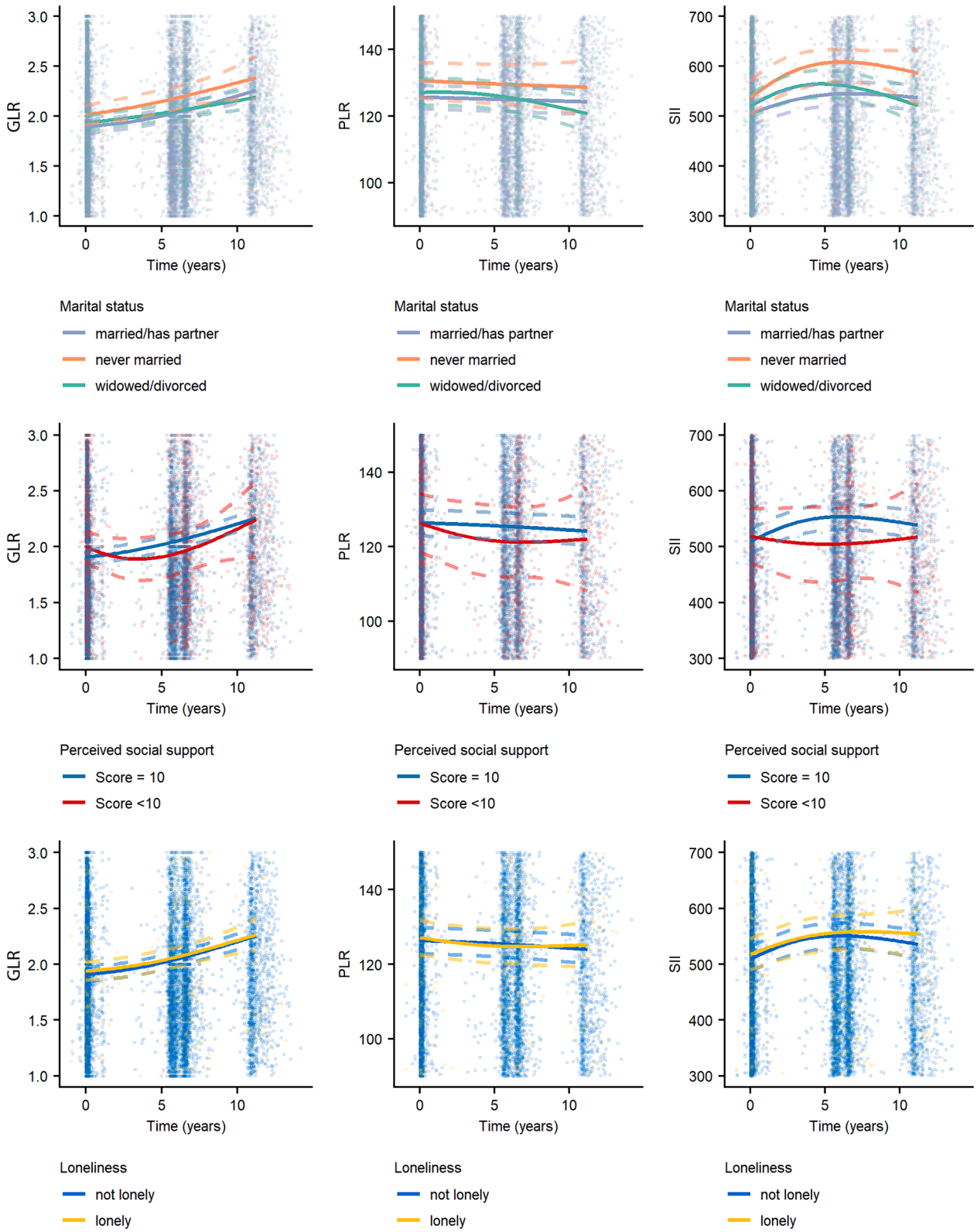

Fig. 2. Longitudinal associations between social health and immune system balance Longitudinal associations between social health markers and immune system balance. Change in granulocyte-to-lymphocyte ratio (GLR, left), platelet-to-lymphocyte ratio (PLR, middle), and systemic immune-inflammation index (SII, right) per social health marker (rows) over 13 years of follow-up. Solid lines represent the marginal (group) change in ratio over time, and dashed lines represent 95 % confidence intervals. Individual data points over follow-up time are presented as dots. Associations are adjusted for age, sex, education, assay batch number, smoking, alcohol consumption, BMI, systolic blood pressure, total and HDL cholesterol, diabetes mellitus, stroke, coronary heart disease, *APOE-ε4* carrier status, MMSE, depressive symptoms score, anxiety, medication (anti-inflammatory/immune-modulating) and lymphocyte count.

Table 4
Associations between social health markers and plasma neurodegeneration biomarkers at baseline.

	Ln(amyloid-β40), mean difference (95 % CI)		
	Model 1	Model 2	Model 3
Loneliness, yes vs. no	0.005 (−0.011; 0.021)	0.001 (−0.015; 0.016)	−0.005 (−0.023; 0.013)
Marital status, never married vs. ref.	**0.028 (0.001; 0.055)**	**0.033 (0.006; 0.061)**	**0.032 (0.005; 0.059)**
Marital status, widowed/divorced vs. ref.	0.005 (−0.010; 0.019)	0.004 (−0.010; 0.018)	0.003 (−0.011; 0.017)
Social support, per point increase	−0.003 (−0.007; 0.001)	−0.002 (−0.006; 0.002)	−0.001 (−0.005; 0.003)
	Ln(amyloid-β42), mean difference (95 % CI)		
	Model 1	Model 2	Model 3
Loneliness, yes vs. no	0.009 (−0.013; 0.031)	0.008 (−0.014; 0.031)	0.005 (−0.021; 0.031)
Marital status, never married vs. ref.	0.026 (−0.012; 0.065)	0.030 (−0.008; 0.068)	0.028 (−0.010; 0.066)
Marital status, widowed/divorced vs. ref.	−0.007 (−0.027; 0.012)	−0.007 (−0.026; 0.013)	−0.009 (−0.028; 0.011)
Social support, per point increase	−0.002 (−0.008; 0.004)	−0.001 (−0.007; 0.004)	−0.001 (−0.007; 0.005)
	Ln(amyloid-β42/40 ratio), mean difference (95 % CI)		
	Model 1	Model 2	Model 3
Loneliness, yes vs. no	0.005 (−0.014; 0.023)	0.008 (−0.010; 0.026)	0.010 (−0.011; 0.031)
Marital status, never married vs. ref.	−0.002 (−0.033; 0.030)	−0.004 (−0.035; 0.028)	−0.004 (−0.035; 0.027)
Marital status, widowed/divorced vs. ref.	−0.012 (−0.028; 0.004)	−0.011 (−0.027; 0.005)	−0.011 (−0.028; 0.005)
Social support, per point increase	0.001 (−0.004; 0.006)	0.000 (−0.004; 0.005)	0.000 (−0.005; 0.005)
	Ln(NfL), mean difference (95 % CI)		
	Model 1	Model 2	Model 3
Loneliness, yes vs. no	0.029 (−0.004; 0.062)	0.024 (−0.008; 0.056)	−0.010 (−0.048; 0.027)
Marital status, never married vs. ref.	0.050 (−0.007; 0.106)	0.032 (−0.023; 0.088)	0.031 (−0.024; 0.087)
Marital status, widowed/divorced vs. ref.	0.007 (−0.022; 0.036)	0.004 (−0.025; 0.033)	−0.003 (−0.032; 0.025)
Social support, per point increase	−0.001 (−0.010; 0.007)	0.002 (−0.007; 0.010)	0.006 (−0.003; 0.014)
	Ln(Total tau), mean difference (95 % CI)		
	Model 1	Model 2	Model 3
Loneliness, yes vs. no	0.025 (−0.004; 0.053)	0.019 (−0.010; 0.047)	0.016 (−0.017; 0.048)
Marital status, never married vs. ref.	0.041 (−0.007; 0.090)	0.047 (−0.002; 0.095)	0.046 (−0.002; 0.095)
Marital status, widowed/divorced vs. ref.	**0.036 (0.011; 0.061)**	**0.036 (0.011; 0.061)**	**0.034 (0.009; 0.059)**
Social support, per point increase	0.001 (−0.007; 0.008)	0.002 (−0.005; 0.009)	0.003 (−0.004; 0.011)

Marital status reference (ref): married/current partner.
Model 1: Age, sex, education, assay batch number.
Model 2: model 1 + smoking, alcohol consumption, BMI, systolic blood pressure, total and HDL cholesterol, diabetes mellitus, stroke, coronary heart disease, *APOE-ε4* carrier status.
Model 3: model 2 + MMSE, depressive symptoms score, anxiety.
Statistically significant results at $p < 0.05$ in bold.
CI: confidence interval; NfL: neurofilament light chain.

response through HPA-axis or noradrenergic activity (Kiecolt-Glaser, 2018; Troubat et al., 2021). Third, higher levels of innate immunity may indicate a state of inflammaging: a chronic, sterile, low-grade inflammation that occurs with aging, which is thought to result from long-term physiological stimulation of the innate immune system (Franceschi et al., 2018). Chronic low-grade inflammation may contribute to a wide range of health outcomes and diseases, including insulin resistance, diabetes mellitus type 2, cardiovascular disease, cerebrovascular disease, and neurodegenerative processes (Franceschi et al., 2018). The associations found in our study may be relevant in understanding physiological mechanisms underlying social relationships and brain health, including in the setting of partner loss through widowhood or divorce.

Never being married was associated with higher plasma amyloid-β40 and being widowed or divorced was associated higher plasma total tau, compared to married peers. Never married males specifically had higher levels of plasma amyloid-β40, amyloid-β42, NfL and tau. Although to our knowledge no prior studies on social health and plasma neurodegeneration makers have been published, associations between social health markers and brain amyloid-β and tau deposition have been described before: widowhood and lower social engagement have been associated with accelerated amyloid-β-related cognitive decline (Biddle et al., 2019; Biddle et al., 2020), and higher cortical amyloid deposition and entorhinal tau pathology have been associated with greater loneliness in older adults without dementia (d'Oleire Uquillas et al., 2018; Donovan et al., 2016). Another study in cognitively-unimpaired older adults reported no associations between social quality of life and amyloid-β deposition (Ourry et al., 2021). Studies on social health and NfL predominantly originate from clinical populations. A study in multiple sclerosis patients found that social functioning scores were inversely associated with serum NfL levels (Galetta et al., 2021). In carriers of the genetic mutation for Huntington's disease, greater social network size and diversity were associated with lower NfL levels, compared to healthy controls (Cruickshank et al., 2020). Taken together, these findings indicate that social health is associated with markers of neurodegeneration, although studies on plasma and serum markers are only starting to emerge. The sex difference found for never married males and never married females may be explained by similar mechanisms as described above but is puzzling in the context of increased all-cause dementia risk for female older adults (Gong et al., 2023). Potentially, mechanisms driving risk of neurodegenerative disorders in females are more heterogeneous than in males (Alzheimer's disease facts and figures Alzheimer's Dementia. 17 3, 2021), which may be less reflected by the plasma neurodegeneration biomarkers used in this study.

Unexpectedly, we did not find any associations of loneliness and perceived social support with plasma neurodegeneration markers. Potentially, the method in which social support and loneliness in our study were measured was not suitable to pick up subtle associations. Given that the associations between social health and plasma neurodegeneration markers were determined cross-sectionally, temporal relationships cannot be inferred. Still, marital status specifically is a dynamic lifetime exposure that is more likely to affect neurodegeneration than the other way around. Further research is required to determine the direction of the association, and the relation of plasma neurodegeneration markers to brain pathology and disease phenotypes.

We did not find mediation effects of immune system balance in associations between social health and cognition or total brain volume. A recent study found that elevated CRP and fibrinogen partially mediated with association between social isolation and poorer cognitive function in older men (Qi et al., 2023). Another study reported that CRP partially mediated the association between socioeconomic position and white matter tract integrity in healthy adults (Gianaros et al., 2013). In the

present study, follow-up may have been too short or effect estimates too small to detect causal mediation or interaction effects, and the exposure and mediator were measured at the same time point. Interaction effects might be present alongside or instead of mediation effects, and these potential effects should be considered in future studies.

Strengths of our study include the prospective design, large sample size and inclusion of several different social health markers. We further used multiple methods for the causal mediation analyses and paid special attention to sex-differences. Limitations include the measurement instruments of several of our variables. Loneliness was measured using a direct, single item question, which may have led to underreporting of loneliness (Shiovitz-Ezra and Ayalon, 2011). The perceived social support score was not formally validated and was high for most individuals, indicating a ceiling effect. The blood-based immune indices only provide a crude estimate of the immune response and do not provide insight in the specific mechanisms that may at play regarding the immune system function and pro-inflammatory cytokine release. Lymphocyte subsets were not assessed in this study. We used granulocyte count as a proxy for neutrophil count. At most, these ratios can reflect a relative balance between adaptive immunity and innate immunity. The plasma neurodegeneration markers similarly are crude indicators of brain pathology and are not diagnostic of all-cause dementia. Previous research has shown that assays used to measure amyloid-β40 and amyloid-β42 in this study only correlate moderately with those measured in CSF, although some other studies have demonstrated good correlation (Janelidze et al., 2021). Finally, the group size of never married male participants was small (N = 42) and the results for this group should thus be interpreted with caution.

5. Conclusion

In conclusion, social health is differentially associated with immune system balance and plasma neurodegeneration markers in males compared to females. For male older adults, being never married or without a partner is associated with a systemic internal milieu that points towards adverse brain health. Female older adults benefit from perceived social support through an imbalance towards the adaptive immune response, whereas males do not. Sex plays an important role in potential pathways from social health to health outcomes, including all-cause dementia. Public and clinical health policies should address sex-specific social health issues surrounding marital status.

CRediT authorship contribution statement

Isabelle F. van der Velpen: Writing – original draft, Conceptualization, Formal analysis. **Amber Yaqub:** Writing – review & editing, Methodology, Data curation. **Meike W. Vernooij:** Writing – review & editing, Supervision, Conceptualization. **Marieke Perry:** Writing – review & editing, Supervision, Conceptualization. **Myrra J.F. Vernooij-Dassen:** Writing – review & editing, Supervision, Conceptualization. **Mohsen Ghanbari:** Writing – review & editing, Supervision, Data curation. **M. Arfan Ikram:** Writing – review & editing, Supervision, Conceptualization. **René J.F. Melis:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.05.031.

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