RESEARCH ARTICLE

Social Health and Cognitive Change in Old Age: Role of Brain Reserve

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Objective: Individual aspects of social health (SH; eg, network, engagement, support) have been linked to cognitive health. However, their combined effect and the role of the structural properties of the brain (brain reserve [BR]) remain unclear. We investigated the interplay of SH and BR on cognitive change in older adults.
Methods: Within the Swedish National Study on Aging and Care–Kungsholmen, 368 dementia-free adults aged ≥60 years with baseline brain magnetic resonance imaging were followed over 12 years to assess cognitive change. A measure of global cognition was computed at each of the 5 waves of assessment by averaging domain-specific *Z* scores for episodic memory, perceptual speed, semantic memory, and letter and category fluency. An SH composite score was computed at baseline by combining leisure activities and social network. BR was proxied by total brain tissue volume (TBTV). Linear mixed models (adjusted for sociodemographic, vascular, and genetic factors) were used to estimate cognitive trajectories in relation to SH and TBTV. Interaction analysis and stratification were used to examine the interplay between SH and TBTV.
Results: Moderate–good SH (n = 245; vs poor, β-slope = 0.01, 95% confidence interval [CI] = 0.002–0.02, $p = 0.018$) and moderate-to-large TBTV (n = 245; vs small, β-slope = 0.03, 95% CI = 0.02–0.04, $p < 0.001$) were separately associated with slower cognitive decline. In stratified analysis, moderate–good SH was associated with higher cognitive levels (but not change) only in participants with moderate-to-large TBTV (β-intercept = 0.21, 95% CI = 0.06–0.37, $p < 0.01$; interaction SH * TBTV, $p < 0.05$).
Interpretation: Our findings highlight the interplay between SH and BR that likely unfolds throughout the entire life course to shape old-age cognitive outcomes.

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Dementia is one of the most burdensome conditions at both the individual and the societal level. Today, there are 50 million people living with dementia worldwide, and this number is expected to double in the next decade.[1] Although pharmacological treatment for dementia is not yet available, encouraging findings from cohort studies and nonpharmacological interventions show that dementia prevention may be feasible by tackling modifiable risk factors, such as health-related behaviors.[2,3] Within the latter category, social isolation has gained increasing attention in recent years, and has been acknowledged as one of the potential modifiable factors in

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the World Health Organization (WHO) 's global action plan for dementia risk reduction.[1]

Social isolation, however, is only one of the factors embedded in the umbrella concept of social health (SH), which encompasses a broader range of social aspects such as social network size, social engagement, and social support.[4] Despite recent progress, it remains unclear whether and how SH can slow cognitive decline during aging. Individually, some of the social factors have been related to reduced risk of dementia and cognitive impairments,[5–7] even in individuals with elevated genetic or cardiometabolic risk profiles for dementia.[8–10] However, social factors are not independent players, but are intertwined and codependent. The different aspects of the social environment of an individual dynamically coexist, contributing to her/his overall state of SH. Therefore, the question of whether and how social factors contribute to cognitive health requires more comprehensive approaches that capture multiple aspects of SH simultaneously.

SH may help preserve cognitive function through mechanisms of resilience against the neuropathological changes of dementia by promoting the efficiency or flexibility of cognitive function.[11] The brain reserve (BR) model emphasizes the role of the structural neuronal capital, suggesting that individuals with larger brains—with more neurons or greater synaptic density—are less susceptible to rapid cognitive deterioration.[12] The interplay between SH (which is believed to influence cognition through functional resilience processes) and BR (which is assumed to influence cognition though structural resilience processes) is yet to be investigated.

This study aimed to investigate the associations between SH and rate of cognitive decline, as well as the interplay between SH and BR in relation to cognitive change, in a dementia-free cohort of older Swedish adults.

Subjects and Methods

Study Population and Design

Participants were drawn from the Swedish National Study on Aging and Care–Kungsholmen (SNAC-K) brain magnetic resonance imaging (MRI) study,[13] an ongoing population-based cohort. At baseline (March 2001–August 2003), SNAC-K MRI included 555 community-dwelling older adults aged ≥60 years, living in central Stockholm (Sweden), who underwent MRI scanning. The population in the Kungsholmen district of central Stockholm (Sweden) was stratified into 11 age cohorts, and a random sample was drawn from each cohort. Younger age cohorts (60, 66, and 72 years) were followed up every 6th year and the older age cohorts (≥78 years) every 3rd year. In the present study, 368 individuals without dementia and neurological disorders at baseline (ie, brain infarcts, arachnoid cyst, meningioma or brain tumors, Guillain–Barré syndrome, arterial aneurysm, cavernoma, severe depression secondary to epilepsy, ischemic encephalopathy, Parkinson disease, or mental/behavioral disorders due to alcohol dependence syndrome), who participated in at least 2 cognitive assessments, were followed over 12 years (until August 2015) to assess global cognitive function (for detailed exclusion criteria, see Fig 1).

The regional ethical review board in Stockholm approved all parts of SNAC-K, including linkage with registries. All participants provided written informed consent.

Data Collection

At each wave, participants took part in a comprehensive assessment performed by physicians, psychologists, and nurses. Information on sociodemographic (eg, age, sex, education), lifestyle and vascular risk factors, medical conditions, and cognitive function was collected following standard protocols (available at https://www.snac-k.se/). Blood samples were taken from all participants.

Social Health. A composite score of SH (hereafter, SH index) was computed by combining social connections, social support, and engagement in leisure activities, all assessed at baseline. For a detailed description of the assessment of variables included in the SH index, see Appendices A and B in Marseglia et al[8] and Appendix B in Marseglia et al.[14]

In brief, trained nurses administered a 10-item questionnaire exploring two components of participants' social network: social connections and social support.[15] Raw scores were *Z*-standardized and averaged to create social connections and social support indices, which were subsequently averaged to generate an overall social network index.

The nurses also asked participants about their engagement during the past 12 months in 26 predefined leisure activities with a predominant social (eg, going to cinema/theater/concerts), mental (eg, playing chess/cards), or physical (eg, gym/golf/other sports) component. Because most of the activities are characterized by more than one component, we summed the 3 scores (social, mental, and physical) into an overall index. The index was then *Z*-standardized, using the mean and standard deviations of 3,041 SNAC-K participants, without missing information on leisure activities or social network.

Finally, the social network and leisure activity indices were averaged to create the SH index. The continuous SH index was divided into tertiles based on the distribution to designate poor (T1 [−1.30 to −0.068]), moderate (T2 [−0.067 to 0.54]), or good (T3 [0.55 to 1.67]) SH.

Structural MRI Indicators of Brain Reserve. Details on the scanning protocol and image processing have been previously described.[14]

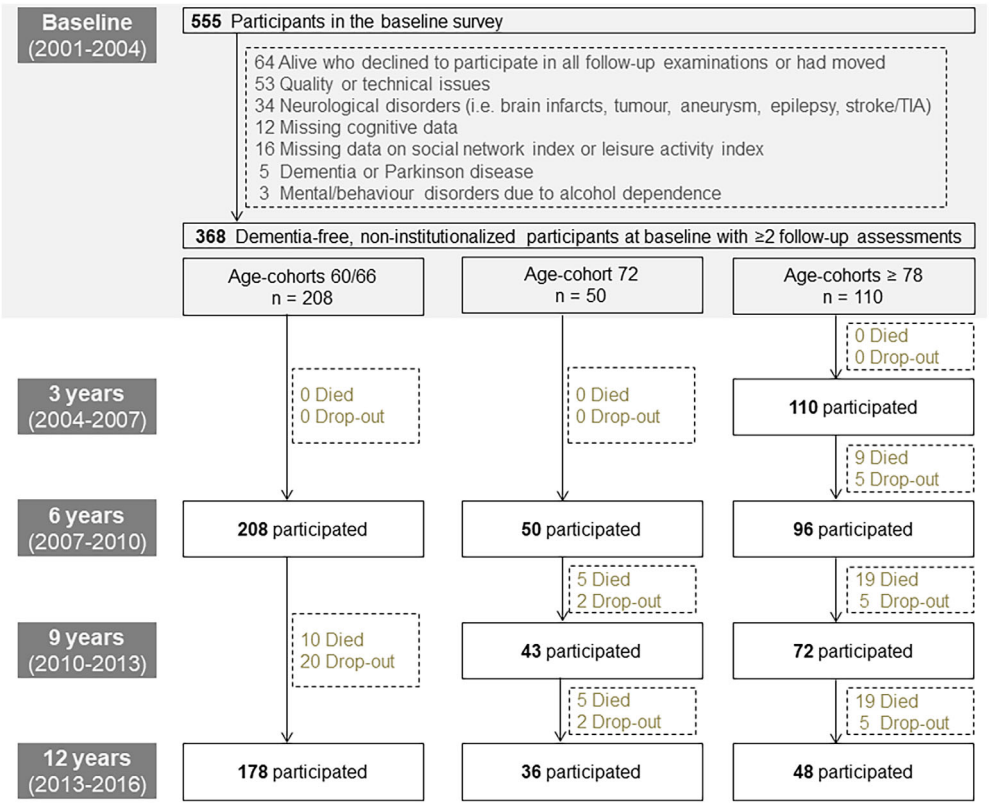

FIGURE 1: Flowchart of the Swedish National Study on Aging and Care–Kungsholmen magnetic resonance imaging study participants. Dropout included refusal (from participant or proxy), language difficulties, canceled testing, and no contact or moved. TIA = transient ischemic attack.

In brief, participants were scanned with a 1.5T MRI scanner (Intera, Philips, Best, the Netherlands). The protocol included an axial 3D T1-weighted fast field echo (repetition time [TR] = 15 milliseconds, echo time [TE] = 7 milliseconds, flip angle [FA] = 15°, field of view [FOV] = 240, 128 slices with slice thickness = 1.5mm and in-plane resolution = 0.94 × 0.94mm, no gap, matrix = 256 × 256) and an axial turbo fluid-attenuated inversion recovery sequence (TR = 6,000 milliseconds, TE = 100 milliseconds, inversion time = 1,900 milliseconds, FA = 90°, echo train length = 21, FOV = 230, 22 slices with slice thickness = 5mm and in-plane resolution = 0.90 × 0.90mm, gap = 1mm, matrix = 256 × 256).

Gray matter volume (GMV), white matter volume (WMV), and cerebrospinal fluid volume (CSFV) were derived after segmentation of the T1-weighted images in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/, Wellcome Trust Centre for Neuroimaging, Functional Imaging Laboratory, London, UK), implemented in MATLAB 10 (MathWorks, Natick, MA), using the improved unified segmentation algorithm that employs an extended set of tissue probability maps. The "light cleanup" option was used to further remove odd voxels from the images. Total intracranial volume (TIV) was calculated by adding the GMV, WMV, and CSFV. All segmentations were inspected by a neuroimaging expert (G.K.). All brain measures were TIV-adjusted using a residual approach.

We used total brain tissue volume (TBTV) as a measure of BR, which was calculated by summing GMV and WMV, adjusted for intracranial volume.[14,16] TBTV was categorized into tertiles, to reflect small, moderate, or large structural BR.

Global Cognitive Function. At each study wave, trained psychologists administered a neuropsychological test battery following a standard procedure.[17] The following domains were assessed: episodic memory (free recall and recognition of words),[17] perceptual speed (digit cancellation and pattern comparison),[18,19] semantic memory (vocabulary and general knowledge),[20,21] letter fluency (F and A),[22] and category fluency (animals and professions).[22]

Raw scores from each test were first *Z*-transformed using baseline mean and standard deviation (SD) from the full sample of participants without dementia, Parkinson disease, schizophrenia, or developmental disorder. For those with at least 3 domains available, a composite score (*G* score) was created by averaging the *Z* scores of the

abovementioned domains into a measure of global cognitive function.

Covariates. Education (elementary school vs professional school, high school, or university) was categorized according to the highest educational attainment. Socioeconomic status (SES; white collar vs blue collar workers) included occupation-based social class, derived from the longest held occupation.[23,24] Smoking (never vs current/former), alcohol consumption (no/occasional vs light-to-heavy current drinking), and body mass index (underweight [<20kg/m^2], normal weight [20–25kg/m^2], overweight [>25–30kg/m^2], or obese [≥30kg/m^2]) were also categorized. Systolic and diastolic blood pressure were measured twice at a 5-minute interval on the left arm in a sitting position; the average of the two measurements was used to identify hypertension (≥140/90mmHg). Chronic medical diseases (diabetes, heart disease, and cerebrovascular disease) were diagnosed according to the International Classification of Diseases–10th edition criteria integrating information from the physician examination, self-report, medication use, or the Swedish National Patient Register, which covers all inpatient and outpatient care in Sweden.[14] Depression was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders–4th edition (DSM-IV) criteria. Clinical diagnoses of dementia were made according to the DSM-IV criteria following a previously described 3-step procedure.[25] Apolipoprotein E (*APOE*; any ε4 allele carriers vs noncarriers) was genotyped. Participants' vital status during follow-up was gathered through the Swedish Cause of Death Registry.

Statistical Analysis

To describe baseline characteristics of the sample by SH levels, we used chi-squared or 1-way analysis of variance, followed by a post hoc test with a Bonferroni correction.

Linear mixed-effect models were used to delineate annual trajectories of global cognitive function by SH over the 12-year follow-up period. SH and BR were first introduced as continuous variables into each model. Continuous SH was only marginally associated with the rate of cognitive decline (p for slope = 0.094). As this did not exclude the possibility of a nonlinear effect of SH on cognition, in a second step, SH and BR were categorized into tertiles, which is common practice in the literature.[14] Because moderate and good SH, as well as moderate and large BR, showed similar associations (direction and magnitude) with rate of cognitive change, we merged their respective high and middle tertiles into single categories of "moderate–good SH" and "moderate-to-large BR." The fixed effects for the final models included baseline SH (low vs moderate and good) or BR (small vs moderate and large) as categorical variables, linear annual follow-up time, and their interactions. Random effects included random intercept for individuals and slope for time. Unstructured covariance matrices and maximum likelihood estimation were applied.

A stepwise forward approach was used, and the following models were estimated: Model 1 included age and sex; Model 2 additionally included sociodemographic factors (education and SES) and cardiovascular conditions (hypertension and heart disease); Model 3 further included *APOE* ε4 status. For ease of presentation, in Tables 3 and 4, only minimally and fully adjusted models are presented, as moderate and full adjustment produced virtually identical results.

We explored the interplay between SH and BR with respect to change in global cognitive function using interactions and stratified analyses. We tested the following: (1) a 2-way interaction SH × BR to assess their interplay on cognitive level and (2) a 3-way interaction SH × BR × follow-up time to assess the interplay of SH and BR on cognitive change. As statistical interaction requires considerable power, interaction analyses were followed by stratified analyses.

Given the sample size, variables associated with both independent variables and outcomes were selected to control for confounding and minimize risk of overadjustment.[25] Age (60/66, 72, and 78–96 years based on the age-stratified design of SNAC-K), sex, education, SES, hypertension, heart disease, and *APOE* ε4 allele were considered as potential confounders.

A 2-sided p value of <0.05 indicated statistical significance. All analyses were performed using Stata SE, version 16.0 (StataCorp, College Station, TX).

Sensitivity Analysis. To limit possible reverse causation related to prodromal dementia and exposure measurement error, all analyses were repeated after excluding incident dementia cases at (1) the 6-year follow-up (n = 11) and (2) the 12-year follow-up (n = 39).

We also tested possible nonlinear cognitive trajectories by fitting a mixed-effect model, which included an additional quadratic term for follow-up time and its interaction with the exposure (exposure × time^2).

Results

Characteristics of the Study Population

Table 1 shows baseline sociodemographic, clinical, and cognitive characteristics of the 368 dementia-free, noninstitutionalized participants by SH status. Participants with moderate or good SH were more likely than those with low SH to be younger and have a higher level of education, higher SES, less hypertension and heart disease, larger TBTV and GMV, and better cognitive function. No differences were observed in relation to *APOE* ε4 or WMV.

During the 12-year follow-up (mean [SD] = 10.1 [2.58] years, range = 2.9–12.9 years), 67 participants (18.2%) died and 39 (10.6%) dropped out (retention rate = 89.4%; see Fig 1). Overall, 83 participants had 2 cognitive assessments, 195 had 3 cognitive assessments, and 90 had 4 or 5 cognitive assessments.

TABLE 1. Baseline Characteristics of the Study Population (N = 368) by Tertiles of Social Health

Characteristic	Poor, n = 123	Moderate, n = 123	Good, n = 122	*p*
Age, yr	72.1 ± 9.32	69.3 ± 8.74[a]	68.3 ± 8.15[a]	0.002
60 and 66	58 (47.2)	71 (57.7)	79 (64.8)	0.082
72	19 (15.5)	18 (14.6)	13 (10.7)	
78+	46 (37.4)	34 (27.6)	30 (24.6)	
Female	78 (63.4)	74 (60.2)	73 (59.8)	0.817
Education				
Elementary	20 (16.3)	16 (13.0)	4 (3.3)	<0.001
Professional school	58 (47.2)	41 (33.3)	35 (28.7)	
High school	15 (12.2)	15 (12.2)	10 (8.2)	
University	30 (24.4)	51 (41.5)	73 (59.8)	
Socioeconomic status				
Blue-collar worker	27 (22.1)	22 (17.9)	6 (4.9)	<0.001
White-collar worker	95 (77.9)	101 (82.1)	116 (95.1)	
Any *APOE* ϵ4 allele	35 (19.2)	27 (22.1)	33 (27.1)	0.441
MMSE score	29.1 ± 1.13	29.1 ± 1.02	29.4 ± 0.82[a]	0.010
Global cognition, *G* score	−0.16 ± 0.53	0.03 ± 0.59[a]	0.31 ± 0.59[a]	<0.001
Vascular risk factors				
Former/current smoking	64 (52.0)	68 (55.3)	71 (58.2)	0.624
Current alcohol drinkers	85 (69.1)	99 (80.5)	98 (80.3)	0.054
BMI, kg/m^2				
Underweight, <20	9 (7.3)	4 (3.3)	2 (1.6)	0.193
Normal, 20–25	48 (39.0)	50 (41.0)	52 (42.6)	
Overweight, 25–30	49 (39.8)	47 (38.5)	56 (45.9)	
Obese, ≥30	17 (13.8)	21 (17.2)	12 (9.8)	
Medical conditions				
Diabetes	5 (4.1)	7 (5.7)	8 (6.6)	0.835
Hypertension	91 (74.0)	72 (58.5)	78 (63.9)	0.035
Heart disease	26 (21.1)	19 (15.5)	12 (9.8)	0.050
Cerebrovascular disease	0 (0.0)	1 (0.8)	3 (2.5)	0.167
Depression	6 (4.9)	4 (3.3)	1 (0.8)	0.175
Brain volume, ml				
Total brain tissue	1,044 ± 75.5	1,072 ± 74.9[a]	1,078 ± 70.6[a]	<0.001
Gray matter	541.0 ± 53.6	557.3 ± 54.5[a]	564.6 ± 51.2[a]	0.002
White matter	503.0 ± 45.1	515.0 ± 42.0	513.2 ± 45.9	0.074

Note: Data are presented as n (%) or mean ± standard deviation. Proportions were compared with chi-squared test and means with 1-way analysis of variance. Missing data: socioeconomic status = 1, *APOE* ϵ4 = 4, BMI = 1, depression = 2.

Abbreviation: *APOE* ϵ4 = apolipoprotein ϵ4 allele; BMI = body mass index; MMSE = Mini-Mental State Examination.

[a]Pairwise means comparison using Bonferroni correction: p value < 0.05 (reference group = baseline participants with poor social health).

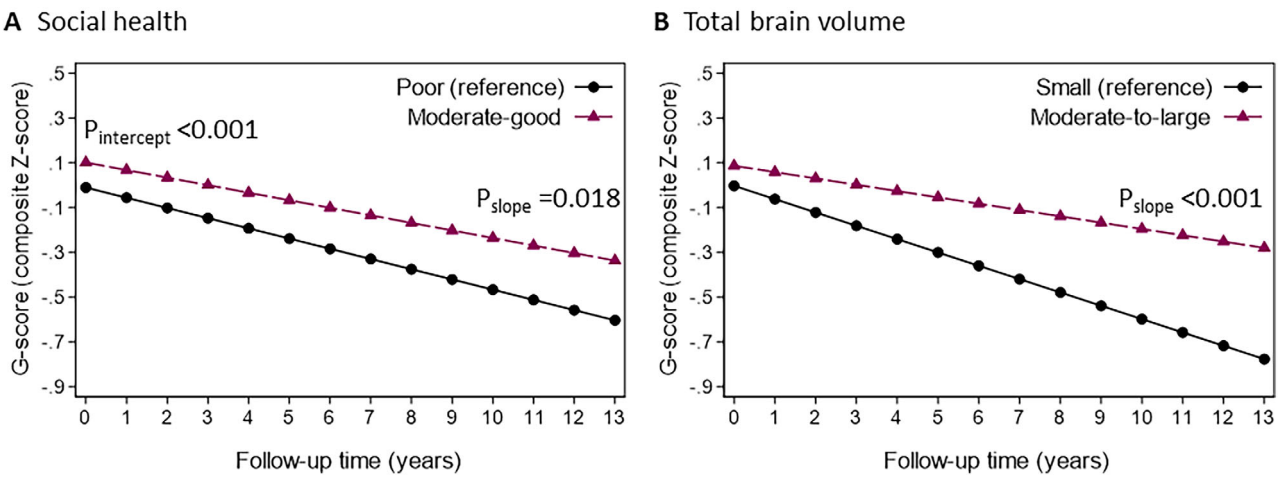

FIGURE 2: Estimated trajectories of global cognitive function over the 12-year follow-up by social health and structural brain reserve. (A) Trajectories of *G* score in participants with poor (reference; *black circles*) versus moderated–good (n = 245; *purple triangles*) social health. (B) *G* score trajectories in participants with small (reference; *black circles*) versus moderate-to-large (n = 245; *purple triangles*) total brain tissue volume, an indicator of structural brain reserve. Linear mixed models were adjusted for baseline age, sex, education, socioeconomic status, hypertension, heart diseases, and *APOE* ε4 allele. Trajectories are plotted based on the mean values of the covariates age and sex.

Social Health and Cognitive Function

Figure 2A shows the trajectories of change in global cognition over follow-up by SH status.

In multiadjusted mixed-effect models, moderate–good SH was associated with slower cognitive decline (β-slope = 0.01, 95% confidence interval [CI] = 0.002–0.02, $p = 0.018$; reference group: poor SH; Model 1 in Table 2). The association remained after adjustment for sociodemographic and genetic factors, and medical conditions (Models 2 and 3).

TABLE 2. Linear Mixed Model β Coefficients and 95% CIs of the Associations between Social Health, Baseline Performance (Intercept), and Annual Changes over 12 Years (Social Health × Time) in Global Cognitive Function (Composite *G* Score)

	Model 1[a]		Model 2[b]		Model 3[c]	
	β (95% CI)	*p*[d]	*β* (95% CI)	*p*[d]	*β* (95% CI)	*p*[d]
Social health, intercept cognition[e]						
Poor	Reference		Reference		Reference	
Moderate–good	0.24 (0.11; 0.37)	<0.000	0.13 (0.01; 0.26)	0.041	0.11 (−0.01; 0.24)	0.083
Time, yr[e]	−0.05 (−0.06; −0.04)	<0.000	−0.05 (−0.06; −0.04)	<0.001	−0.05 (−0.06; −0.04)	<0.001
Social health × time, yr[e]						
Poor × time	Reference		Reference		Reference	
Moderate–good × time	0.01 (0.002; 0.02)	0.018	0.01 (0.002; 0.02)	0.022	0.01 (0.002; 0.02)	0.040

Abbreviation: CI = confidence interval.
[a]Adjusted for baseline age and sex.
[b]Adjusted for Model 1 + education, socioeconomic status, hypertension, and heart diseases.
[c]Adjusted for Model 2 + apolipoprotein E ε4 allele.
[d]$p < 0.05$ (Bonferroni-adjusted p value for 3 comparisons < 0.018).
[e]*Social health, intercept cognition* represents the baseline *G* score for the group with moderate–good social health. *Time* represents the annual change in *G* score (slope). *Social health × time* represents the additional annual change in *G* score for the moderate–good group.

TABLE 3. Linear Mixed Model β Coefficients and 95% CIs of the Associations between Baseline Brain Volumes, Baseline Performance (Intercept), and Annual Changes over 12 Years (Brain Volumes × Time) in Global Cognitive Function (*G* Score)

	Total Brain Tissue Volume				Gray Matter Volume			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
	β (95% CI)	*p*[c]	*β* (95% CI)	*p*[c]	*β* (95% CI)	*p*[c]	*β* (95% CI)	*p*[c]
Brain volume, intercept cognition[d]								
Small	Reference		Reference		Reference		Reference	
Moderate-to-large	0.09 (−0.08; 0.26)	0.295	0.08 (−0.08; 0.24)	0.334	−0.01 (−0.17; 0.16)	0.944	−0.07 (−0.23; 0.09)	0.394
Time, yr[d]	−0.06 (−0.07; −0.05)	<0.001	−0.06 (−0.07; −0.05)	<0.001	−0.05 (−0.06; −0.05)	<0.001	−0.06 (−0.06; −0.05)	<0.001
Brain volume × time, yr[d]								
Small × time	Reference		Reference		Reference		Reference	
Moderate-to-large × time	0.03 (0.02; 0.04)	<0.001	0.03 (0.02; 0.04)	<0.001	0.02 (0.01; 0.04)	<0.001	0.02 (0.01; 0.04)	<0.001

Abbreviation: CI = confidence interval.

[a]Adjusted for baseline age and sex.

[b]Adjusted for Model 1 + education, socioeconomic status, hypertension, heart diseases, and apolipoprotein E ε4 allele.

[c]$p < 0.05$.

[d]*Brain volume, intercept cognition* represents the baseline *G* score for the group with moderate-to-large exposure. *Time* represents the annual change in *G* score (slope) for the reference group. *Brain volume* × *time* represents the additional annual change in *G* score for the groups with moderate-to-large total brain volume or gray matter volume.

Brain Reserve, Social Health, and Cognitive Change

Moderate-to-large TBTV was associated with slower cognitive decline over the 12-year follow-up (see Fig 2B, Table 3).

We also found positive cross-sectional associations of baseline SH (moderate–good) with baseline TBTV (multiadjusted linear regression $\beta = 15.8$, 95% CI = 4.08–27.4, $p = 0.008$) and GMV (multiadjusted linear regression $\beta = 9.59$, 95% CI = 0.44–18.7, $p = 0.040$).

The interplay between SH and BR for cognition was investigated in 2 ways: (1) adding interaction terms between SH and BR to the model and (2) performing stratified analysis by TBTV. In the interaction analysis, the combined effect of moderate–good SH and moderate-to-large TBTV was statistically significant only for baseline cognitive level ($\beta = 0.30$, 95% CI = 0.04–0.55, $p = 0.022$). The 3-way interaction moderate–good SH × moderate-to-large TBTV × follow-up time, which captures the combined effect of SH and BR on changes in cognitive function, was not statistically significant. In stratified analyses (Table 4), moderate–good SH was associated with better global cognitive function at baseline only and among participants with moderate-to-large TBTV (β-intercept = 0.21, 95% CI = 0.06–0.37, $p = 0.007$). Such association was not observed among participants with small TBTV.

Sensitivity Analysis

Model 3 in Table 2 was additionally adjusted for TBTV (β-slope = 0.01, 95% CI = 0.001–0.02, $p = 0.040$) and baseline Mini-Mental State Examination score (β-slope = 0.01, 95% CI = 0.001–0.02, $p = 0.049$), producing similar estimates for SH-associated cognitive change. Repeating the analysis after excluding incident dementia cases after 6 years of follow-up (n = 11) did not alter the principal findings. We further excluded incident dementia cases after 12 years of follow-up (n = 39). Although moderate–good SH was no longer associated with less cognitive decline, the point estimates from these models (Table 5) were virtually identical to those from the original analyses, likely reflecting reduced statistical power.

TABLE 4. Associations between Social Health, Baseline Performance (Intercept), and Annual Change over 12 years (Social Health × Time) in Global Cognitive Function (Composite *G* Score) by Total Brain Volume, Indicating Small and Moderate-to-Large Structural Brain Reserve

	Small Total Brain Volume					Moderate-to-Large Total Brain Volume				
		Model 1		Model 2			Model 1		Model 2	
	n	β (95% CI)[a]	*p*[b]	β (95% CI)[c]	*p*[b]	n	β (95% CI)[a]	*p*[b]	β (95% CI)[c]	*p*[b]
Social health, intercept cognition										
Poor	58	Reference		Reference		65	Reference		Reference	
Moderate–good	65	−0.02 (−0.25; 0.20)	0.841	−0.07 (−0.30; 0.16)	0.554	180	0.25 (0.09; 0.41)	0.001	0.21 (0.06; 0.37)	0.007
Time, yr[d]		−0.07 (−0.09; −0.05)	<0.001	−0.07 (−0.08; −0.05)	<0.001		−0.03 (−0.04; −0.02)	<0.001	−0.03 (−0.04; −0.02)	<0.001
Social health × time, yr[d]										
Poor × time		Reference		Reference			Reference		Reference	
Moderate–good × time		0.01 (−0.01; 0.04)	0.308	0.01 (−0.02; 0.03)	0.493		0.002 (−0.01; 0.01)	0.711	0.001 (−0.01; 0.01)	0.935

Note: Interaction SH × BR for baseline cognition: β coefficient = 0.30 (95% CI = 0.04; 0.55), $p = 0.022$. Interaction SH × BR × time (for cognitive change): β coefficient = −0.01 (95% CI = −0.04; 0.01), $p = 0.308$.

Abbreviations: BR = brain reserve; CI = confidence interval; SH = social health.

[a]Mixed models adjusted for baseline age, sex, and education.

[b]$p < 0.05$.

[c]Mixed models adjusted for Model 1 + socioeconomic status, hypertension, heart diseases, and apolipoprotein E ε4 allele.

[d]*Time* represents the annual change in *G* score (slope) for the reference group with poor social health, whereas *Social health* × *time* represents the additional annual change in *G* score for the group with moderate–good social health.

TABLE 5. Linear Mixed Model β Coefficients and 95% CIs of the Association between Social Health, Baseline Performance (Intercept), and Annual Changes over 12 Years (Social Health × Time) in Global Cognitive Function, after Excluding 39 Incident Dementia Cases at 12-Year Follow-up

	Model 1[a]		Model 2[b]		Model 3[c]	
	β (95% CI)	*p*[d]	β (95% CI)	*p*[d]	β (95% CI)	*p*[d]
Social health, intercept cognition						
Poor	Reference		Reference		Reference	
Moderate–good	0.25 (0.11; 0.38)	<0.000	0.14 (0.01; 0.27)	0.041	0.12 (−0.02; 0.25)	0.089
Time, yr[e]	−0.04 (−0.04; −0.03)	<0.000	-0.04 (−0.04; −0.03)	<0.001	−0.03 (−0.04; −0.03)	<0.001
Social health × time, yr[e]						
Poor × time	Reference		Reference		Reference	
Moderate–good × time	0.01 (−0.002; 0.02)	0.103	0.01 (−0.002; 0.02)	0.103	0.01 (−0.004; 0.02)	0.207

Abbreviation: CI = confidence interval.

[a]Adjusted for baseline age and sex.

[b]Adjusted for Model 1 + education, socioeconomic status, hypertension, and heart diseases.

[c]Adjusted for Model 2 + apolipoprotein E ε4 allele.

[d]$p < 0.05$.

[e]*Time* represents the annual change in *G* score (slope) for the reference group, whereas *Social health* × *time* represents the additional annual change in *G* score for the moderate good social health group.

To understand how attrition may have influenced the findings, we compared the baseline characteristics of those who participated in all waves (n = 262) versus those who died (n = 67) or dropped out (n = 39) at any point during follow-up. Compared to the surviving participants, those who died or did not participate were more likely to be older and males, and to have less formal education, poorer SH, more cardiovascular comorbidities, and smaller brain volumes. These differences remained unchanged after excluding 39 participants who were diagnosed with dementia over the follow-up. We did not find evidence of a nonlinear association between SH and cognitive trajectories.

Discussion

In this population-based longitudinal cohort study, we found that moderate–good SH as well as moderate-to-large TBTV (indicating larger structural BR) were associated with higher baseline cognitive performance and slower rate of cognitive decline. Examining their interplay revealed that better SH was associated with higher cognitive levels (but not with less decline) only in individuals with moderate-to-large TBTV. These findings imply that SH and BR are important correlates of cognitive aging, and their cognitive influences are likely intertwined and unfold throughout the entire life.

As human beings are a social species, having good social health is a crucial part of a person's well-being throughout life. Two recent meta-analyses have shown that different aspects of SH (eg, supportive social network, frequent contacts with relatives/friends, social participation) are associated with a reduced risk of dementia.[6] In contrast, only a few longitudinal studies have assessed potential cognitive benefits of SH-related aspects on cognitive decline,[7,26,27] showing mixed results, and our study contributes to this emerging literature. A recent study reported that older adults with frequent social contacts at midlife had higher cognitive performance that could be maintained over a decade.[7] Another study reported that, among several social resources, the size of the network was associated with better cognitive performance at baseline, but not over time.[28]

SH incorporates complex interactional (ie, frequency of contact, social engagement, and social support) and structural (ie, network size) aspects. These aspects are so intertwined and codependent that it is difficult to address them separately, to understand how SH impacts cognitive function.[29] To our knowledge, our findings are the first to show that having a good overall SH (combining interactional and structural aspects) in late life is associated with attenuated age-related cognitive decline, independent of socioeconomic and health-related factors. Although good SH in late life could reflect beneficial SH throughout life, a hypothesis we are unable to test with the current data, our findings tentatively suggest that promoting SH in late life may constitute one strategy to forestall the progression to cognitive impairment. Several multidomain interventions have targeted improvement of cognitive and physical health, but not SH, although social interaction was an integral part of the trial designs.[30,31] Our results, alongside the acknowledgment of poor social participation as one of the 12 modifiable risk factors for dementia by the WHO,[1] highlight the need for future interventions that target the improvement of individual's overall SH.

BR reflects the neurobiological capital, that is, the quantifiable brain resources (eg, number of neurons/synapses) that may help enhance or maintain cognitive function.[11,12] SH likely contributes to cognitive preservation through two resilience mechanisms: cognitive reserve and brain maintenance.[12] On one hand, social stimulation may enhance brain network efficiency and flexibility, enabling individuals to resist age-related neuropathological changes, thus postponing the clinical manifestation of dementia (cognitive reserve). On the other hand, social stimulation could enable the absorption of age-related brain changes, insults, or diseases (eg, proteinopathy-related neurodegeneration or cerebrovascular injury), resulting in no or minimal brain alterations (brain maintenance). Our cross-sectional findings revealed a positive association between SH and BR, although we were able neither to examine the direct influences of SH on BR, nor to assess whether SH was predominantly a result of cognitive reserve-related or brain maintenance-related processes. To our knowledge, only a handful of epidemiological studies have investigated the associations between SH and its neuroanatomical substrates, showing mixed results.[32] One cross-sectional study found that engagement in social activities was associated with larger GMV,[33] whereas others have not observed such an association.[32,34,35] On the other hand, a randomized intervention study from China reported that dementia-free participants assigned to the social interaction arm (engaging in group discussions 3 times/wk) had increased brain volumes and improved cognitive performance after a 5-month intervention.[36] Differences in findings may reflect methodological aspects, including small sample size and assessment of independent variables. Future studies need to replicate our findings using longitudinal designs to better understand how SH may be related to changes in structural markers of BR and cognition.

Although we were unable to examine BR as a possible mechanism behind SH's influences, a novel aspect of our work lies in our ability to assess the interplay of these

two constructs for cognitive trajectories. We observed that the benefits of greater SH were restricted to individuals with larger structural BR and only in relation to baseline cognition. It is possible that this finding is a product of lifelong stability of above-average cognition in people with high TBTV, which also facilitates their engagement in socially rewarding lifestyles. Several studies have suggested that lifelong activity participation may be an indicator of the use of an individual's cognitive abilities in their day-to-day living.[37,38] In contrast, in people with small TBTV, SH may have been less downstream of their initial cognitive levels, ultimately weakening the relationship between the two at baseline. Together, these two processes could give rise to an SH × BR interaction observed for cognitive levels. Future studies need to test this hypothesis by assessing SH, BR, and cognition earlier in life. Notably, SH was still associated with slower cognitive decline in our data after adjusting for TBTV, suggesting that for cognitive decline, SH effects may operate through pathways other than those linked to BR or lifelong stability of cognition. Therefore, future research is required to elucidate the directionality between SH and BR, with a particular emphasis on their lifelong stability, and to explore alternative pathways linking good SH with cognitive change.

Our findings also showed that in addition to the positive cross-sectional association with TBTV, SH was positively related to GMV, suggesting that SH in late life could play a role in limiting cerebral proteinopathies. This hypothesis could be tested in future studies by integrating longitudinal measures of SH (from early to late life) with in vivo biomarkers of proteinopathies (eg, amyloid-β, tau, neurofilament light, TDP-43) and cerebrovascular pathology (eg, small vessel disease, integrity of the blood–brain barrier).[39–41]

Strengths and Limitations

Long-term follow-up, comprehensive measurements of SH and cognition, and an extensive set of adjustment variables, including a marker of cerebrovascular pathology, are among the strengths of this study.

Some limitations need to be acknowledged. First, reverse causation may have occurred, whereby individuals in the preclinical stage of dementia could disengage from social engagement. We aimed to limit reverse causation by excluding not only prevalent dementia cases, but also those with incident dementia diagnosis over 6 and 12 years of follow-up, with no major attenuation of results. Second, as in all longitudinal studies, selection bias may have arisen from missing values because of death or dropout during follow-up. As participants who died or dropped out were less healthy at study entry, this may have led to an underestimation of the detected associations. Third, the use of TBTV may reflect the combination of two antipodean processes: BR and neurodegenerative changes. Notably, our results remained largely consistent after excluding participants with cognitive impairment with no dementia, suggesting limited bias due to neurodegeneration. Nonetheless, a unified measure of BR remains to be agreed upon, and future studies should replicate these findings, as well as test the predictive value of other measures of BR in relation to cognitive changes. Fourth, we could not account for the presence of neurodegenerative changes that are common in old age alongside cerebrovascular changes. Future studies using automated segmentation to quantify lesion volumes are required to clarify the interplay between neurodegenerative and cerebrovascular pathologies as a measure of age-related pathology in the resilience framework. Fifth, we lacked data to assess the interplay of SH with not only brain structure, but also function, given that resilience mechanisms may also involve functional connectivity pathways. Sixth, to capture leisure activities, we considered engagement in various not only socially but also mentally and physically stimulating activities. We did so because mental and physical activities also likely involve social stimulation (eg, doing sports, playing chess/cards, picking mushrooms/berries). Future studies may consider alternative operationalizations of leisure within SH, although previous work on the same study population suggests that high scores of mental, physical, and social leisure activities are associated with similarly reduced risk of dementia,[42] and it is the totality of leisure engagement, rather than its predominant domain, that appears to be most relevant. Also, the study population originated from an ethnically homogenous and affluent area of Stockholm, which has implications for generalizability to older adults of diverse backgrounds. That said, given that the SNAC-K participants are relatively healthy and wealthy, it is likely that our findings represent underestimations of true associations. Finally, despite an extensive set of adjustments, residual confounding remains a possibility.

Conclusions

In conclusion, we found that a composite indicator of social health, which incorporated interactional and structural aspects, was associated with less cognitive decline after age 60 years. However, when considered alongside TBTV (a marker of structural BR), social health exerted protective influences on cognition only in individuals who also had high levels of BR, and this effect was only observed at baseline. Future studies need to examine the

mechanistic relationship between social health, structural BR, and cognition from a life-course perspective.

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Author Contributions

A.M., S.D., and A.-K.W. contributed to the conception and design of the study. A.M., L.B., G.K., and E.J.L. contributed to the acquisition and analysis of data. A.M., S.D., G.K., E.J.L., J.M., P.P., H.-X.W., L.B., E.W., and A.-K.W. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability Statement

For confidentiality and ethical reasons, supporting data can only be made available to researchers upon request and approval from the SNAC-K data management and maintenance committee. For further information on the data and how to request access, visit https://www.snac-k.se/for-researchers/.

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