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Social isolation is linked to declining grey matter structure and cognitive functions in the LIFE-Adult panel study

Running title: **Social isolation and the aging brain**

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Abstract

Social isolation has been suggested to increase the risk to develop cognitive decline. However, our knowledge on causality and neurobiological underpinnings is still limited. In this preregistered analysis, we tested the impact of social isolation on central features of brain and cognitive aging using a longitudinal population-based magnetic resonance imaging (MRI) study. Assaying 1335 cognitively healthy participants (50-80 years old, 659 women) at baseline and 895 participants after ~6 years follow-up, we found baseline social isolation and change in social isolation to be associated with smaller volumes of the hippocampus, reduced cortical thickness and poorer cognitive functions. Combining advanced neuroimaging outcomes with prevalent lifestyle characteristics from a well-characterized population of middle- to older aged adults, we provide evidence that social isolation contributes to human brain atrophy and cognitive decline. Within-subject effects of social isolation were similar to between-subject effects, indicating an opportunity to reduce dementia risk by promoting social networks.

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Introduction

Over 50 million humans suffer from dementia today. In just 20 years this number will likely double. Already now, dementia's global annual costs exceed one trillion US$(Prince et al., 2015) and its detrimental effects on the lives of the afflicted makes it a major contributor to the world's burden of disease(Abbafati et al., 2020).

Research on pharmacological interventions targeting dementia pathogenesis have not yielded any result with a clear clinical benefit yet(Knopman et al., 2021) and available drugs targeting cognitive symptoms offer at most a minor alleviation(Knight et al., 2018). Henceforth, prevention is of cardinal importance and potentially modifiable risk factors are our most promising target(Livingston et al., 2020).

Systematic reviews and meta-analyses have concluded that social isolation, the objective lack of social contact, is such a risk factor for dementia (Kuiper et al., 2015; Penninkilampi et al., 2018) and its main feature cognitive decline(Evans et al., 2019; Kuiper et al., 2016). Assuming causal relationships, Livingston et al. calculated population attributable fractions for risk factors for dementia and concluded that 3.5% of cases could be attributed to social isolation. This is almost as many as to obesity, hypertension and diabetes combined(Livingston et al., 2020).

Risk factors of later dementia development often affect the structural brain changes dementia is characterized by: vascular degeneration, amyloid plaques, tau fibrillary tangles, neural degeneration and grey matter loss. Neuroimaging correlates of these brain changes have been observed multiple years prior to symptom onset in autosomal dominant dementia(Gordon et al., 2018) and can already be detected in cognitively healthy persons using neuroimaging(Ewers et al., 2011; Clifford R Jr Jack et al., 2013). Thus, brain magnetic resonance imaging (MRI) can be a potent dementia-risk indicator(Wang et al., 2019), might offer pivotal guidance to identify patients for intensive dementia prevention(Ten Kate et al., 2018) and serve as secondary outcome for intervention trials(Stephen et al., 2019). Still, the link between brain structure and social connection, the umbrella term encompassing social isolation, social support and loneliness, has not received much attention(Wassenaar et al., 2019). Few studies have linked low social connection to an elevated "brain age" gap estimate(de Lange et al., 2021), changes in microstructural(Molesworth et al., 2014; Spreng et al., 2020; Tian et al., 2014) and volumetric measures in brain regions including the hippocampus and the prefrontal cortex(Blumen & Verghese, 2019; Cotton et al., 2020; Düzel

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et al., 2019; James et al., 2012; Schurz et al., 2021; Shen et al., 2022; Spreng et al., 2020; Taebi et al., 2020), however these cross-sectional designs render conclusions about causality difficult. In a longitudinal study using a small sample of 70 participants (37 at follow-up) > 80 years old, microstructural deteriorations and a larger total white matter hyperintensity volume correlated with decreases in predominantly social activities (Köhncke et al., 2016). Furthermore, it suggested that white matter changes mediated the positive association between social activities and perceptual speed (Köhncke et al., 2016). Mortimer et al. conducted a small RCT with older adults and found increased total brain volumes and cognitive function in participants after a social interaction intervention compared to a non-intervention control group(Mortimer et al., 2012).

Taken together, the current evidence suggests social isolation to have an adverse effect on brain health. Still, data from longitudinal studies are required to distinguish between and within-participant effects on brain structure and cognitive function and to gain insights into temporal dynamics and causal relationships. Furthermore, to pointedly leverage the power of such datasets for an improved understanding of the effect of social isolation, conceptual clarity regarding the dimensions of social connection is pivotal but still lacking.

Moreover, no solid evidence on the mechanistic underpinnings of the relationship between social isolation and accelerated brain ageing exists. Several mutually non-exclusive, partly overlapping theories are used to explain the beneficial effects of social interaction. (Hultsch et al., 1999; Kawachi & Berkman, 2001). Amongst them, the stress-buffering hypothesis puts forward the beneficial effects of social support in strenuous times on mental, cognitive, and immunological health(Kawachi & Berkman, 2001), yet this mediating effect has not been explored regarding brain measures.

Longitudinal population-based neuroimaging studies now offer reliable sample sizes to gain knowledge on effect sizes and to disentangle correlation from causation to better understand the impact of social isolation on brain and cognitive aging. In this pre-registered analysis, we aimed to determine the relationship between social isolation, measured using the Lubben social network scale (LSNS-6,(Lubben et al., 2006)), and brain structure and cognitive functions, measured using freesurfer segmentations on advanced high-resolution MRI at 3 Tesla and neuropsychological testings, in a large well-characterized longitudinal sample of mid- to late-life individuals (n > 1900) from the Health Study of the Leipzig Research Centre for Civilization Diseases (LIFE)(Engel et al., 2022).

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To this end, we applied linear mixed effects modeling and structural equation modelling to predict volume of the hippocampus, a focal point of age-related atrophy and Alzheimer's disease pathology (Rodriguez et al., 2020), by baseline social isolation and change in social isolation over time. Analogously, we modeled memory performance, processing speed, and executive function, as well as whole-brain vertex-wise cortical thickness. Significance was evaluated based on frequentist p-values and Bayes factors, and we adjusted for control variables including age in all models. Details on MRI preprocessing and pre-defined statistical analyses were preregistered at https://osf.io/8h5v3/.

We hypothesized that both baseline and change in social isolation would correlate with smaller hippocampal volume, cognitive functions (memory, processing speed, executive functions) and cortical thickness. Additionally, we hypothesized interaction effects of baseline social isolation with change in age in the same direction. Moreover, we aimed to test a mediating role of chronic stress as well as hippocampal volume on cognition in these models and explored possible gender differences in stratified analyses.

Results

We included all individuals equal or over the age of 50 with available neuroimaging of LIFE (Engel et al., 2022), due to the accelerated volume shrinkage starting at about 50 years of age in the hippocampus (Fjell et al., 2013). To avoid reverse causation, we further excluded cognitive impairment or prior brain pathology such as history of stroke, neurodegenerative disease or brain tumor. In total, we analysed 1335 participants at baseline and 895 participants at follow-up with a mean age of 67 and 73 years, respectively, thereof 49% and 52% women, respectively and a ~6 years mean change in age at follow-up. For various sensitivity analyses, we reincluded participants that did not meet our preregistered inclusion criteria from the entire sample of 1992 participants at baseline and 1409 at follow-up. The sample displayed a high prevalence of cardiovascular risk factors, with 60% hypertension and < 20% diabetes, and 11-13% had no tertiary education (Table 1).

Individuals exhibited LSNS scores ranging across the whole spectrum, with an average score of 16 and 19.7% scoring below the accepted threshold of 12, indicating elevated risk of social isolation, similar to other populations (Lubben et al., 2006). Note that for further analyses, LSNS values were calculated as 30 – LSNS to make larger values indicate greater social isolation and coefficients should thus be interpreted accordingly. Hippocampus volumes derived from T1-weighted high-resolution anatomical MRI scans at 3 T (Reuter et al.,

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2012)showed shrinkage with higher age of about -0.75% per year (Fig. 1, left panel), similar to previous estimates (Fjell et al., 2013). To test the effects of social isolation on hippocampal volume, we conducted hierarchical linear mixed effects models adjusting for confounding effects of age, gender and random effects of the individual in a first model (model 1), and additionally for cardiovascular risk factors in a second model (model 2). We differentiated within and between subject effects(van de Pol & Wright, 2009) of social isolation and investigated the interaction effect of baseline LSNS and change in age to test whether participants that are socially more isolated at baseline experienced more pronounced age-related changes. Please see osf.io/8h5v3/and Methods for details.

Table 1.

Variable	**BL**, N = 1,992	**FU**, N = 1,409
gender (female)	921 (46%)	656 (47%)
baseline age (years)	67 (7) | 50 | 82 | 0	68 (7) | 50 | 84 | 0
change in age (years)	0.00 (0.00) | 0.00 | 0.00 | 0	5.89 (1.97) | 0.00 | 9.50 | 15
baseline LSNS	14.1 (5.2) | 0.0 | 30.0 | 181	13.7 (5.1) | 0.0 | 30.0 | 20
change in LSNS	0.00 (0.00) | 0.00 | 0.00 | 0	0.38 (4.37) | -21.00 | 18.00 | 115
HCV (mm^3)	3,671 (411) | 2,022 | 4,871 | 83	3,487 (430) | 1,913 | 4,579 | 665
BMI (kg/m^2)	27.9 (4.2) | 16.8 | 46.8 | 0	27.7 (4.1) | 18.1 | 46.5 | 0
hypertension	1,218 (61%)	830 (59%)
diabetes	367 (18%)	239 (17%)
education	255 (13%)	151 (11%)
CESD	10 (6) | 0 | 48 | 104	10 (6) | 0 | 48 | 62
memory (SD)	0.03 (0.97) | -8.79 | 1.70 | 84	-0.06 (1.04) | -5.84 | 1.64 | 315
processing speed (SD)	0.09 (0.92) | -7.80 | 1.73 | 12	-0.14 (1.10) | -7.80 | 1.61 | 214
executive functions (SD)	0.13 (0.95) | -4.59 | 3.26 | 11	-0.21 (1.04) | -4.43 | 3.29 | 210
TICS	58 (27) | 0 | 166 | 1,480	56 (27) | 0 | 146 | 825
pandemic	0 (0%)	412 (31%)

Descriptive Statistics. Values for categorical variables: n (%) yes; Values for continuous variables: Mean (SD) | minimum | maximum | n missing
HCV, right-left average hippocampal volume; BMI, body-mass-index; LSNS, Lubben Social Network Scale, calculated as 30 – LSNS to make larger values indicate greater social isolation; TICS, Trierer Inventar zum chroischen Stress; CESD, Center for Epidemiological Studies Depression Scale; SD, standard deviation; education, no tertiary education

Social isolation and hippocampal volume

Accordingly, we found that both, stronger baseline social isolation (values for models 1/2: $\beta = -5.5/-5.7$ mm^3/point on the LSNS (pt), FDR-corrected q-value(q) = 0. 0044/0.0075) and

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increases in social isolation (β = −4.9/−4.9 mm^3/pt, q = 0. 0095/0.0174) significantly predict smaller hippocampal volumes independent of confounders (Table 2, Figs 1-3). Furthermore, the interaction of baseline social isolation and change in age indicated that stronger baseline social isolation led to smaller hippocampal volumes with increasing follow-up time (β = −0.56/−0.54 mm^3/(pt*year), q = 0.045/0.076). Significance of these findings are further underlined by Bayes factors of 15 to 20 for baseline social isolation and of around 3 for change in social isolation. The effect size of one point on the LSNS is equivalent to a 2.5-month difference in baseline age.

Table 2

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippo-campal Volume	1	LSNS_base	-5.5	-9.1, -1.9	0.0015**	0.0044**	14.61**
		LSNS_change	-4.9	-8.5, -1.3	0.0039**	0.0095**	2.9
		age_base	-25.8	-28.6, -22.9			
		age_change	-27.4	-29.7, -25.1			
	2	LSNS_base	-5.7	-9.5, -1.8	0.0019**	0.0075**	19.51**
		LSNS_change	-4.9	-8.7, -1.1	0.0058**	0.0174*	3.31*
		age_base	-23.9	-26.9, -20.9			
		age_change	-27.7	-30.1, -25.3			

Adjusted regression coefficients and measures of significance for the effect of social isolation on hippocampal volume. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, q-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
The unit of effect sizes is mm^3/point on the LSNS.
Social isolation significantly predicts hippocampal volume after multiplicity control. Bayes Factors provide strong evidence in favour of the alternative hypotheses for baseline social isolation and anecdotal to moderate evidence for change in social isolation. The effect size of one point on the LSNS is equivalent to a baseline age difference of around two and a half months.

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Social Isolation and cognitive functions

In analogous linear mixed effects models, we tested the effects of social isolation on cognition, measured using domain-specific composite scores based on z-scored results of the trail-making test (TMT A and B) and the CERAD-plus test battery (CERAD - Consortium to Establish a Registry for Alzheimer's Disease, RRID:SCR_003016) assessed under standardized conditions(Beyer et al., 2017). Overall, stronger baseline social isolation and to a lesser extent increases in social isolation, linked to worse cognitive performance (Table 3, Fig 1). Specifically, stronger social isolation at baseline significantly predicted lower executive functions (β = −0.026/−0.015 SD/pt, q = 1.0e-07/0.0046) and lower processing speed (β = −0.018/−0.018 SD/pt, q= 1.0e-05/1.2e-04). The link to lower memory (β = −0.014/−0.008 SD/pt, q = 0.002/0. 0775) was strong in model 1 but did not survive FDR-correction when controlling for additional covariates. Increases in social isolation over time significantly predicted lower memory in model 1 (β = −0.013/−0.009 SD/pt, q = 0.045/0.157) and lower processing speed in model 2 before FDR correction (β = −0.008/−0.012 SD/pt, q = 0.163/0.076) but not executive functions (β = 0.003/0.006 SD/pt, q = 0.787/0.856). Very high Bayes Factors corroborate and substantiate the evidence for the negative effect of baseline social isolation on cognitive functions. Figs. 2-3 allow comparisons of these effects with other predictors for the different dependent variables.

We did not observe interaction effects of social isolation on cognitive performance with age. Tables S3-5 provide a comprehensive summary of all LMEs and predictors including covariates.

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Table 3

dv	Model	Predictor	Esti-mate	95% CI	p-value	FDR	BF
Executive Functions	1	LSNS_base	-0.026	-0.035, -0.017	8.4e-09****	1.0e-07****	1.5e+06****
		LSNS_change	0.003	-0.011, 0.018	0.6787	0.787	0.08
		age_base	-0.020	-0.027, -0.013			
		age_change	-0.053	-0.063, -0.042			
	2	LSNS_base	-0.015	-0.025, -0.006	8e-04****	0.0046**	43.65***
		LSNS_change	0.006	-0.009, 0.021	0.7842	0.8555	0.07
		age_base	-0.014	-0.022, -0.007			
		age_change	-0.054	-0.065, -0.043			
Memory	1	LSNS_base	-0.014	-0.022, -0.006	5e-04****	0.002**	49.05***
		LSNS_change	-0.013	-0.026, 0	0.0262*	0.0449*	1.12
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.018	-0.027, -0.009			
	2	LSNS_base	-0.008	-0.016, 0.001	0.0452*	0.0775	1.25
		LSNS_change	-0.009	-0.023, 0.005	0.1046	0.1569	0.48
		age_base	-0.033	-0.04, -0.026			
		age_change	-0.017	-0.027, -0.008			
Processing Speed	1	LSNS_base	-0.018	-0.026, -0.011	1.7e-06****	1.0e-05****	9.4e+03****
		LSNS_change	-0.008	-0.021, 0.005	0.1087	0.163	0.39
		age_base	-0.038	-0.044, -0.032			
		age_change	-0.033	-0.043, -0.024			
	2	LSNS_base	-0.018	-0.026, -0.01	9.6e-06****	1e-04****	2.5e+03****
		LSNS_change	-0.012	-0.025, 0.001	0.038*	0.076	1.33
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.031	-0.041, -0.022			

Adjusted regression coefficients and measures of significance for the effect of social isolation on cognitive functions. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, q-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
The unit of effect sizes is standard deviation/point on the LSNS

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Baseline social isolation significantly predicts cognitive functions after FDR-correction and BFs provide very strong to decisive evidence in favour of the alternative hypotheses. Only for model 2 of memory evidence is weak. No association of change in social isolation with executive functions is detected and evidence for associations with memory and processing speed are limited.

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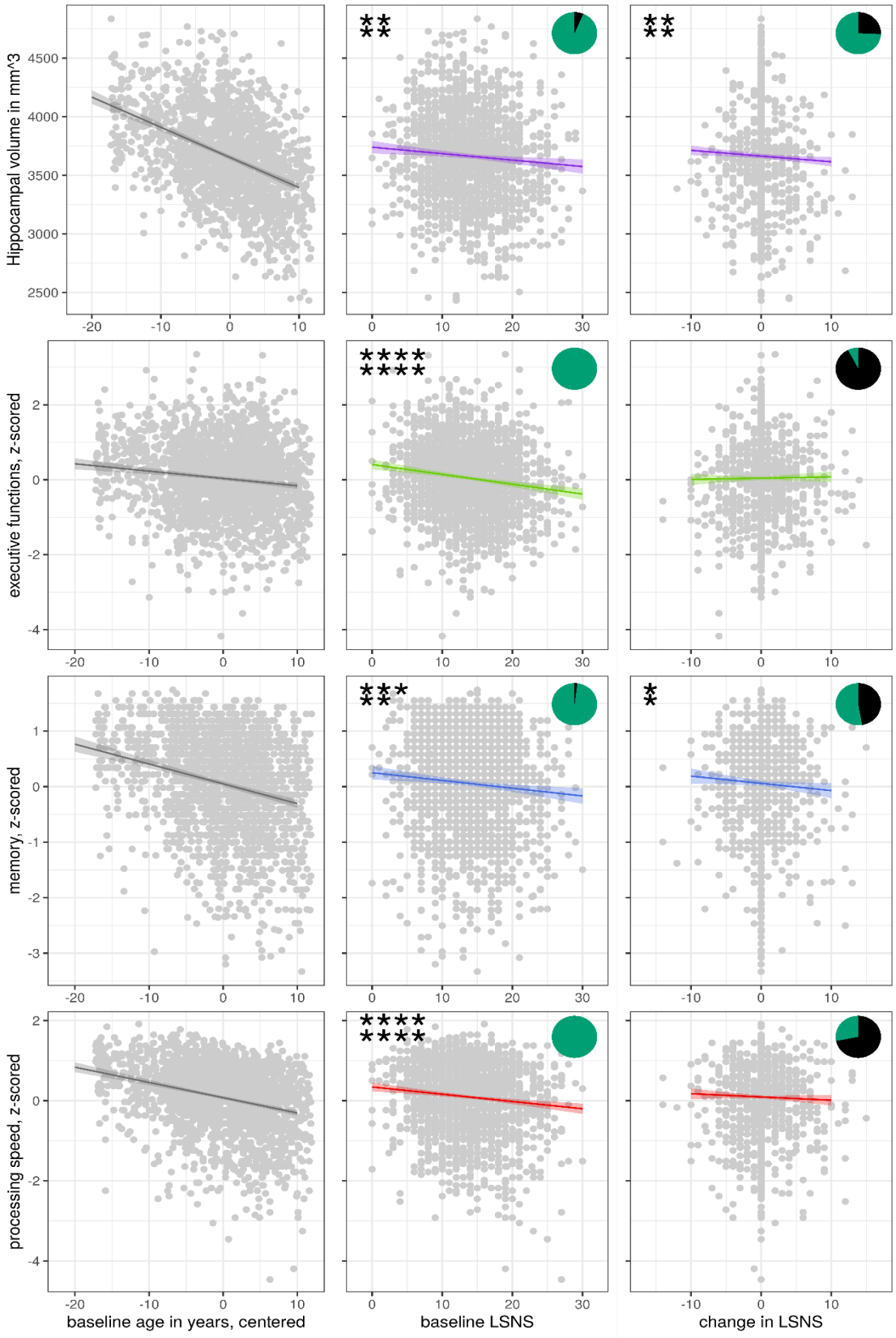
Figure 1

Scatterplots with regression lines and 95% confidence intervals for model 1.



Asterisks show frequentist levels of significance. The 1st and 2nd line show values before and after FDR, respectively. **** $p < 0.0001$, *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$.

Pie charts show bayesian relative evidences. The green and black arc lengths represent the evidence in favour of the alternative and the null hypothesis, repectively.

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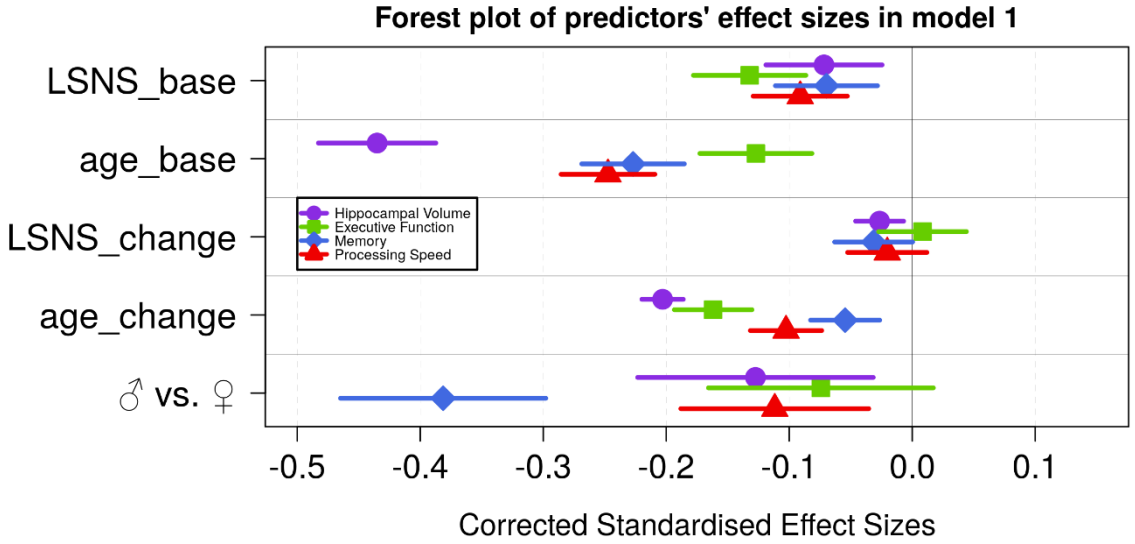
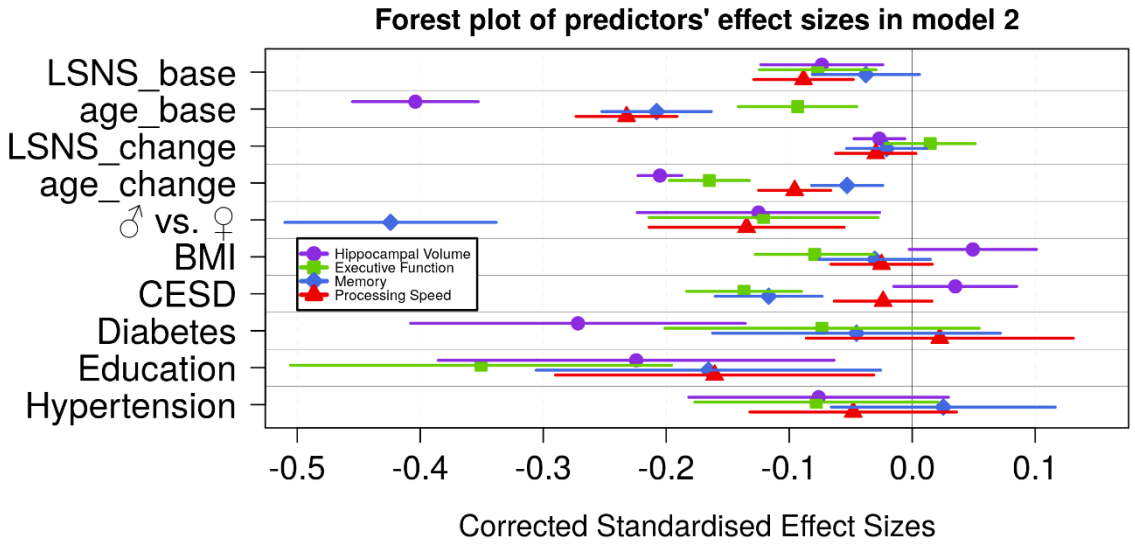
Figure 2



Forest plot of predictors' effect sizes in model 1. For the gender variable and for the education variable being women and having at least a tertiary degree were coded as 0, respectively.
Betas were standardized by the standard deviations of the dependent and independent variable.
LSNS_base, baseline Lubben Social Network Scale; age_base, baseline age; LSNS_change, change in Lubben Social Network Scale; age_change, change in age.

Figure 3



Forest plot of predictors' effect sizes in model 2. For the gender variable and for the education variable being women and having at least a tertiary degree were coded as 0, respectively.
Betas were standardized by the standard deviations of the dependent and independent variable.
LSNS_base, baseline Lubben Social Network Scale; age_base, baseline age; LSNS_change, change in Lubben Social Network Scale; age_change, change in age.

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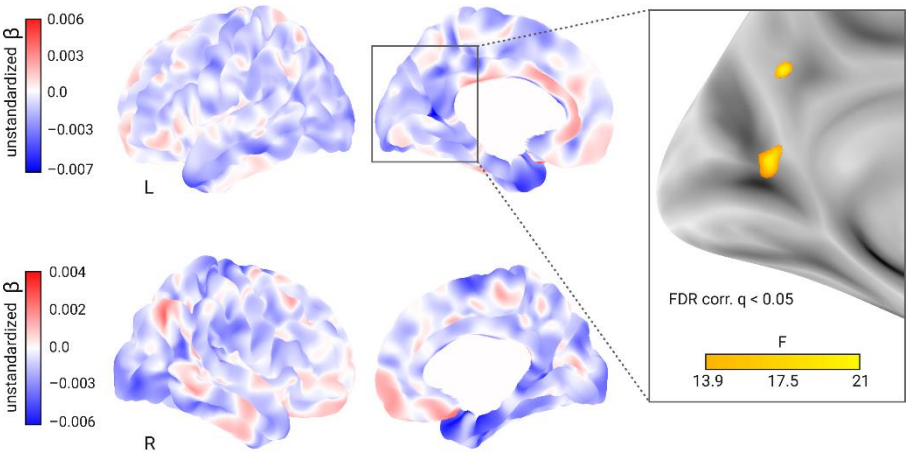
Social isolation and cortical thickness

To explore whether social isolation affects regional cortical thickness, we conducted whole-brain vertex-wise linear mixed effects analyses on Freesurfer-derived 3D cortical maps(Reuter et al., 2012). In model 1, we found a total of four clusters of significantly decreased cortical thickness associated with stronger baseline social isolation after FDR correction with an α-level of 5% (Fig 4). The clusters were located in the left precuneus and right supramarginal gyrus, superior temporal gyrus and cuneus. Increases in social isolation over time were linked to decreased cortical thickness in 7 clusters in the right middle and superior frontal gyri, orbitofrontal and lateral occipital cortex (Fig 5). When controlling additionally for cardiovascular covariates (model 2), three of these in the middle/superior frontal and lateral occipital gyrus remained significantly associated, with the largest one splitting into two smaller clusters. Table 4 lists these clusters, their locations and sizes.

Figure 4
Whole brain analysis of the effect of baseline social isolation on cortical thickness



Whole brain analysis of the effect of baseline social isolation on cortical thickness. Unstandardized betas are the vertex-wise effect sizes of baseline social isolation in mm/point on the Lubben Social Network Scale corrected for baseline age, change in age, change in social isolation and gender. The first row shows the left hemisphere. Areas in which stronger isolation links to reduced thickness are marked in blue, the inverse in red. The right hemisphere is shown below. First and second column show the lateral and medial view, respectively. The box on the right shows two clusters of lower cortical thickness associated with social isolation in the left precuneus that remained significantly associated after FDR-correction and the F-value of each significant vertex. Significantly associated FDR-corrected clusters in the supramarginal gyrus and cuneus in the right hemisphere are not highlighted.

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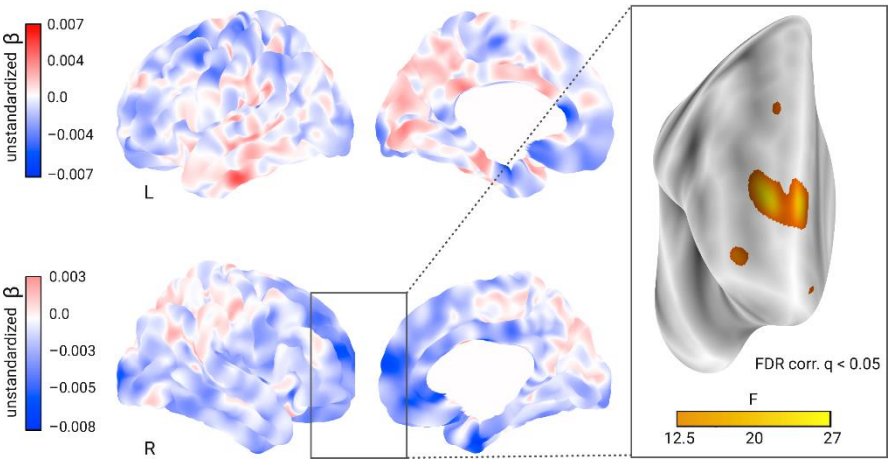
Figure 5
Whole brain analysis of the effect of change in social isolation on cortical thickness



Whole brain analysis of the effect of change in social isolation on cortical thickness.
Unstandardized betas are the vertex-wise effect sizes of change in social isolation in mm/point on the Lubben Social Network Scale corrected for baseline age, change in age, baseline social isolation and gender. The first row shows the left hemisphere. Areas in which stronger isolation links to reduced thickness are marked in blue, the inverse in red. The right hemisphere is shown below. First and second column show the lateral and medial view, respectively. The box on the right shows clusters of lower cortical thickness associated with social isolation in the right superior and middle frontal gyrus, and lateral and medial orbitofrontal cortex that were significant after FDR-correction and the F-value of each significant vertex. Additionally, we detected another significant cluster after FDR-correction in the lateral occipital cortex that is not highlighted in this figure.

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Table 4

poi	hemisphere	cortical region	maximum p-value	size in mm²	NVtxs	model
LSNS_base	rh	supramarginal	2.1e-05	27.70	73	1
LSNS_base	rh	cuneus	5.5e-05	11.49	17	1
LSNS_base	lh	precuneus	3.0e-06	201.78	455	1
LSNS_base	lh	precuneus	3.6e-06	50.10	94	1
LSNS_change	rh	rostralmiddlefrontal	1.9e-07	764.18	1,015	1
LSNS_change	rh	lateraloccipital	5.5e-05	91.99	104	1
LSNS_change	rh	rostralmiddlefrontal	8.5e-06	90.22	121	1
LSNS_change	rh	superiorfrontal	8.1e-05	40.36	58	1
LSNS_change	rh	medialorbitofrontal	1.4e-04	21.08	32	1
LSNS_change	rh	lateralorbitofrontal	1.7e-04	11.21	34	1
LSNS_change	rh	lateralorbitofrontal	1.6e-04	10.89	29	1
LSNS_change	rh	rostralmiddlefrontal	1.3e-06	253.31	343	2
LSNS_change	rh	superiorfrontal	6.4e-06	113.76	161	2
LSNS_change	rh	lateraloccipital	1.4e-05	95.17	104	2
LSNS_change	rh	rostralmiddlefrontal	3.9e-05	21.90	29	2

FDR-corrected clusters of reduced cortical thickness significantly associated with social isolation. poi, predictor of interest; MNIX/Y/Z, MNI305 x/y/z coordinates of the maximumn; NVtxs, Number of vertices constituting the cluster; LSNS_base, baseline social isolation; LSNS_change, change in social isolation; rh, right hemisphere; lh, left hemisphere
full model 1: cortical thickness ~ LSNS_base + LSNS_change + age_base + age_change + sex
full model 2: model 1 + hypertension + diabetes + education + depression + BMI

Mediation analyses

Turning to the stress-buffering hypothesis, we investigated whether perceived stress, measured using the Trierer Inventar zum chronischen Stress (TICS)(Schulz & Schlotz, 1999), mediated the relationship of social isolation and hippocampal volume. Moreover, we investigated whether hippocampal volume mediated the association between social isolation and cognitive functions. Specifically, we investigated the indirect path resulting from the regressions of follow-up mediator on baseline LSNS and follow-up dependent variable on baseline mediator.

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Neither the mediation analyses with chronic stress as a mediator (n = 62 complete observations) nor the mediation analyses with hippocampal volume as a mediator (n = 313-331) yielded significant results. Due to the requirements of the model design and over 50% missingness in the stress questionnaire the sample sizes of the mediation analyses were gravely diminished. Details on the mediation analyses are provided in Table S6.

Sensitivity Analyses

In addition to these pre-registered analyses, we conducted sensitivity analyses to test the robustness of our results on hippocampal volume and cognitive functions. These included possible effects of the Covid-19 pandemic, effects related to the definition of exclusion criteria or confounder specificities. Analyses accounting for a) potential effects of measurements before compared to during the Covid-19 pandemic, b) reducing the exclusion criteria (i.e., not excluding cognitively impaired participants, participants taking centrally active medication and participants with recent cancer treatment), c) only including participants with two timepoints and using mean and within scores, d) using a hypertension cut-off of 140mmHg and e) using an MMSE cut-off of <27 confirmed the regression coefficients of our models in terms of direction and size (Tables S7-16).

Of note, neuroscience has historically neglected sex and gender differences, predominantly resulting in increased misdiagnoses of and relatively worse treatments for women(Shansky & Murphy, 2021). Therefore, we recalculated analyses in gender-stratified samples (n women = 1125 observations, n male = 1105 observations) to test for differences in the effects of social isolation (Table S17). No clear pattern of difference emerged between women and men. A minor observable difference was that the interaction of baseline social isolation with change in age on hippocampal volume was more pronounced in men.

In order to further investigate the nature of the correlations, we calculated bivariate latent change score (BLCS) models. In these models we simultaneously tested for an effect of baseline social isolation on change in cognitive functions or hippocampal volume and vice versa (see Fig. S2 for a visualization). The bivariate latent change score models did not produce solid evidence regarding directionality (Table S18). As in the mediation analyses, the design of the BLCS resulted in smaller sample sizes (n = 333-548 complete observations).

Discussion

In this pre-registered study, we investigated the associations of social isolation with brain structure and cognition in a large cognitively healthy mid- to late-life longitudinal sample. In

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line with our pre-specified hypotheses, we showed a significant link between stronger baseline social isolation and increases in social isolation over the course of ~ 6 years and smaller hippocampal volumes. Both predictors had an effect size per point on the LSNS comparable to a two and a half-month difference in baseline age in this age range. Simply put, assuming that if everything else remained stable, the difference between having one or 3-4 close and supportive friends is comparable to a one-year difference in hippocampal aging. Furthermore, we found significant associations of stronger baseline social isolation with lower executive functions, memory and processing speed. The link to executive functions was particularly strong with an effect size larger than a one-year difference in baseline age. For increases in social isolation, confidence intervals were wider but effect sizes, except for executive functions, were similar in magnitude to that of baseline social isolation. Moreover, there was an interaction effect of baseline social isolation with change in age on hippocampal volumes indicating accelerated brain aging in more isolated individuals. In multiple sensitivity analyses we showed the robustness of these findings. Neither applying less exclusion criteria, only including participants with two timepoints, nor controlling for the impact of the ongoing pandemic changed our results substantially. Moreover, we found clusters of decreased cortical thickness in the cuneus, precuneus, lateral occipital cortex, supramarginal gyrus, orbitofrontal cortex and superior and middle frontal gyrus associated with social isolation cross-sectionally or longitudinally. Mediation analysis in smaller sample sizes testing potential effects of social isolation through lowering adverse effects of stress revealed no significant effects.

Hippocampal volume

Our findings indicate that social isolation contributes to grey matter loss in the hippocampus, a focal point of atrophy in mild cognitive impairment(Devanand et al., 2007) and dementia(N. C. Fox et al., 1996).

Notably, not only baseline social isolation (a between-subject effect) but also change in social isolation (a within-subject effect) significantly predicted hippocampal volume. Through the employment of statistical LMEs, we were able to distinguish and study effects at these different levels(van de Pol & Wright, 2009) and the design helped us to avoid fallacious inferences from single level data(Robinson, 1950) to which simple linear regressions would have been susceptible. Specifically for the study of social isolation as a risk factor for dementia, it is crucial to disentangle between- and within-subject effects. Social isolation has both been described as a trait(Noonan et al., 2021), implying it to be an invariant between-

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subject characteristic and as a potential target for interventions(Hussenoeder & Riedel-Heller, 2018), implying it to be a modifiable within-subject effect. The finding of a significant within-subject effect of change in social isolation therefore offers hope for modifiability as it implies that the observed associations are not (exclusively) the effect of an invariant trait. Thus, our data point towards that reducing social isolation could help to maintain hippocampus integrity in aging.

However, this assumes a causal effect of social isolation. As associations with social isolation could also have resulted from reverse causation through health selection, i.e. that participants with accelerated brain aging are more likely to become socially isolated, this assumption needs careful consideration. On the one hand, our interaction models designed to test the temporality of the effect, provided evidence for an interaction of baseline social isolation and change in age on hippocampal volume, pointing towards a detrimental effect of social isolation. Bayesian statistics, however, imply the absence of an interaction effect for all other dependent variables and the bivariate latent change score models did not provide evidence in favour of causality in the hypothesized direction. This inconclusiveness might result from our reduced follow-up sample size and thus related lower power, especially in the latent score models. For example, data from the English Longitudinal Study of Aging from > 6000 older adults measured at up to 6 two-year intervals supports the assumed causality of social isolation with regards to memory performance(Read et al., 2020). Moreover, the presence of considerable effect sizes and the high statistical confidence in these estimates on multiple outcomes in this healthy sample without cognitive impairment speaks against the competing hypothesis of reverse causality through health selection and in favour of a causal role of social isolation. Furthermore, the lack of any strong increase in effect size when including health-impaired participants corroborates this interpretation.

Cognitive functions

Baseline social isolation, and to a lesser extent, change in social isolation, were significantly associated with cognitive performance, i.e. executive functions, processing speed and memory, all of which undergo decline in (pathological) aging(Blazer et al., 2015). Again, our results thus imply a detrimental role of social isolation on cognitive functions. We could however not observe that social isolation lowered memory performance through reductions in hippocampal volume, a hypothesis raised by considerations of the central role of the hippocampus in memory(Buzsáki & Moser, 2013). Similarly, we could not find evidence that social isolation affected hippocampal volume through higher chronic stress measured with

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questionnaires, a hypothesis put forward by the stress buffering theory(Kawachi & Berkman, 2001). However, these latter analyses suffered from small sample sizes and a limited number of timepoints.

Cortical thickness

Overall, comparing our brain morphometric results with those of existing cross-sectional studies on social isolation, detected brain regions coincide. A rather small-sampled study did not find a link between social isolation and grey matter volumes(Lin et al., 2020) but James et al. (occipital lobe)(James et al., 2012) and Blumen and Verghese (hippocampus, precuneus, superior frontal gyrus, medial frontal gyrus)(Blumen & Verghese, 2019) and Shen et al. (hippocampus, right supramarginal gyrus)(Shen et al., 2022) found decreased volumes in regions we detected, too.

Several of the cortical regions identified in our study (precuneus, orbitofrontal cortex) belong to the pattern of exacerbated regional atrophy found in Alzheimer's disease. Furthermore, we detected regions known for increased cortical thinning in the healthy process of aging (cuneus, lateral occipital cortex, inferior frontal gyrus) and both in healthy and pathological aging (supramarginal gyrus, medial frontal gyrus)(Bakkour et al., 2013; Pini et al., 2016). This indicates an aggravating role of social isolation in cortical thinning that may contribute to normal and accelerated brain aging processes. However, the findings of lower cortical thickness must be interpreted cautiously due to the limited consistency between cross-sectional and longitudinal effects and the exploratory approach of whole brain analyses.

Limitations

A limitation of this study is its uncertain generalizability to the general population because the sample was probably affected by selection and attrition bias common to longitudinal studies (Chatfield et al., 2005). Attrition bias might have mostly affected the mediation and BLCS models that thus offered reduced interpretability, in spite of the comparatively large neuroimaging cohort. However, the LMEs were mostly unscathed by this problem due to their ability to make use of datapoints of participants with only one full observation. In addition, our population represents a WEIRD sample (i.e., western, educated, industrialised, rich, democratic) which might skew our understanding of how social isolation affects brain health(Laird, 2021). Considering hippocampus segmentations, it has been argued that FreeSurfer systematically overestimates volumes compared to manual volumetry, however, this difference did barely emerge in participants over the age of 50 (Wenger et al., 2014). A

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further limitation are ceiling effects in the CERAD word list memory task in healthy adults, potentially limiting the sensitivity to detect subtle differences. Additionally, covariance of social isolation with other variables such as hypertension or diabetes could have influenced the results. However, note that all VIFs were acceptable indicating low reason for concern regarding multicollinearity. Lastly, inferences from our results on dementia etiology must be made with caution as we did not investigate clinically diagnosed dementia patients.

In quantitative studies, despite its importance in shaping the research process and conclusions, e.g. in functional MRI analysis (Botvinik-Nezer et al., 2020), researchers' influence is often disregarded. In the supplementary text we offer a brief reflexivity section to make relevant influences on this study transparent and to shortly discuss the value of reflexivity for quantitative science.

Implications for public health and future work

This pre-registered large-scale population neuroimaging analysis adds robust support to the view that social isolation is associated with accelerated brain aging and cognitive decline in non-demented adults in mid- to late-life. Our findings further imply that social contact protects from detrimental processes and thereby preserves brain structure and function. Henceforth, targeting social isolation through tailored strategies might contribute to maintaining brain health into old age.

While we see evidence converging on social isolation as a causal risk factor for dementia and cognitive decline, future neuroimaging studies should pay particular attention to questions of temporality in their design to clear up remaining uncertainties. Intervention studies will be the gold standard to provide evidence with regards to the causal role and effect size of social isolation. Yet, multidomain interventions for dementia prevention justifiably become the norm(Stephen et al., 2019), so that effects of reduced social isolation must be investigated as a likely contribution to an aggregate effect.

Illuminating the mechanistic underpinnings of the association should be another focus for future research. Studies might prioritise obtaining reliable proxies for the hypothesized mediators. As elevated cortisol levels, in line with the stress-buffering hypothesis, may exert detrimental effects on cognition and contribute to AD pathology(Ouanes & Popp, 2019), using hair cortisol, a reliable measure of chronic stress(Staufenbiel et al., 2013), could be a promising choice to further investigate this proposed mechanism. Furthermore, alternative mechanistic theories should be investigated. The main-effect theory postulates that social

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relationships foster beneficial health behaviours, affective states and neuroendocrine responses, ultimately protecting neuronal tissue(Kawachi & Berkman, 2001). Others point out that socializing is cognitively demanding and requires engagement with complex environments. In the "use-it-or-lose-it" theory, this is crucial for the maintenance of cognitive function(Hultsch et al., 1999). Promising approaches to answer this research question could be interventions specifically targeting one of the hypothesized detrimental processes in isolated individuals and mediation analyses of multi-wave studies with larger sample sizes. Lastly, reverse causality or simultaneity can not be completely ruled out yet. However, the observed solid correlations in our healthy sample and the lack of an increase in effect sizes when including participants with dementia or low MMSE scores renders this alternative hypothesis to a causal role of social isolation unlikely.

Moreover, studies investigating social isolation due to lockdown measures and its impact on cognitive and brain health will be of great significance.

In light of the relevance of social isolation for cognitive and general health and wellbeing(National Academies of Sciences, 2020), its pervasiveness in the elderly population of the global north (Livingston et al., 2020) is alarming. Physical distancing measures have caused an unprecedented rise in the attention to the impact of social isolation but social isolation has been a grave problem before Covid-19 and it will remain a central public health concern thereafter. Existing and future research on the role of social isolation in health and disease should provide guidance for the urgently needed development and evaluation of tailored strategies against social isolation and its detrimental effects. These should address social isolation both through intervention strategies on the individual but also societal level, leveraging values like solidarity and communality.

Methods

Study Design and Preregistration

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and Committee on Best Practices in Data Analysis and Sharing (COBIDAS) on MRI guidelines in our reporting wherever appropriately applicable.

The study's preregistration can be found on https://osf.io/8h5v3/. Please refer to it for information on the authors' previous knowledge of the data and a comprehensive overview of our pre-specified hypotheses and models.

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Study Population

We used longitudinal data from the "Health Study of the Leipzig Research Centre for Civilization Diseases" (LIFE). The study was approved by the institutional ethics board of the Medical Faculty of the University of Leipzig and conducted according to the declaration of Helsinki. The LIFE-Adult-Study is a population-based panel study of around 10,000 randomly selected participants from Leipzig, a major city with 550,000 inhabitants in Germany. A sub-group of around 2600 participants underwent MRI testing at baseline. The baseline examination was conducted from August 2011 to November 2014. Follow-up assessments were performed around six to seven years after the respective first examinations(Engel et al., 2022). Around 1000 participants of the MRI-subsample returned for follow-up testing.

we included all participants over 50 with MRI data that did not fullfil any of the following exclusion criteria:

- Anamnestic history of stroke
- any medical condition (i.e., epilepsy, Multiple sclerosis, Parkinson's disease) / chronic medication use that would compromise cognitive testing - (i.e., cancer treatment in the past twelve months or drugs affecting the central nervous system)
- diagnosed dementia or Mini-Mental State Examination (MMSE)-score <24
- a trained radiologist considered the MRI scans unusable due to brain tumors, or acute ischemic, hemorrhagic or traumatic lesions

If no MMSE data were available, the participants were excluded if their overall performance in cognitive tests negatively deviated from the wave's mean by 2 standard deviations (SDs) which is a stricter criterion excluding ~2.6% of the sample compared to ~0.8% excluded based on the MMSE. The exclusion criteria were chosen to reduce the potential of reverse causality, i.e. dementia symptoms leading to a loss of social connections, as correlations observed in this cognitively intact sample should not stem from dementia symptoms.

MRI Data Acquisition, Processing and Quality Control

We obtained T1-weighted images on a 3 Tesla Siemens Verio MRI scanner (Siemens Healthcare, Erlangen, Germany) with a 3D MPRAGE protocol and the following parameters: inversion time, 900 ms; repetition time, 2,300 ms; echo time, 2.98 ms; flip angle, 9°; field of view, 256 × 240 × 176 mm3; voxel size, 1 × 1 × 1 mm^3. We processed the scans with

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FreeSurfer (FreeSurfer, V5.3.0, RRID:SCR_001847) and the standard cross-sectional pipeline recon-all. FreeSurfer automatically measures hippocampal volume, vertex-wise cortical thickness and intracranial volume. To ensure high within-subject reliability, we employed FreeSurfer's longitudinal pipeline on all scans, including those of participants without a follow-up scan. Please see(Reuter et al., 2012) for details. Moreover, we smoothed the cortical thickness surfaces with a 10mm kernel to improve reliability and power(Liem et al., 2015). Different Linux kernels and Ubuntu versions constituted the computational infrastructure during the data acquisition and processing.

Visual quality control was based on the recommendations of Klapwijk et al.(Klapwijk et al., 2019). After the baseline data were acquired, our team visually controlled all results of the cross-sectional recon-all pipeline. Additionally, we controlled the outputs of the longitudinal stream of all participants with follow-up data and those whose cross-sectional runs required editing. If we detected errors in the processed scans, we manually edited them (N=283). We excluded participants from analyses using MRI measures if we deemed the processed scans to be unusable (n=68).

Variable Construction

Social Isolation

We used the standard Lubben Social Network Scale (LSNS) -6(Lubben et al., 2006) to measure the participants' social isolation. The questionnaire is a suitable tool to measure social isolation(Valtorta et al., 2016) has a high internal consistency (Cronbach's $\alpha = 0.83$), a stable factor structure of the family and non-kin subscale (rotated factor loading comparisons = 0.99) and good convergent validity (correlations with caregiver / emotional support availability and group activity all 0.2 to 0.46 across multiple sites)(Lubben et al., 2006). In order to make larger scores imply more isolation, we subtracted the actual score from the maximum score of 30.

To quantify changes in social isolation, we subtracted the baseline from the follow-up score. For all baseline observation change in LSNS = 0.

Gray matter measures

We used the hippocampal volume derived from FreeSurfer's segmentation and averaged it over both hemispheres. Furthermore, we adjusted it for intracranial volume according to the following formula:

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$HCV_{adjusted,\ i} = HCV_{raw,\ i} - \beta * (ICV_{raw,\ i} - ICV_{mean})$

where β is the unstandardized regression coefficient of hippocampal volume (HCV) on intracranial volume (ICV) from a linear mixed-effects model (LME)(C R Jr Jack et al., 1998).

For whole brain analyses we used the FreeSurfer fsaverage template and cortical thickness as a vertex-wise outcome.

Cognitive Functions

We calculated domain-specific composite scores and calculated them as follows(Beyer et al., 2017) :

Executive functions consisted of phonemic and semantic fluency, combined with TMT B/A: executive functions = (z_phonemic fluency + z_semantic fluency + z((TMT B – TMT A)/TMT A))/3

For the memory score, we defined learning as the sum of three consecutive learning trials of the CERAD word list (10 words), recall as the sum of correctly recalled words after a delay, in which participants performed a nonverbal task, and recognition as the number of correctly recognized words out of a list of 20 presented afterwards. memory = (z_learning + z_recall + z_recognition)/3

Processing speed was defined as the negated z-scored TMT part A score.

Sum-score = z_phonemic fluency + z_semantic fluency + z_sum_learning + z_recall + z_recognition + z((TMT B – TMT A)/TMT A)

Stress

Trierer Inventar zum chronischen Stress (TICS) is a German questionnaire assessing perceived stress (57 items, six sub-scales, 0-4 points per item). Its sum score is our measure of participants' chronic stress. The subscales have acceptable to excellent internal consistency (Cronbach's α = 0.76-.091) and criterion validity of the work overload sub-scale has been shown by demonstrating a significant correlation with cortisol levels over the course of a work days and its ability to differentiate tinnitus patients from healthy controls(Schulz & Schlotz, 1999).

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Control variables

Month and year of birth of the participants and the date of the MRIs were recorded and used to calculate the age to one decimal point. Age = YOM.MOM – YOB.MOB (YOM/MOM = year/month of MRI, YOB/MOB = year/month of birth). If no MRI was available, we used the date of the LSNS.

For follow-up observations, we calculated: change in age = age at follow-up - baseline age. For all baseline observations change in age = 0.

Data on the following variables was only available for the baseline. Henceforth, we used the baseline values of these control variables for both timepoints.

We calculated the body-mass-index (BMI) according to the standard formula: BMI = weight [kg] / (height [m])2

In order to control for hypertension and diabetes, we used dichotomized variables. Participants were categorised as hypertensive if they had a previous diagnosis of hypertension, took antihypertensive medication or had an average systolic blood pressure over 160mmHg. The systolic blood pressure was measured three times. The first measurement was performed after 5 minutes of rest and 3 additional minutes of rest passed between each of the following measurements. Participants were categorised as diabetic if they had a previous diagnosis of diabetes, took antidiabetic medication or HbA1C measured by turbidimetry was >= 6%.

The participants' education was assessed using an extensive questionnaire(Lampert et al., 2012) and dichotomously categorized based on prior research on education as a protective factor against dementia(Then et al., 2016). Please see the supplementary text for details.

Participants had to choose their gender in a binary female/male question. Note that the German "Geschlecht" does not differentiate between sex and gender. The lack of a clarification and other options is lamented by the authors.

We used the sum-score of the Center for Epidemiological Studies Depression Scale (CES-D) to measure depressive symptoms(Radloff, 1977).

For a sensitivity analysis we created a dichotomous variable coded as 1 if participants answered the LSNS questionnaire after March 22nd, 2020 (1st SARS-CoV-2 lockdown in Germany).

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To improve the interpretability of our results, we z-transformed the variables BMI, CESD, TICS, executive function, memory performance and processing speed and demeaned the variable baseline age.

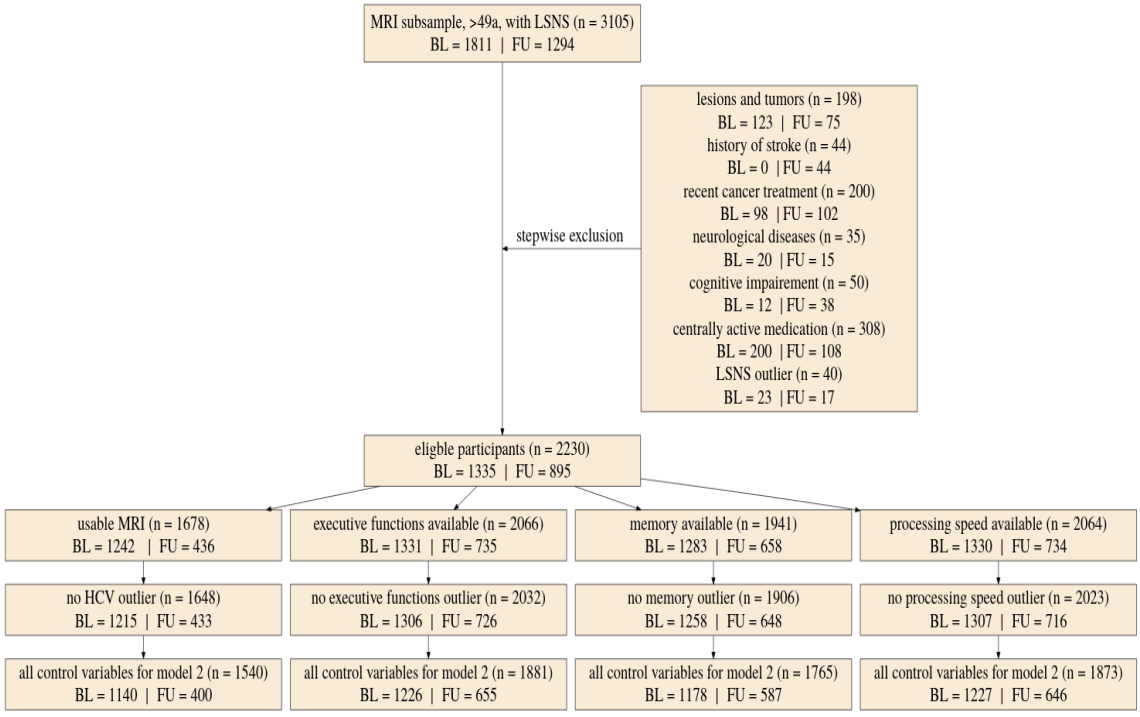
Outliers and Imputation

We excluded outliers for our core variables based on a cut-off of 3 SDs (LSNS-score, adjusted hippocampal volume, cognitive functions). Please see Fig. 6 (Flowchart) for the limited effect of outlier exclusion on sample sizes of the different models. For further details on outlier detection and handling regarding covariates please see the supplementary text.

To avoid an excessive reduction in sample size due to missing data we performed imputations for missing predictor variables using the sample mean, distributions based on existing data, or the participant's mean. Please see the supplementary text for information on our procedures of the respective measures.

Furthermore, we used FIML for analyses using structural equation modelling.

Figure 6
Flowchart of stepwise application of exclusion criteria



Flowchart of stepwise application of exclusion criteria. Small rectangles show the number of participants fulfilling the respective criteria in total and for baseline and follow-up. The large box shows how many participants were excluded due to various exclusion criteria in total for baseline and follow-up. Missing control variables in model 2 were the Center for Epidemiological Studies Depression scores. LSNS, Lubben Social Network Scale; HCV, hippocampal volume; BL, baseline; FU, follow-up.

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Statistical Analyses

All code can be found on https://github.com/LaurenzLammer/socialisolation. Please see the supplementary text for information on the software used for the analyses.

Statistical Modelling

Linear mixed effects models

To investigate the link between social isolation and our outcomes of interest, we employed LMEs with individual as a random effect.

The general structure of the models in the lme4 syntax was:

Dependent variable ~ baseline LSNS + change in LSNS + baseline age + change in age + control variables + (1|participant). Please see the supplementary text for explicit formulations of all models. We calculated two models for each hypothesis. In model 1 we included age and gender as control variables. Model 2 additionally included education, hypertension, diabetes, depressive symptoms and BMI. In model 1 the other risk factors are assumed to mediate the effect of social isolation. In model 2 they are assumed to be confounders (see Fig. S1 for a visualization). To measure the effect of aging, we controlled for baseline age and change in age. Analogously, we differentiated within and between subject effects(van de Pol & Wright, 2009) of social isolation. Likewise, we calculated the interaction effect of baseline LSNS and change in LSNS. With this methodology we regressed hippocampal volume, the three cognitive functions, and cortical thickness on baseline LSNS, change in LSNS, and the interaction terms. To measure the overall effect of our predictors of interest, we performed a full-null-model comparison(Bolker et al., 2009). In addition to standard p-values, we calculated Bayes Factors (BFs). The relative evidence was measured by dividing the BF for the full model by the BF of the null model(Rouder et al., 2016). This allows us to evaluate the evidence in favour of the full-hypothesis compared to the null-hypothesis and thus also provide evidence for the absence of an effect(Keysers et al., 2020). We report both measures of significance to offer our readers a comprehensive insight into the data, combining the familiarity of classical frequentist inference with the additional implications of BFs(Keysers et al., 2020).

Sensitivity analyses

For the first analysis we added whether participants were tested after the start of lockdown measures to all LMEs. In the second analysis we didn't exclude participants due to the intake

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of centrally active or cancer medication and cognitive impairment. To probe the reliability of the coefficients for LSNS_change, we ran an analysis excluding all participants with only one timepoint and used standard mean and within score calculation. Furthermore, we ran two sensitivity analysis testing whether using a hypertension cut-off of 140mmHg or an MMSE cut-off of <27 as an exclusion criterion would affect our results. Moreover, to test for potential differences in the effect of social isolation between women and men, we divided our dataset by gender and recalculated the frequentist LMEs with both resulting datasets.

Statistical inference

We report one-sided p-values based on the direction of the predictor/path of interest's regression coefficient and the direction of our pre-defined hypotheses. To obtain one-sided BFs we sampled 10,000 times from the posterior distribution of our predictor of interest's effect. Then we multiplied the BF by two and the percentage of sampled effects in the direction of our pre-defined hypotheses.

Multiplicity control

Our threshold for significance for all tests was $p < 0.05$. To control for multiple hypothesis testing we FDR-corrected families of tests and each individual whole brain analysis (see the supplementary text for definition of families).

BFs of 3 to 10 and BFs of 10 to 30 are commonly considered to be moderate or strong evidence in favour of a hypothesis. To evaluate these thresholds in light of multiplicity, we conducted two simulation studies described in the supplementary text that revealed that using a BF threshold of 10.75 rather than 3 would keep α below 5% and that this would not substantially decrease power.

Model assumptions

To ensure that our continuous predictors are normally distributed, we plotted their histograms. We had to log-transform the CES-D-score to obtain a normal distribution.

To rule out major collinearity, we calculated Variance Inflation Factors (VIFs). The VIFs did not surpass the threshold of 10(Myers, 1990) in any model.

Furthermore, we tested the stability of our LMEs in R by comparing the estimates obtained from the model based on all data with those obtained from models with the levels of the random effects excluded one at a time. This revealed the models to be fairly stable. Moreover, we visually controlled them for heteroskedasticity with both a histogram and a qq-plot. The

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qq-plots show a heavy-tailed distribution of the residuals in some models. This is only a minor deficit as the models are not intended to make accurate predictions at specific points(Gelman & Hill, 2006).

Fit indices providing further information on the quality of a model fit using structural equation modelling can be found in Tables S1-2(Schermelleh-Engel et al., 2003). Fit index thresholds were surpassed by multiple mediation models. As the BLCS models are saturated, fit indices are uninformative.

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Data availability

This study obtained access to the data from LIFE (Leipziger Forschungszentrum für Zivilisationserkrankungen) under project agreement PV-573. Data are available from LIFE (https://www.uniklinikum-leipzig.de/einrichtungen/life) for researchers who meet the criteria for access to confidential data.

Competing Interest

The authors have declared no competing interest.

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Supplement

Supplementary text

Outliers

We excluded the datapoints (all measures of the timepoint) of all participants with measures deviating from the mean by 3SD for our core variables (LSNS-score, adjusted hippocampal volume, cognitive functions). In case of TICS-score deviations by 3SD we replaced the values with "NA" and hence did not include them in mediation analyses.

Considering confounders, highly implausible values (+/- 4 SD) for CES-D-score or BMI were treated as missing datapoints and we replaced them with values imputed according to our imputation plans listed below in order not to overly reduce the sample size.

All outlier analyses were conducted separately for baseline and follow-up measurements.

Imputation

The data on the control variables education, BMI, diabetes, hypertension, age, and gender were complete or mostly complete. Henceforth, we could impute missing datapoints without inducing severe bias by using the sample mean for continuous variables or values drawn from a distribution determined by the existing data for categorical variables.

However, CES-D-scores were an exception amongst our control variables because the questionnaires often missed a single or a few items. As suggested by Bono et al., we imputed up to 4 missing items per participant using the person mean(Bono et al., 2007). Similarly, we imputed up to one item in the LSNS and up to six items in the TICS using the person mean.

If results from one of the cognitive tests required to calculate a composite score for a cognitive function was missing, we calculated the score based on the average performance in the remainder of available tests contributing to the composite score, if at least two tests were available.

Fig. S3 provides an overview of missingness in relevant variables at different LSNS scores.

Families of tests

The LMEs with hippocampal volume and the cognitive functions as dependent variables form one large family except for models regressing on the interaction of baseline LSNS and change in LSNS. In each family, we separately corrected model one and model two analyses resulting in two families of twelve tests. Additionally, we FDR-corrected each individual whole brain analysis using the sided two-stage adaptive FDR-correction in the FreeSurfer-toolbox.(66) All other analyses and the whole brain analyses were considered to be exploratory and must be evaluated as such.

Education

The participants' education was assessed using an extensive questionnaire and given a score ranging from 1 (no degree at all) to 7 (A-levels + master's degree (or equivalent) or promotion) according to prior research(Lampert et al., 2012). The effects of education and the significance of different degrees are likely to be culture specific. Fortunately, a recent study

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examined the effects of education in a population of elderly residents of the city of Leipzig. In this study education operationalised as having a tertiary degree or not was found to be a significant predictor of dementia incidence(Then et al., 2016). This is approximated with a cut-off at a score < 3.6.

Simulation Studies

Although it is sometimes claimed that Bayesian Statistics do not require any multiplicity control(Gelman et al., 2012), we do not believe that this is the case in our study. A truly Bayesian approach would require researchers to adjust the priors to all other tests with non-independent hypotheses or datasets(Sjölander & Vansteelandt, 2019). This is hardly feasible and hence, in practice, Bayesian statistics are usually employed without taking all dependencies into account and their results are measured against thresholds similar to those of frequentist statistics. Fig. S4 shows how this results in an increasing familywise error rate (FWER) with an increasing number of tests in both Bayesian and frequentist statistics using an example from Keysers et al.(Keysers et al., 2020). De Jong has provided a solution for this problem for ANOVAs that has been implemented in the JASP software(Jong et al., 2019) but there is still a great lack of available tools for researchers using other statistical methods. Henceforth, we decided to conduct a simulation study to find a Bayes Factor threshold adjustment that should control our FWER similar to α-adjustments in frequentist statistics.

To find the expected number of false positives for a given number of tests and threshold, we replaced the variables for baseline social isolation and change in social isolation with random normally distributed values with the same SD and kept the original dataset otherwise untouched. Then we calculated our 24 LMEs belonging to the families of tests with the modified dataset and repeated this process 42 times. At a BF threshold of 3, 14 of the 1008 tests were false positives and 881 were detected as true negatives. Fig. S5 shows a histogram of the resulting Bayes Factors. The study suggests that for the family size of twelve tests in our study a threshold of about 10.75 would ensure a FWER below 5%. Table S19 gives an overview of the false positives and FWERs.

Furthermore, we wanted to see how this threshold adjustment would affect the power of our study. For this simulation study we generated a dataset that closely resembles the actual dataset but has different regression coefficients for baseline social isolation and change in social isolation. Instead of the actual coefficients we set the effect size per point on the LSNS to 0.1, 0.2 or 0.5 years of baseline age. We simulated a dataset and calculated a Bayes Factor for each model and each effect size. As we only calculated the LMEs without interaction terms for reasons of simplicity this resulted in a number of 48 Bayes Factors from simulated data for each of our 13 runs totalling 624 tests. While our power for the smallest effect sizes was generally small (<10%), it was 85.6% for baseline social isolation with an effect size of half a year of baseline age. Increasing the threshold to 10.75 would not substantially decrease it (81.7%). Tables S20-21 provide an overview of the percentages of false negatives and true positives using the thresholds 3 and 10.75.

Deviations from our Preregistration

For the most part, we stuck closely to our preregistered plan in this study but departed from it at some points for different reasons.

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We used the function qvalue instead of p.adjust for the FDR correction for the simple reason that it provides us with a more comprehensive output. As we set the argument pi to 1, qvalue is equivalent to the classic procedure(Storey, 2002).

We originally intended to first perform a full-null model comparison using an anova and only follow this up with the function drop1 in case of a significant value for the respective predictor of interest. Our intention was to avoid any multiplicity problems due to testing all predictors. Using the scope argument of drop1 solved the problem more parsimoniously.

Our plan to exclude participants with two or more lesions in their MRI was the result of an internal equivocation regarding the meaning of an abbreviation. We excluded participants based on the type of lesions but not based on lesion count.

Furthermore, we used FIML for analyses using structural equation modelling. The similar results obtained using our preregistered approach can be found in the pre-print(Lammer et al., 2021).

Lastly, we changed from the term sex to gender as it seems more appropriate.

Software

We performed most analyses using R (R Project for Statistical Computing, V3.6.1, RRID:SCR_001905). For the whole brain analyses we used Matlab (MATLAB, V9.10 (2021a) RRID:SCR_001622).

We used the package lme4 (R package: lme4, RRID:SCR_015654) to calculate LMEs in R. To obtain reliable p-values, we used the Satterthwaite option from the lmerTest package(R package: lmerTest, RRID:SCR_015656)(Kuznetsova et al., 2017). In the whole brain analyses we employed the Matlab-toolbox provided by FreeSurfer to calculate vertex-wise LMEs(Bernal-Rusiel, Greve, et al., 2013). For mediation analyses and BLCS models we used the sem function from the lavaan package(Rosseel, 2012).

We calculated BFs for all LMEs in R using the BayesFactor package and the functions posterior and generalTestBF with default priors(Rouder & Morey, 2012).

FDR-correction was performed using the qvalue function (R package: Qvalue, RRID:SCR_001073) in R and the sided two-stage adaptive FDR-correction in the FreeSurfer-toolbox(Bernal-Rusiel, Reuter, et al., 2013).

VIFs were calculated using the package car(J. Fox & Weisberg, 2019).

Reflexivity

Reflexivity, a sensitivity to and acknowledgment of the ways in which scientists shape the collected data and research findings, is an established hallmark of scientific rigour in qualitative research(Mays & Pope, 2000; Sandelowski & Barroso, 2002). The challenges addressed by reflexivity are perhaps more pronounced in but by no means exclusive to qualitative studies. Nevertheless, (at least in an openly conducted form) it is largely absent from quantitative studies(Ryan & Golden, 2006). Methodological reforms in quantitative research like preregistrations and registered reports(Nosek et al., 2018; Nosek & Lakens, 2014) are valuable tools to limit the researchers' potential to make data fit their prior assumptions but their scope is limited. They do not address some of the most fundamental issues in epidemiology: Which analogies are used to make sense of the data, which questions

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are being raised and answered and which theories are chosen to explain phenomena(Krieger, 2011)? Disclosing personal characteristics, researchers' values and positionality relative to the object of research(Berger, 2013) thus helps readers assess a study and its findings more thoroughly. Additionally, an external evaluation of the presence and prevalence of non-empirical decision vectors(Solomon, 2001) in a field of research can be greatly facilitated. Furthermore, as Stephen J. Gould has put it: "It is dangerous for a scholar even to imagine that he might attain complete neutrality, for then one stops being vigilant about personal preferences and their influences – and then one truly falls victim to the dictates of prejudice."(Gould, 1996)

Henceforth, I, as the first author, want to expand this study by a brief reflection on influences that might have played a role in the formation of this study. I am a medical doctoral student with no prior experience in research and conducted this study as the centrepiece of my planned dissertation. Thus, I entered this project with little prior knowledge. I believe that this both made me more flexible and restricted in my choices. On the one hand I was not dedicated to any specific research programme or topic, but on the other hand my reliance on the advice and support from more senior researchers made me emulate their work and methods in many aspects. Further, my worldview has probably made me tend to epidemiological theories (social epidemiology, eco-social theory)(Berkman et al., 2015; Krieger, 2014) broader than the study of lifestyle-factors and hence made me choose social isolation as my research topic. A further characteristic that might be of interest to readers, is that during the course of the research, two of my relatives struggled with dementia. Ultimately, this reflexivity is inherently limited, as the use of secondary data precludes me from reflecting on the pivotal processes of data acquisition and participant recruitment.

Explicit equations of all LMEs using the lme4 syntax.

Variables in bold are dropped in the null model.

H 1.1 Social isolation is negatively associated with hippocampal volume across individuals.

Model111: HCV ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + (1|subject)

Model112: HCV ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + hypertension + diabetes + BMI + CESD + education + (1|subject)

H 1.3 Social isolation is negatively associated with hippocampal volume within individuals.

Model131: HCV ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + (1|subject)

Model132: HCV ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + hypertension + diabetes + BMI + CESD + education + (1|subject)

H 1.5 Participants that are socially more isolated at baseline will experience aggravated age-related changes in hippocampal volume over the follow-up period.

Model151: HCV ~ LSNS_bl + LSNS_change + age_bl + age_change + **LSNS_bl*age_change** + sex + (1|subject)

Model152: HCV ~ LSNS_bl + LSNS_change + age_bl + age_change +

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LSNS_bl*age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

H 2.1 Social isolation is negatively associated with cognitive functions across individuals.

Model211a: executive function ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + (1|subject)

Model212a: executive function ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

Model211b: memory performance ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + (1|subject)

Model212b: memory performance ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

Model211c: processing speed ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + (1|subject)

Model212c: processing speed ~ **LSNS_bl** + LSNS_change + age_bl + age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

H 2.2 Social isolation is negatively associated with cognitive functions within individuals.

Model221a: executive function ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + (1|subject)

Model222a: executive function ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

Model221b: memory performance ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + (1|subject)

Model222b: memory performance ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

Model221c: processing speed ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + (1|subject)

Model222c: processing speed ~ LSNS_bl + **LSNS_change** + age_bl + age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

H 2.3 Participants that are socially more baseline will experience aggravated age-related changes in cognitive function over the follow-up period.

Model231a: executive function ~ LSNS_bl + age_bl + age_change + **LSNS_bl*age_change**

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+ sex + (1|subject)

Model231a: executive function ~ LSNS_bl + age_bl + age_change + **LSNS_bl*age_change**

+ sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

Model231b: memory performance ~ LSNS_bl + age_bl + age_change +

LSNS_bl*age_change + sex + (1|subject)

Model231b: memory performance~ LSNS_bl + age_bl + age_change +

LSNS_bl*age_change + sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

Model231c: processing speed ~ LSNS_bl + age_bl + age_change + **LSNS_bl*age_change**

+ sex + (1|subject)

Model231c: processing speed~ LSNS_bl + age_bl + age_change + **LSNS_bl*age_change**

+ sex + hypertension + diabetes + BMI + CES.D + education + (1|subject)

H 5.1 In people who are socially more isolated at baseline, an increase in social isolation from baseline to follow-up will have a stronger negative association with HCV than in people who are less socially isolated at baseline.

Model511: HCV ~ LSNS_bl + LSNS_change + **LSNS_bl*LSNS_change** + age_bl +

age_change + sex + (1|subject)

Model512: HCV ~ LSNS_bl + LSNS_change + **LSNS_bl*LSNS_change** +

age_bl + age_change + sex + hypertenison + diabetes + BMI + CES.D +

education + (1|subject)

Explicit equations of all LMEs using the FreeSurfer LME syntax.

H 1.2 Social isolation is negatively associated with vertex-wise cortical thickness across individuals.

For model 1 we built a matrix consisting of six columns: intercept (all ones), age_bl, age_change, sex, LSNS_bl and LSNS_change.

The corresponding contrast matrix was [0 0 0 0 1 0].

For model 2 we built a matrix consisting of eleven columns: intercept (all ones), age_bl, age_change, sex, hypertension, diabetes, education, BMI, CES_D, LSNS_bl and LSNS_change.

The corresponding contrast matrix was [0 0 0 0 0 0 0 0 0 1 0].

H 1.4 Social isolation is negatively associated with vertex-wise cortical thickness within

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individuals.

For model 1 we built a matrix consisting of six columns: intercept (all ones), age_bl, age_change, sex, LSNS_bl and LSNS_change.

The corresponding contrast matrix was [0 0 0 0 0 1].

For model 2 we built a matrix consisting of eleven columns: intercept (all ones), age_bl, age_change, sex, hypertension, diabetes, education, BMI, CES_D, LSNS_bl and LSNS_change.

The corresponding contrast matrix was [0 0 0 0 0 0 0 0 0 0 1].

H 1.6 Participants that are socially more isolated at baseline, will experience aggravated age-related changes in cortical thickness over the follow-up period.

For model 1 we built a matrix consisting of seven columns: intercept (all ones), age_bl, age_change, sex, LSNS_bl, LSNS_change and LSNS_bl*age_change. The last term is an interaction between baseline LSNS and age_change.

The corresponding contrast matrix was [0 0 0 0 0 0 1].

For model 2 we built a matrix consisting of twelve columns: intercept (all ones), age_bl, age_change, sex, hypertension, diabetes, education, BMI, CES_D, LSNS_bl, LSNS_change and LSNS_bl*age_change. The last term is an interaction between baseline LSNS and age_change.

The corresponding contrast matrix was [0 0 0 0 0 0 0 0 0 0 0 1].

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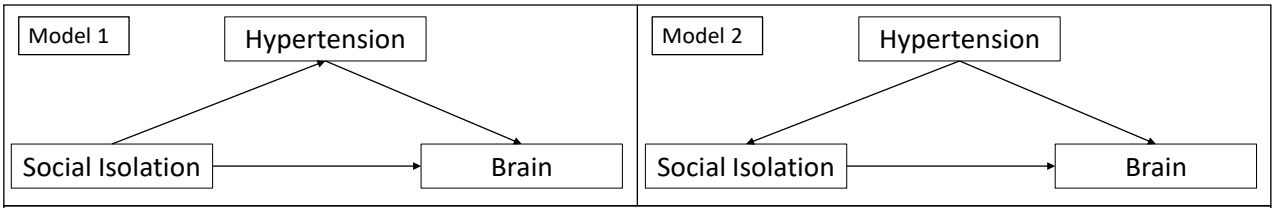
Fig. S1

Directed acyclic graphs demonstrating the theoretical underpinnings of model 1 and 2.



In model 1 the additional risk factors are assumed to be mediators and do not have to be controlled for. In model 2 they are assumed to be confounders. Therefore, they have to be controlled for.

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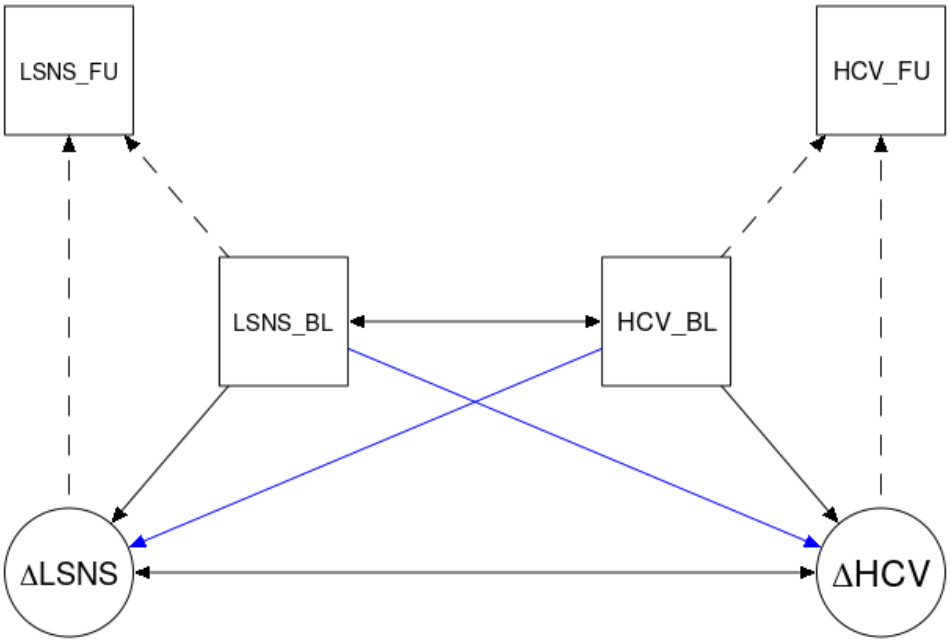
Fig. S2

Simplified plot of the bivariate latent change score models



LSNS, Lubben Social Network Scale; HCV, hippocampal volume; BL, baseline; FU, follow-up; Δ, change in.

The blue arrows show our paths of interest.

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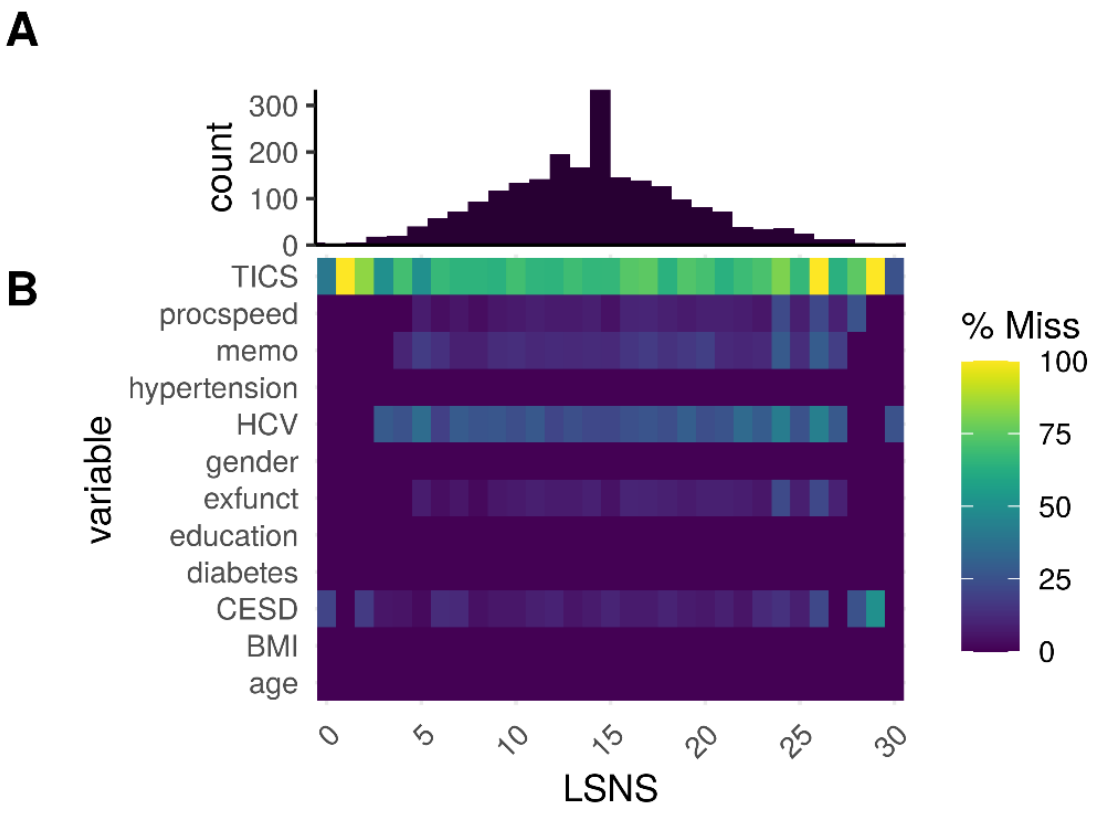
Fig. S3



A) Histogram of LSNS scores by individual observation. B) Heatmap of proportional missingness of variables for different LSNS scores.

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Fig. S4

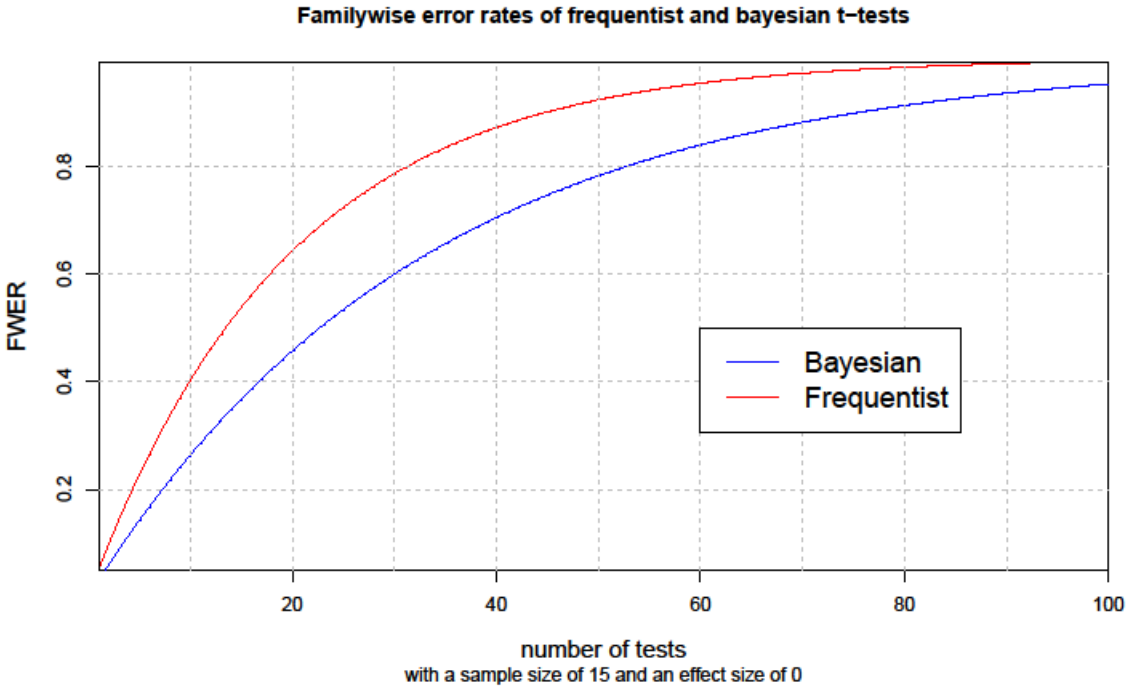

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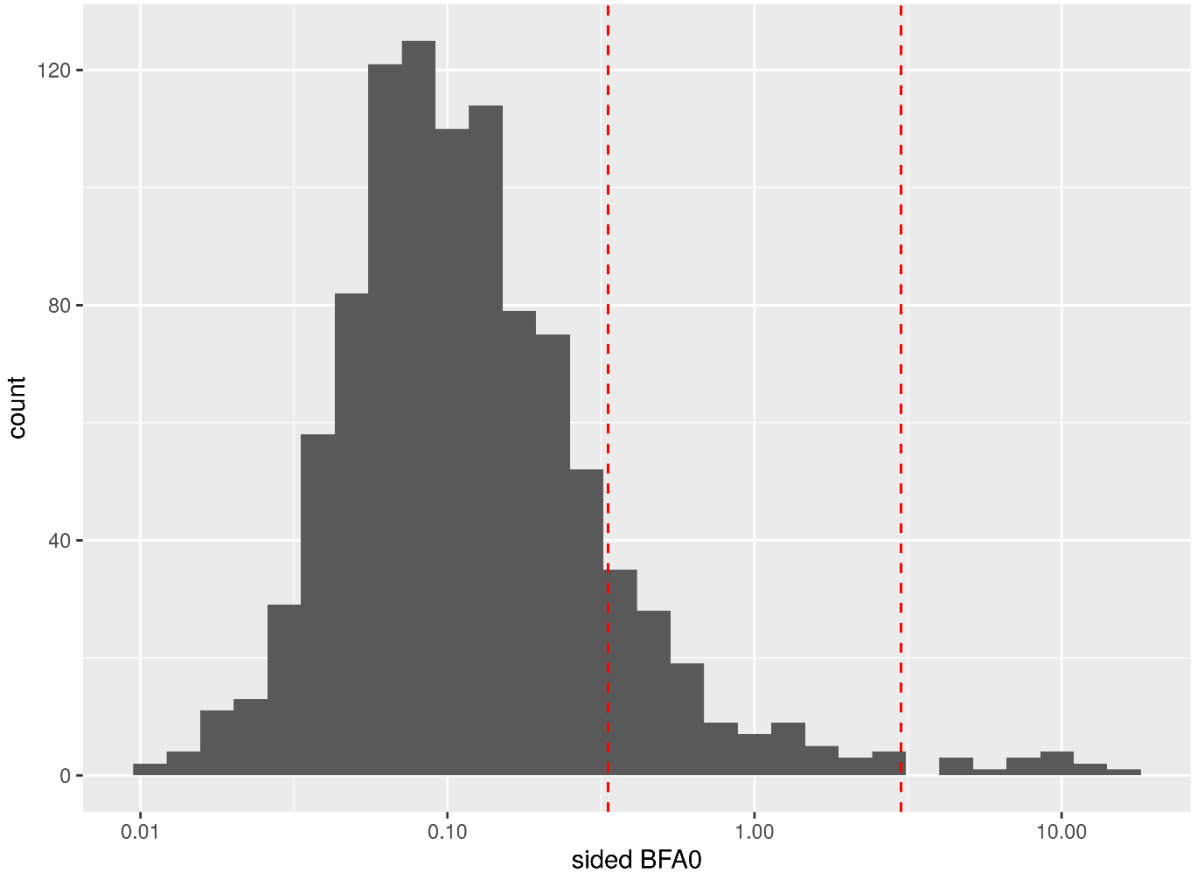
Fig. S5

Histogram of BFs with randomly simulated values for our predictors of interest.



The red lines show the traditional thresholds at 1/3 and 3.

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Table S1

fit index	**311**	**ok?**	**411a**	**ok?**	**411b**	**ok?**	**411c**	**ok?**
chisq	3.765		0.842		0.238		0.160	
df	1.000		1.000		1.000		1.000	
p-value	0.052	good fit	0.359	good fit	0.625	good fit	0.689	good fit
chisq/df	3.765	unacceptable fit	0.842	good fit	0.238	good fit	0.160	good fit
rmsea	0.042	good fit	0.000	good fit	0.000	good fit	0.000	good fit
rmsea_lower	0.000		0.000		0.000		0.000	
rmsea_upper	0.091		0.065		0.053		0.050	
srmr	0.019	good fit	0.003	good fit	0.001	good fit	0.001	good fit
nnfi	0.945	unacceptable fit	1.003	unacceptable fit	1.012	unacceptable fit	1.021	unacceptable fit
cfi	0.996	good fit	1.000	good fit	1.000	good fit	1.000	good fit

Fit indices of mediation analyses of model 1. chisq, chi squared; df, degrees of freedom
311: Indirect effect of social isolation on hippocampal volume via chronic stress
411a: Indirect effect of social isolation on executive functions via hippocampal volume
411b: Indirect effect of social isolation on memory via hippocampal volume
411c: Indirect effect of social isolation on processing speed via hippocampal volume

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Table S2

fit index	**312**	**ok?**	**412a**	**ok?**	**412b**	**ok?**	**412c**	**ok?**
chisq	9.260		0.083		0.958		0.068	
df	5.000		1.000		1.000		1.000	
p-value	0.099	good fit	0.773	good fit	0.328	good fit	0.794	good fit
chisq/df	1.852	good fit	0.083	good fit	0.958	good fit	0.068	good fit
rmsea	0.023	good fit	0.000	good fit	0.000	good fit	0.000	good fit
rmsea_lower	0.000		0.000		0.000		0.000	
rmsea_upper	0.047		0.045		0.066		0.043	
srmr	0.017	good fit	0.001	good fit	0.002	good fit	0.000	good fit
nnfi	0.972	good fit	1.014	unacceptable fit	1.001	unacceptable fit	1.026	unacceptable fit
cfi	0.994	good fit	1.000	good fit	1.000	good fit	1.000	good fit

Fit indices of mediation analyses of model 2. chisq, chi squared; df, degrees of freedom
312: Indirect effect of social isolation on hippocampal volume via chronic stress
412a: Indirect effect of social isolation on executive functions via hippocampal volume
412b: Indirect effect of social isolation on memory via hippocampal volume
412c: Indirect effect of social isolation on processing speed via hippocampal volume

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Table S3

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippo-campal Volume	1	LSNS_base	-5.500	-9.122, -1.878	0.0015**	0.0044**	14.61**
		LSNS_change	-4.894	-8.492, -1.29	0.0039**	0.0095**	2.9
		age_base	-25.755	-28.582, -22.929			
		age_change	-27.383	-29.659, -25.115			
		gender	-48.683	-85.261, -12.107			
	2	LSNS_base	-5.672	-9.503, -1.84	0.0019**	0.0075**	19.51**
		LSNS_change	-4.928	-8.741, -1.107	0.0058**	0.0174*	3.31*
		age_base	-23.879	-26.9, -20.858			
		age_change	-27.725	-30.141, -25.32			
		gender	-47.733	-85.365, -10.105			
		BMI	18.831	-0.946, 38.609			
		CESD	13.369	-5.716, 32.455			
		diabetes	-103.777	-155.724, -51.827			
		education	-85.695	-147.143, -24.244			
		hypertension	-29.051	-69.373, 11.27			
Executive Functions	1	LSNS_base	-0.026	-0.035, -0.017	8.4e-09****	1.0e-07****	1.5e+06****

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		LSNS_change	0.003	-0.011, 0.018	0.6787	0.787	0.08
		age_base	-0.020	-0.027, -0.013			
		age_change	-0.053	-0.063, -0.042			
		gender	-0.074	-0.166, 0.017			
	2	LSNS_base	-0.015	-0.025, -0.006	8e-04****	0.0046**	43.65***
		LSNS_change	0.006	-0.009, 0.021	0.7842	0.8555	0.07
		age_base	-0.014	-0.022, -0.007			
		age_change	-0.054	-0.065, -0.043			
		gender	-0.121	-0.214, -0.028			
		BMI	-0.079	-0.128, -0.031			
		CESD	-0.137	-0.183, -0.09			
		diabetes	-0.073	-0.201, 0.054			
		education	-0.351	-0.505, -0.196			
		hypertension	-0.078	-0.177, 0.021			
Memory	1	LSNS_base	-0.014	-0.022, -0.006	5e-04****	0.002**	49.05***
		LSNS_change	-0.013	-0.026, 0	0.0262*	0.0449*	1.12
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.018	-0.027, -0.009			
		gender	-0.381	-0.465, -0.298			
	2	LSNS_base	-0.008	-0.016, 0.001	0.0452*	0.0775	1.25

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		LSNS_change	-0.009	-0.023, 0.005	0.1046	0.1569	0.48
		age_base	-0.033	-0.04, -0.026			
		age_change	-0.017	-0.027, -0.008			
		gender	-0.424	-0.51, -0.338			
		BMI	-0.030	-0.076, 0.015			
		CESD	-0.117	-0.16, -0.073			
		diabetes	-0.045	-0.162, 0.072			
		education	-0.166	-0.306, -0.026			
		hypertension	0.025	-0.066, 0.116			
Processing Speed	1	LSNS_base	-0.018	-0.026, -0.011	1.7e-06****	1.0e-05****	9.4e+03****
		LSNS_change	-0.008	-0.021, 0.005	0.1087	0.163	0.39
		age_base	-0.038	-0.044, -0.032			
		age_change	-0.033	-0.043, -0.024			
		gender	-0.112	-0.188, -0.035			
	2	LSNS_base	-0.018	-0.026, -0.01	9.6e-06****	1e-04****	2.5e+03****
		LSNS_change	-0.012	-0.025, 0.001	0.038*	0.076	1.33
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.031	-0.041, -0.022			
		gender	-0.135	-0.214, -0.055			
		BMI	-0.025	-0.066, 0.016			

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		CESD	-0.024	-0.063, 0.016			
		diabetes	0.022	-0.086, 0.131			
		education	-0.161	-0.29, -0.031			
		hypertension	-0.048	-0.132, 0.036			

Adjusted regression coefficients and measures of significance of models without interaction terms. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
The unit of effect sizes on hippocampal volume and cognitive functions are mm^3/point on the LSNS and standard deviation/point on the LSNS, respectively.

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Table S4

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippo-campal Volume	1	LSNS_base*age_change	-0.556	-1.099, -0.014	0.0223*	0.0446*	0.52
		LSNS_base	-5.033	-8.682, -1.383			
		LSNS_change	-6.630	-10.591, -2.665			
		age_base	-25.728	-28.554, -22.902			
		age_change	-19.876	-27.531, -12.217			
		gender	-48.216	-84.786, -11.649			
	2	LSNS_base*age_change	-0.538	-1.107, 0.03	0.0318*	0.076	0.63
		LSNS_base	-5.211	-9.072, -1.35			
		LSNS_change	-6.541	-10.702, -2.374			
		age_base	-23.854	-26.874, -20.834			
		age_change	-20.416	-28.492, -12.334			
		gender	-47.198	-84.822, -9.579			
		BMI	18.804	-0.965, 38.576			
		CESD	13.639	-5.442, 32.721			
		diabetes	-103.725	-155.653, -51.793			
		education	-85.668	-147.094, -24.239			
		hypertension	-28.670	-68.981, 11.639			

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Executive Functions	1	LSNS_base*age_change	0.001	-0.001, 0.003	0.7946	0.7946	0.06
		LSNS_base	-0.028	-0.037, -0.018			
		LSNS_change	0.006	-0.01, 0.021			
		age_base	-0.020	-0.027, -0.013			
		age_change	-0.066	-0.098, -0.033			
		gender	-0.075	-0.166, 0.017			
	2	LSNS_base*age_change	0.002	-0.001, 0.004	0.9062	0.9062	0.07
		LSNS_base	-0.018	-0.028, -0.008			
		LSNS_change	0.010	-0.006, 0.026			
		age_base	-0.014	-0.022, -0.007			
		age_change	-0.076	-0.111, -0.041			
		gender	-0.122	-0.215, -0.029			
		BMI	-0.079	-0.127, -0.03			
		CESD	-0.137	-0.184, -0.091			
		diabetes	-0.075	-0.203, 0.053			
		education	-0.352	-0.507, -0.197			
		hypertension	-0.080	-0.179, 0.018			
Memory	1	LSNS_base*age_change	0.001	-0.001, 0.003	0.7214	0.787	0.06
		LSNS_base	-0.015	-0.024, -0.006			
		LSNS_change	-0.011	-0.026, 0.003			
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.027	-0.057, 0.004			

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		gender	-0.382	-0.465, -0.298			
	2	LSNS_base*age_change	0.001	-0.001, 0.003	0.7451	0.8555	0.08
		LSNS_base	-0.009	-0.018, 0.001			
		LSNS_change	-0.007	-0.022, 0.008			
		age_base	-0.033	-0.04, -0.026			
		age_change	-0.028	-0.059, 0.004			
		gender	-0.425	-0.51, -0.339			
		BMI	-0.030	-0.076, 0.015			
		CESD	-0.117	-0.16, -0.074			
		diabetes	-0.046	-0.163, 0.071			
		education	-0.167	-0.307, -0.027			
		hypertension	0.024	-0.067, 0.116			
Processing Speed	1	LSNS_base*age_change	-0.001	-0.003, 0.001	0.17	0.2266	0.25
		LSNS_base	-0.017	-0.025, -0.008			
		LSNS_change	-0.011	-0.025, 0.003			
		age_base	-0.038	-0.044, -0.032			
		age_change	-0.019	-0.05, 0.011			
		gender	-0.111	-0.187, -0.035			
	2	LSNS_base*age_change	-0.001	-0.003, 0.001	0.2411	0.3215	0.22
		LSNS_base	-0.017	-0.025, -0.008			
		LSNS_change	-0.014	-0.028, 0			
		age_base	-0.036	-0.042, -0.029			

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		age_change	-0.021	-0.052, 0.011			
		gender	-0.134	-0.213, -0.055			
		BMI	-0.025	-0.066, 0.016			
		CESD	-0.023	-0.063, 0.016			
		diabetes	0.023	-0.085, 0.132			
		education	-0.160	-0.29, -0.031			
		hypertension	-0.047	-0.131, 0.037			

Adjusted regression coefficients and measures of significance of models with interaction term of baseline social isolation with change in age. * p<0.05, BF>3; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~ LSNS_base*age_change+LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD

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Table S5

dv	Model	Predictor	Estimate	95% CI	p-value	BF
Hippocampal Volume	1	LSNS_base*LSNS_change	0.11	-0.61, 0.82	0.6146	0.03
		LSNS_base	-5.50	-9.12, -1.88		
		LSNS_change	-6.30	-16.43, 3.82		
		age_base	-25.75	-28.58, -22.93		
		age_change	-27.25	-29.69, -24.82		
		gender	-48.66	-85.24, -12.09		
	2	LSNS_base*LSNS_change	0.13	-0.62, 0.88	0.6335	0.06
		LSNS_base	-5.67	-9.5, -1.84		
		LSNS_change	-6.67	-17.4, 4.05		
		age_base	-23.88	-26.9, -20.86		
		age_change	-27.57	-30.14, -25.01		
		gender	-47.73	-85.36, -10.1		
		BMI	18.85	-0.92, 38.63		
		CESD	13.34	-5.74, 32.43		
		diabetes	-103.63	-155.58, -51.68		
		education	-85.72	-147.17, -24.27		
		hypertension	-29.01	-69.34, 11.3		

Adjusted regression coefficients and measures of significance of models with interaction term of baseline social isolation with change in social isolation. dv, dependent variable; CI, confidence interval; BF, Bayes

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Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD

Table S6

Mediator	dv	Model	Estimate	SE	z-value	p-value
TICS	Hippocampal Volume	1	-0.0005	0	-0.56	0.29
		2	-0.0004	0	-0.37	0.36
Hippocampal Volume	Executive Functions	1	-0.0010	0	-0.80	0.21
		2	-0.0013	0	-0.94	0.17
	Memory	1	-0.0010	0	-0.82	0.20
		2	-0.0013	0	-1.00	0.16
	Processing Speed	1	-0.0002	0	-0.27	0.40
		2	-0.0004	0	-0.38	0.35

Indirect effects of social isolation on hippocampal volume and cognitive functions. dv, dependent variable; SE, standard error; TICS, Trierer Inventar zum chronischen Stress (stress questionnaire)
model1: corrected for baseline age, change in age and gender
model2: model1 + hypertension+diabetes+education+BMI+CESD

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Table S7

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippocampal Volume	1	LSNS_base	-5.5	-9.1, -1.9	0.0014**	0.0042**	18.65**
		LSNS_change	-5.4	-9, -1.8	0.0017**	0.0042**	7.6*
		age_base	-25.7	-28.6, -22.9			
		age_change	-25.5	-28.3, -22.7			
		pandemic	-38.5	-71.2, -5.8			
	2	LSNS_base	-5.7	-9.5, -1.9	0.0018**	0.0073**	20.97**
		LSNS_change	-5.5	-9.3, -1.7	0.0024**	0.0073**	6.8*
		age_base	-23.9	-26.9, -20.8			
		age_change	-25.8	-28.8, -22.9			
		pandemic	-38.8	-73.5, -3.8			

Adjusted regression coefficients and measures of significance of hippocampal volume models adjusting for the effect of lockdown measures. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression; pandemic, 0/1 answered LSNS before/after beginning of 1st SARS-CoV-2 lockdown in Germany
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender+pandemic
full model2: model1 + hypertension+diabetes+education+BMI+CESD
The effect sizes hardly change when including whether the LSNS was filled out after the begin of lockdown measures in the model. The effect of this control variable itself tends to be associated with smaller hippocampal volume but the confidence interval is very broad.

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Table S8

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Executive Functions	1	LSNS_base	-0.026	-0.035, -0.017	7.7e-09****	9.2e-08****	1.7e+06****
		LSNS_change	0.005	-0.01, 0.019	0.733	0.7911	0.08
		age_base	-0.020	-0.027, -0.013			
		age_change	-0.060	-0.073, -0.048			
		pandemic	0.133	0.004, 0.262			
	2	LSNS_base	-0.015	-0.025, -0.006	8e-04****	0.0046**	36.51***
		LSNS_change	0.007	-0.008, 0.022	0.8314	0.9067	0.09
		age_base	-0.014	-0.022, -0.007			
		age_change	-0.061	-0.074, -0.048			
		pandemic	0.136	0.001, 0.27			
Memory	1	LSNS_base	-0.014	-0.022, -0.006	5e-04****	0.0021**	49.92***
		LSNS_change	-0.014	-0.028, -0.001	0.0159*	0.0272*	1.89
		age_base	-0.036	-0.042, -0.029			

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		age_change	-0.009	-0.02, 0.002			
		pandemic	-0.170	-0.29, -0.05			
	2	LSNS_base	-0.008	-0.017, 0.001	0.0444*	0.0761	1.33
		LSNS_change	-0.010	-0.024, 0.003	0.0698	0.1047	0.85
		age_base	-0.033	-0.04, -0.026			
		age_change	-0.010	-0.021, 0.002			
		pandemic	-0.158	-0.283, -0.031			
Processing Speed	1	LSNS_base	-0.018	-0.026, -0.011	1.7e-06****	1.0e-05****	9.7e+03****
		LSNS_change	-0.008	-0.021, 0.005	0.1055	0.1582	0.42
		age_base	-0.038	-0.044, -0.032			
		age_change	-0.032	-0.044, -0.021			
		pandemic	-0.020	-0.136, 0.097			
	2	LSNS_base	-0.018	-0.026, -0.01	9.6e-06****	1e-04****	2.3e+03****
		LSNS_change	-0.012	-0.025, 0.001	0.0366*	0.0732	1.49
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.030	-0.042, -0.018			
		pandemic	-0.020	-0.14, 0.1			

Adjusted regression coefficients and measures of significance of cognitive function models adjusting for the effect of lockdown measures. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression; pandemic, 0/1 answered LSNS before/after beginning of 1st SARS-CoV-2 lockdown in Germany
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender+pandemic
full model2: model1 + hypertension+diabetes+education+BMI+CESD

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The effect sizes hardly change when including whether the LSNS was filled out after the begin of lockdown measures in the model. The effect of this control variable itself is inconsistent between the different models.

Table S9

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippo-campal Volume	1	LSNS_base	-3.9	-7.3, -0.5	0.013*	0.0222*	2.39
		LSNS_change	-5.5	-8.5, -2.4	2e-04****	7e-04****	32.58***
		age_base	-27.3	-29.9, -24.6			
		age_change	-28.6	-30.6, -26.5			
	2	LSNS_base	-3.2	-6.8, 0.4	0.0399*	0.0684	0.97
		LSNS_change	-5.7	-9, -2.5	3e-04****	0.0017**	28.41**
		age_base	-25.5	-28.4, -22.7			
		age_change	-29.0	-31.1, -26.8			

Adjusted regression coefficients and measures of significance of hippocampal volume models based on datasets with reduced exclusion criteria. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
Participants were not excluded for intake of cancer or centrally active medication and cognitive impairement
When applying less exclusion criteria, no major changes occur. For hippocampal volume baseline social isolation becomes deemphasized while the absolute effect size for change in social isolation becomes larger.

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Table S10

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Executive Functions	1	LSNS_base	-0.030	-0.038, -0.022	5.1e-13****	6.1e-12****	1.6e+10****
		LSNS_change	-0.009	-0.021, 0.003	0.0759	0.1138	0.5
		age_base	-0.017	-0.024, -0.011			
		age_change	-0.051	-0.06, -0.042			
	2	LSNS_base	-0.019	-0.028, -0.011	4.5e-06****	5.4e-05****	4.6e+03****
		LSNS_change	-0.005	-0.018, 0.008	0.2223	0.3335	0.27
		age_base	-0.011	-0.018, -0.005			
		age_change	-0.052	-0.062, -0.043			
Memory	1	LSNS_base	-0.017	-0.025, -0.009	2.6e-05****	1e-04****	745.27****
		LSNS_change	-0.015	-0.027, -0.003	0.0079**	0.0158*	3.1*
		age_base	-0.041	-0.048, -0.033			
		age_change	-0.024	-0.032, -0.015			
	2	LSNS_base	-0.009	-0.018, -0.001	0.0164*	0.0328*	2.91

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		LSNS_change	-0.014	-0.026, -0.001	0.0143*	0.0328*	2.49
		age_base	-0.038	-0.045, -0.03			
		age_change	-0.025	-0.034, -0.016			
Processing Speed	1	LSNS_base	-0.015	-0.022, -0.008	6.1e-06****	3.7e-05****	2.6e+03****
		LSNS_change	-0.016	-0.026, -0.005	0.0022**	0.0053**	9.29*
		age_base	-0.038	-0.043, -0.033			
		age_change	-0.035	-0.043, -0.026			
	2	LSNS_base	-0.012	-0.019, -0.005	5e-04****	0.002**	58.77***
		LSNS_change	-0.017	-0.028, -0.006	0.0012**	0.0037**	21.76**
		age_base	-0.035	-0.04, -0.029			
		age_change	-0.033	-0.041, -0.025			

Adjusted regression coefficients and measures of significance of cognitive functions models based on datasets with reduced exclusion criteria. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
When applying less exclusion criteria, the direction and magnitude of effect sizes tends to stay the same. The direction of change in social isolation becomes negative but is still small. Most significances are more pronounced. Given the larger sample size, this is to be expected.

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Table S11

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippo-campal Volume	1	mean LSNS	-6.9	-11.3, -2.6	9e-04****	0.0036**	26.01**
		LSNS within	-4.7	-8.3, -1.1	0.0054**	0.0161*	1.92
		mean age	-26.1	-29.4, -22.7			
		age within	-26.5	-28.8, -24.2			
	2	mean LSNS	-6.7	-11.2, -2.1	0.0021**	0.0101*	17.76**
		LSNS within	-4.6	-8.4, -0.8	0.009**	0.027*	1.87
		mean age	-24.6	-28.1, -21			
		age within	-26.8	-29.2, -24.4			

Adjusted regression coefficients and measures of significance of hippocampal volume models only including participants with two timepoints. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; mean LSNS, subject's mean Lubben Social Network Score; LSNS within, within subject variation in Lubben Social Network Score; mean age, subject's mean age; age within, within subject variation in age; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
In this sensitivity analysis only participants with two timepoints were included and standard mean and within scores rather than baseline and change scores were calculated. In terms of effect size and direction our original model is corroborated. Smaller measures of significance in this smaller sample were expectable.

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Table S12

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Executive Functions	1	mean LSNS	-0.027	-0.037, -0.016	5.9e-07****	7.1e-06****	2.7e+04****
		LSNS within	0.005	-0.011, 0.021	0.7316	0.7607	0.08
		mean age	-0.014	-0.023, -0.006			
		age within	-0.055	-0.066, -0.045			
	2	mean LSNS	-0.016	-0.027, -0.005	0.0025**	0.0101*	16.1**
		LSNS within	0.005	-0.012, 0.021	0.7176	0.7829	0.11
		mean age	-0.008	-0.016, 0.001			
		age within	-0.055	-0.065, -0.044			
Memory	1	mean LSNS	-0.010	-0.019, 0	0.0225*	0.045*	2.02
		LSNS within	-0.010	-0.024, 0.004	0.0874	0.1498	0.43
		mean age	-0.031	-0.039, -0.024			
		age within	-0.018	-0.027, -0.009			
	2	mean LSNS	-0.006	-0.016, 0.004	0.1243	0.2131	0.66

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
		LSNS within	-0.006	-0.021, 0.008	0.2046	0.307	0.3
		mean age	-0.027	-0.035, -0.02			
		age within	-0.016	-0.025, -0.006			
Processing Speed	1	mean LSNS	-0.015	-0.024, -0.006	4e-04****	0.0027**	58.1***
		LSNS within	-0.006	-0.02, 0.009	0.2218	0.3305	0.2
		mean age	-0.039	-0.046, -0.032			
		age within	-0.033	-0.043, -0.023			
	2	mean LSNS	-0.014	-0.024, -0.005	0.0017**	0.0101*	21.84**
		LSNS within	-0.011	-0.026, 0.004	0.0721	0.1441	0.66
		mean age	-0.038	-0.045, -0.031			
		age within	-0.031	-0.041, -0.021			

Adjusted regression coefficients and measures of significance of cognitive functions models only including participants with two timepoints. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; mean LSNS, subject's mean Lubben Social Network Score; LSNS within, within subject variation in Lubben Social Network Score; mean age, subject's mean age; age within, within subject variation in age; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
In this sensitivity analysis only participants with two timepoints were included and standard mean and within scores rather than baseline and change scores were calculated. As for hippocampal volume, this sensitivity analysis corroborates our original model.

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Table S13

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippocampal Volume	1	LSNS_base	-5.5	-9.1, -1.9	0.0015**	0.0044**	19.53**
		LSNS_change	-4.9	-8.5, -1.3	0.0038**	0.0091**	2.34
		age_base	-25.8	-28.6, -22.9			
		age_change	-27.4	-29.6, -25.1			
	2	LSNS_base	-5.7	-9.5, -1.9	0.0018**	0.0073**	17.34**
		LSNS_change	-4.9	-8.7, -1.1	0.0055**	0.0164*	3.37*
		age_base	-24.2	-27.2, -21.1			
		age_change	-27.7	-30.1, -25.3			
		hypertension	-15.6	-57.1, 25.8			

Adjusted regression coefficients and measures of significance of hippocampal volume models using a hypertension cut-off of 140mmHg. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; mean LSNS, subject's mean Lubben Social Network Score; LSNS within, within subject variation in Lubben Social Network Score; mean age, subject's mean age; age within, within subject variation in age; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
Social isolation significantly predicts hippocampal volume after multiplicity control. Bayes Factors provide strong evidence in favour of the alternative hypotheses for baseline social isolation and anecdotal to moderate evidence for change in social isolation. The effect size of one point on the LSNS is equivalent to a baseline age difference of around two and a half months.

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Table S14

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Executive Functions	1	LSNS_base	-0.026	-0.035, -0.017	8.2e-09	9.9e-08	1.5e+06
		LSNS_change	0.003	-0.011, 0.018	0.6775	0.7893	0.08
		age_base	-0.019	-0.026, -0.012			
		age_change	-0.053	-0.063, -0.042			
	2	LSNS_base	-0.015	-0.025, -0.006	8e-04	0.0047	50.05
		LSNS_change	0.006	-0.009, 0.021	0.78	0.851	0.09
		age_base	-0.013	-0.021, -0.006			
		age_change	-0.054	-0.065, -0.044			
		hypertension	-0.120	-0.222, -0.018			
Memory	1	LSNS_base	-0.014	-0.022, -0.006	5e-04	0.002	48.6
		LSNS_change	-0.013	-0.026, 0	0.0265	0.0454	1.11
		age_base	-0.036	-0.042, -0.029			
		age_change	-0.018	-0.027, -0.009			
	2	LSNS_base	-0.007	-0.016, 0.001	0.0501	0.086	1.15
		LSNS_change	-0.009	-0.023, 0.005	0.1033	0.1549	0.49
		age_base	-0.032	-0.039, -0.025			
		age_change	-0.018	-0.027, -0.008			
		hypertension	-0.006	-0.1, 0.089			
Processing Speed	1	LSNS_base	-0.018	-0.025, -0.01	2.4e-06	1.4e-05	6.8e+03
		LSNS_change	-0.008	-0.021, 0.005	0.1074	0.1611	0.36
		age_base	-0.038	-0.044, -0.032			
		age_change	-0.034	-0.043, -0.024			

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dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
	2	LSNS_base	-0.018	-0.026, -0.009	1.2e-05	1e-04	1.8e+03
		LSNS_change	-0.012	-0.025, 0.001	0.0371	0.0741	1.56
		age_base	-0.037	-0.043, -0.031			
		age_change	-0.032	-0.041, -0.022			
		hypertension	-0.002	-0.088, 0.085			

Adjusted regression coefficients and measures of significance of cognitive functions models using a hypertension cut-off of 140mmHg. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; mean LSNS, subject's mean Lubben Social Network Score; LSNS within, within subject variation in Lubben Social Network Score; mean age, subject's mean age; age within, within subject variation in age; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
Baseline social isolation significantly predicts cognitive functions after FDR-correction and BFs provide very strong to decisive evidence in favour of the alternative hypotheses. Only for model 2 of memory evidence is weak. No association of change in social isolation with executive functions is detected and evidence for associations with memory and processing speed are limited.

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Table S15

dv	Model	Predictor	Estimate	95% CI	p-value	FDR	BF
Hippo-campal Volume	1	LSNS_base	-7.3	-11.2, -3.4	1e-04	4e-04	192.27
		LSNS_change	-4.5	-8.2, -0.8	0.0093	0.0223	1.18
		age_base	-24.5	-27.5, -21.6			
		age_change	-27.7	-30.1, -25.3			
	2	LSNS_base	-7.1	-11.2, -3	4e-04	0.0042	81.34
		LSNS_change	-4.6	-8.6, -0.7	0.0103	0.0309	1.7
		age_base	-22.4	-25.6, -19.2			
		age_change	-27.7	-30.2, -25.2			

Adjusted regression coefficients and measures of significance of hippocampal volume models excluding participants with MMSE score < 27. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; mean LSNS, subject's mean Lubben Social Network Score; LSNS within, within subject variation in Lubben Social Network Score; mean age, subject's mean age; age within, within subject variation in age; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
Social isolation significantly predicts hippocampal volume after multiplicity control. Bayes Factors provide strong evidence in favour of the alternative hypotheses for baseline social isolation and anecdotal to moderate evidence for change in social isolation. The effect size of one point on the LSNS is equivalent to a baseline age difference of around two and a half months.

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Table S16

Model	Predictor	Estimate	95% CI	p-value	FDR	BF
1	LSNS_base	-0.023	-0.033, -0.013	1.9e-06	2.3e-05	9.4e+03
	LSNS_change	0.004	-0.01, 0.019	0.7159	0.7159	0.08
	age_base	-0.016	-0.024, -0.009			
	age_change	-0.058	-0.068, -0.047			
2	LSNS_base	-0.014	-0.024, -0.003	0.0049	0.0194	8.81
	LSNS_change	0.007	-0.008, 0.022	0.8175	0.8384	0.09
	age_base	-0.012	-0.02, -0.004			
	age_change	-0.058	-0.069, -0.048			
1	LSNS_base	-0.014	-0.023, -0.005	0.0011	0.0034	24.53
	LSNS_change	-0.013	-0.027, 0.001	0.0308	0.0615	1.08
	age_base	-0.033	-0.039, -0.026			
	age_change	-0.028	-0.038, -0.018			
2	LSNS_base	-0.009	-0.018, 0.001	0.0355	0.0852	1.66
	LSNS_change	-0.009	-0.023, 0.006	0.1181	0.169	0.51
	age_base	-0.029	-0.036, -0.021			
	age_change	-0.026	-0.036, -0.016			
1	LSNS_base	-0.016	-0.024, -0.008	1e-04	4e-04	198.61
	LSNS_change	-0.007	-0.02, 0.006	0.1509	0.2012	0.31
	age_base	-0.038	-0.045, -0.032			
	age_change	-0.038	-0.047, -0.028			
2	LSNS_base	-0.014	-0.023, -0.005	8e-04	0.005	40.5
	LSNS_change	-0.010	-0.023, 0.004	0.0827	0.1418	0.8
	age_base	-0.036	-0.043, -0.029			
	age_change	-0.035	-0.045, -0.025			

Adjusted regression coefficients and measures of significance of cognitive functions models excluding participants with MMSE score < 27. * p<0.05, BF>3; ** p<0.01, BF>10; *** p<0.001, BF>30; **** p<0.0001, BF>100; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; BF, Bayes Factor in favour of alternative hypothesis; mean LSNS, subject's mean Lubben Social Network Score; LSNS within, within subject variation in Lubben Social Network Score; mean age, subject's mean age; age within, within subject variation in age; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change+gender
full model2: model1 + hypertension+diabetes+education+BMI+CESD
Baseline social isolation significantly predicts cognitive functions after FDR-correction and BFs provide very strong to decisive evidence in favour of the alternative hypotheses. Only for model 2 of memory evidence is

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weak. No association of change in social isolation with executive functions is detected and evidence for associations with memory and processing speed are limited.

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Table S17

dv	Model	gender	Predictor	Estimate	95% CI	p-value	FDR
Hippo-campal Volume	1	female	LSNS_base	-7.265	-12.546, -1.984	0.0036**	0.0142*
			LSNS_change	-3.826	-8.389, 0.75	0.0503	0.1006
			LSNS_base*age_change	-0.311	-0.992, 0.37	0.1847	0.2463
			LSNS_base*LSNS_change	-0.026	-0.865, 0.812	0.4755	
	1	male	LSNS_base	-4.418	-9.407, 0.572	0.0414*	0.0827
			LSNS_change	-5.821	-11.462, -0.17	0.0218*	0.0655
			LSNS_base*age_change	-0.793	-1.656, 0.066	0.0356*	0.0827
			LSNS_base*LSNS_change	0.426	-0.831, 1.696	0.7466	
	2	female	LSNS_base	-9.402	-15.042, -3.762	6e-04****	0.0068**
			LSNS_change	-3.452	-8.28, 1.395	0.0807	0.1614
			LSNS_base*age_change	-0.255	-0.971, 0.462	0.2422	0.3229
			LSNS_base*LSNS_change	0.027	-0.842, 0.895	0.5248	
	2	male	LSNS_base	-3.046	-8.299, 2.207	0.1277	0.2554
			LSNS_change	-6.344	-12.289, -0.39	0.0185*	0.1111
			LSNS_base*age_change	-0.796	-1.692, 0.095	0.0403*	0.1209
			LSNS_base*LSNS_change	0.448	-0.876, 1.783	0.7464	
Executive Functions	1	female	LSNS_base	-0.032	-0.045, -0.018	1.6e-06****	1.9e-05****

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dv	Model	gender	Predictor	Estimate	95% CI	p-value	FDR
			LSNS_change	-0.006	-0.026, 0.014	0.2797	0.3357
			LSNS_base*age_change	0.001	-0.002, 0.004	0.7135	0.7135
	1	male	LSNS_base	-0.022	-0.034, -0.009	4e-04****	0.0022**
			LSNS_change	0.013	-0.007, 0.033	0.9021	0.9021
			LSNS_base*age_change	0.001	-0.002, 0.005	0.8056	0.8789
	2	female	LSNS_base	-0.020	-0.034, -0.006	0.0032**	0.019*
			LSNS_change	0.001	-0.02, 0.022	0.547	0.6564
			LSNS_base*age_change	0.002	-0.002, 0.005	0.8642	0.8642
	2	male	LSNS_base	-0.012	-0.025, 0	0.0293*	0.1173
			LSNS_change	0.012	-0.009, 0.033	0.8653	0.8653
			LSNS_base*age_change	0.002	-0.002, 0.005	0.8482	0.8653
Memory	1	female	LSNS_base	-0.011	-0.023, 0.001	0.0345*	0.0827
			LSNS_change	-0.017	-0.034, -0.001	0.0218*	0.0655
			LSNS_base*age_change	0.000	-0.003, 0.003	0.5141	0.5609
	1	male	LSNS_base	-0.016	-0.028, -0.004	0.0035**	0.0141*
			LSNS_change	-0.007	-0.028, 0.013	0.2454	0.4081
			LSNS_base*age_change	0.001	-0.002, 0.005	0.7892	0.8789
	2	female	LSNS_base	-0.004	-0.017, 0.008	0.2417	0.3229
			LSNS_change	-0.015	-0.032, 0.003	0.0494*	0.1185
			LSNS_base*age_change	0.000	-0.002, 0.003	0.612	0.6677

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dv	Model	gender	Predictor	Estimate	95% CI	p-value	FDR
	2	male	LSNS_base	-0.010	-0.022, 0.003	0.0644	0.1544
			LSNS_change	-0.002	-0.023, 0.02	0.4446	0.5928
			LSNS_base*age_change	0.001	-0.002, 0.004	0.7429	0.8653
Processing Speed	1	female	LSNS_base	-0.017	-0.028, -0.005	0.0028**	0.0142*
			LSNS_change	-0.009	-0.026, 0.009	0.1632	0.2448
			LSNS_base*age_change	-0.002	-0.005, 0.001	0.127	0.2177
	1	male	LSNS_base	-0.020	-0.03, -0.01	6.6e-05****	8e-04****
			LSNS_change	-0.006	-0.025, 0.013	0.2721	0.4081
			LSNS_base*age_change	0.000	-0.003, 0.003	0.4427	0.5903
	2	female	LSNS_base	-0.016	-0.029, -0.004	0.0053**	0.0211*
			LSNS_change	-0.015	-0.033, 0.002	0.0449*	0.1185
			LSNS_base*age_change	-0.001	-0.004, 0.002	0.1922	0.3229
	2	male	LSNS_base	-0.018	-0.029, -0.008	4e-04****	0.0051**
			LSNS_change	-0.007	-0.028, 0.013	0.2368	0.4059
			LSNS_base*age_change	0.000	-0.003, 0.003	0.4265	0.5928

Adjusted regression coefficients and measures of significance of models stratified by gender. * p<0.05 ; ** p<0.01; *** p<0.001; **** p<0.0001; dv, dependent variable; CI, confidence interval; FDR, p-values after FDR-correction; LSNS_base, baseline Lubben Social Network Score; LSNS_change, change in Lubben Social Network Score; CESD, Center for Epidemiological Studies-Depression
full model1: dv~LSNS_base+LSNS_change+age_base+age_change
full model2: model1 + hypertension+diabetes+education+BMI+CESD
The unit of effect sizes on hippocampal volume and cognitive functions for non-interaction models are mm^3/point on the LSNS and standard deviation/point on the LSNS, respectively. For interaction models the unit in the denominator is multiplied by year or point on the LSNS.

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Table S18

dv	predictor	estimate	se	p-value	q value
ΔHCV	LSNS_base	-0.002	0.005	0.315	0.420
ΔLSNS	HCV_base	-0.139	0.175	0.213	0.284
ΔEF	LSNS_base	-0.014	0.007	0.029*	0.116
ΔLSNS	EF_base	-0.149	0.170	0.189	0.284
ΔMemo	LSNS_base	0.001	0.006	0.576	0.576
ΔLSNS	Memo_base	-0.308	0.168	0.033*	0.133
ΔPS	LSNS_base	-0.005	0.008	0.250	0.420
ΔLSNS	PS_base	-0.102	0.179	0.285	0.285

Relevant Regressions of Bivariate Latent Change Score Models. *, $p < 0.05$; dv, dependent variable; se, standard error; _base, baseline score of; Δ, change in; LSNS, Lubben Social Network Score; HCV, z-transformed hippocampal volume; EF, executive functions; Memo, memory; PS, processing speed

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Table S19

BFA0	FWER in %	n
15.744	1.18	1
13.634	2.36	2
13.139	3.51	3
10.926	4.66	4
10.632	5.79	5
9.196	6.91	6
8.728	8.02	7
8.510	9.12	8
7.749	10.20	9
7.191	11.28	10
6.081	12.34	11
4.746	13.39	12
4.044	14.42	13
4.003	15.45	14

Simulated Bayes Factors above the threshold of 3. BFA0, Sided Bayes factor in favour of the alternative hypothesis; FWER, familywise error rate if the threshold would be set just below BFA0
In the simulation with randomly simulated values for our predictors of interest, 14 BFs exceeded the standard threshold of three. Given a family size of 12 tests, a threshold of 10.75 would maintain the FWER below 5%.

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Table S20

Category	BFA0b > 3 in %	3 >= BFA0b >= 1/3 in %	BFA0b < 1/3 in %	BFA0c > 3 in %	3 >= BFA0c >= 1/3 in %	BFA0c < 1/3 in %	n
overall	44.23	31.41	24.36	28.85	30.45	40.71	312
model 1	45.51	30.13	24.36	30.13	30.13	39.74	156
model 2	42.95	32.69	24.36	27.56	30.77	41.67	156
effect = 0.1	9.62	38.46	51.92	5.77	24.04	70.19	104
effect = 0.2	37.50	44.23	18.27	21.15	39.42	39.42	104
effect = 0.5	85.58	11.54	2.88	59.62	27.88	12.50	104

Results of Power Simulation of Bayes Factors. BFA0b, Sided Bayes factor in favour of the alternative hypothesis of baseline social isolation; BFA0c, Sided Bayes factor in favour of the alternative hypothesis of change in social isolation; n, number of simulations in the category; model 1, model with reduced number of control variables; model 2, model with full number of control variables; effect, effect size per point in the Lubben Social Network Scale in years of baseline age
Percentages of Bayes Factors giving moderate or stronger evidence in favour of the alternative hypothesis (>3), giving anecdotal evidence (3>=BF>=1/3) and giving moderate or stronger evidence in favour of the null hypothesis (< 1/3).

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Table S21

Category	BFA0b > 10.75 in %	10.75 >= BFA0b >= 1/3 in %	BFA0b < 1/3 in %	BFA0c > 10.75 in %	10.75 >= BFA0c >= 1/3 in %	BFA0c < 1/3 in %	n
overall	37.18	38.46	24.36	20.83	38.46	40.71	312
model 1	38.46	37.18	24.36	21.79	38.46	39.74	156
model 2	35.90	39.74	24.36	19.87	38.46	41.67	156
effect = 0.1	5.77	42.31	51.92	0.96	28.85	70.19	104
effect = 0.2	24.04	57.69	18.27	14.42	46.15	39.42	104
effect = 0.5	81.73	15.38	2.88	47.12	40.38	12.50	104

Results of Power Simulation of Bayes Factors with adjusted thresholds for a family of 12 tests. BFA0b, Sided Bayes factor in favour of the alternative hypothesis of baseline social isolation; BFA0c, Sided Bayes factor in favour of the alternative hypothesis of change in social isolation; n, number of simulations in the category; model 1, model with reduced number of control variables; model 2, model with full number of control variables; effect, effect size per point in the Lubben Social Network Scale in years of baseline age. Percentages of Bayes Factors giving moderate or stronger evidence in favour of the alternative hypothesis (>10.75), giving anecdotal evidence (10.75>=BF>=1/3) and giving moderate or stronger evidence in favour of the null hypothesis (< 1/3).

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