Supplementary Information

1. Group differences when using a self-reported measure of lifetime depressive symptoms instead of current depressive symptoms

SI Table 1: The total N was 18,188 after removing participants with missing data on lifetime depressive symptoms. The table shows the difference between individuals reporting loneliness (n = 2343) and individuals not reporting loneliness (n = 15,845) on a single yes/no item, based on independent sample t-tests (t) and Cohen's d effect size (d). CI = confidence interval. P-values are reported before (p) and after (p_{corr}) FDR correction. TS dep. index = Townsend deprivation index.

Factor	$\boldsymbol{t}$	$\boldsymbol{p}$	$\boldsymbol{p_{corr}}$	$\boldsymbol{d}[\boldsymbol{CI}]$
Social isolation	14.35	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.352 [0.351, 0.353]
Neuroticism	52.46	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	1.194 [1.192, 1.195]
Depression (lifetime)	26.70	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.531 [0.530, 0.532]
TS dep. index	6.92	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.159 [0.158, 0.160]
Income	-12.89	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.289 [0.288, 0.290]
Education	-4.32	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.096 [0.095, 0.097]
Smoking status	1.02	0.307	0.307	0.023 [0.022, 0.024]
Alcohol intake	-5.92	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.131 [0.130, 0.132]
Physical activity	-4.32	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.095 [0.094, 0.096]
BMI	4.75	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.114 [0.113, 0.115]
Hypertension	-6.28	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.135 [0.134, 0.136]
Age	-8.63	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.189 [0.188, 0.190]
Sex*	-8.57	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.187 [0.186, 0.188]

*Sex = 0 for women and 1 for men

2. Main effects - each factor versus brain age gap, adjusted for age

SI Table 2: Regression analyses with brain age gap as dependent variable and each factor as independent variables, including age as a covariate. *P*-values are reported before (p) and after (p_{corr}) FDR correction. *P*-values < 0.05 are highlighted in bold. SE = standard error; TS dep. index = Townsend deprivation index.

Factor	$\boldsymbol{\beta \pm SE}$	$\boldsymbol{t}$	$\boldsymbol{p}$	$\boldsymbol{p_{corr}}$
Loneliness	0.020 ± 0.021	0.960	0.337	0.368
Neuroticism	0.026 ± 0.021	-1.198	0.231	0.308
Depression	0.022 ± 0.021	1.052	0.293	0.352
Social isolation	0.098 ± 0.021	4.637	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
TS dep. index	0.190 ± 0.021	8.950	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
Income	0.037 ± 0.022	1.691	0.091	0.156
Education	0.029 ± 0.021	1.362	0.173	0.260
Alcohol intake	0.178 ± 0.021	8.366	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
Physical activity	0.019 ± 0.021	0.874	0.382	0.382
BMI	0.139 ± 0.021	6.556	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
Hypertension	0.076 ± 0.022	3.478	$< 1.00 \times 10^{-3}$	0.001
Sex*	0.155 ± 0.021	7.299	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$

*Sex = 0 for women and 1 for men

3. Main effects - each factor versus brain age gap, adjusted for age and birth weight

SI Table 3: Regression analyses with brain age gap as dependent variable and each factor as independent variables, including age and birth weight as covariates in a sub-sample with available data (n = 15,298). *P*-values are reported before (p) and after (p_{corr}) FDR correction. *P*-values < 0.05 are highlighted in bold. SE = standard error; TS dep. index = Townsend deprivation index.

Factor	$\boldsymbol{\beta \pm SE}$	$\boldsymbol{t}$	$\boldsymbol{p}$	$\boldsymbol{p_{corr}}$
Loneliness	0.063 ± 0.027	2.346	0.019	0.033
Neuroticism	0.004 ± 0.027	0.148	0.883	0.883
Depression	0.039 ± 0.027	1.459	0.145	0.217
Social isolation	0.105 ± 0.027	3.907	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
TS dep. index	0.188 ± 0.027	7.012	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
Income	0.019 ± 0.028	0.700	0.484	0.528
Education	0.031 ± 0.027	1.166	0.244	0.325
Alcohol intake	0.169 ± 0.027	6.266	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
Physical activity	0.021 ± 0.027	0.797	0.425	0.510
BMI	0.113 ± 0.027	4.198	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$
Hypertension	0.069 ± 0.027	2.514	0.012	0.024
Sex*	0.136 ± 0.027	5.021	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$

*Sex = 0 for women and 1 for men

4. Interaction effects (loneliness × each factor) versus brain age gap, adjusted for age

SI Table 4: Regression analyses with brain age gap as dependent variable, and interaction terms representing loneliness (L) × each factor as independent variables, including age as a covariate. *P*-values are reported before (p) and after (p_{corr}) FDR correction. *P*-values < 0.05 are highlighted in bold. SE = standard error; TS dep. index = Townsend deprivation index.

Factor	$\boldsymbol{\beta \pm SE}$	$\boldsymbol{t}$	$\boldsymbol{p}$	$\boldsymbol{p_{corr}}$
L×Neuroticism	0.04 ± 0.07	0.54	0.587	0.717
L×Depression	0.05 ± 0.05	0.95	0.340	0.717
L×Social isolation	0.10 ± 0.06	1.71	0.088	0.717
L×TS dep. index	0.03 ± 0.06	0.43	0.667	0.733
L×Income	0.08 ± 0.06	-1.32	0.185	0.717
L×Education	0.01 ± 0.06	0.21	0.836	0.836
L×Alcohol intake	0.06 ± 0.06	-0.89	0.372	0.717
L×Physical activity	0.04 ± 0.06	0.66	0.510	0.717
L×BMI	0.04 ± 0.06	-0.65	0.514	0.717
L×Hypertension	0.05 ± 0.06	0.75	0.452	0.717
L×Sex	0.04 ± 0.06	0.57	0.566	0.717

5. Loneliness versus social isolation: group differences in risk factors and brain age gap

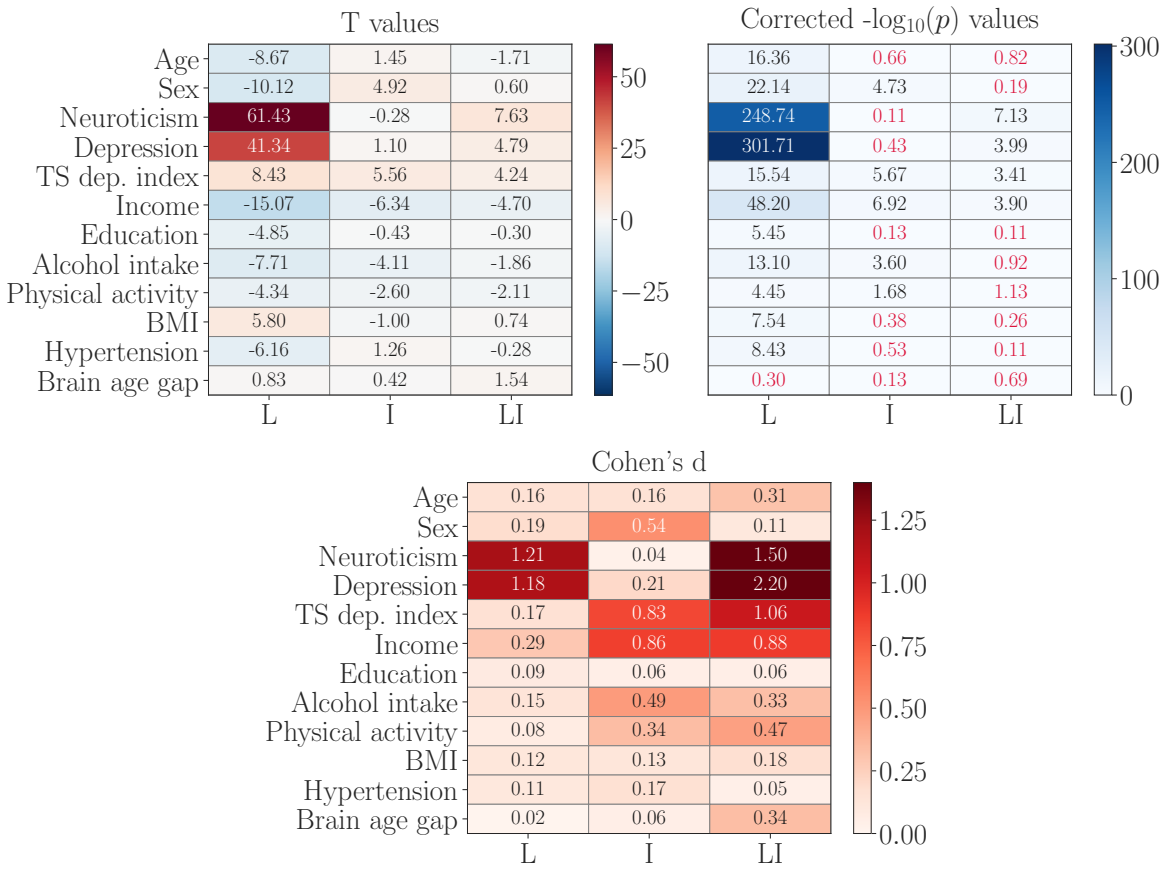
SI Table 5: Difference between individuals reporting loneliness (n = 2785) and individuals reporting both loneliness and social isolation (n = 409), based on independent sample t-tests (t) and Cohen's d effect size (d). CI = confidence interval; TS dep. index = Townsend deprivation index. P-values are reported before (p) and after (p_{corr}) FDR correction. Sex was coded 0 for women and 1 for men.

Factor	t	p	p_{corr}	$d[CI]$
Age	0.50	0.620	0.647	0.026 [0.021, 0.032]
Sex	-4.38	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.236 [0.230, 0.241]
Neuroticism	1.57	0.117	0.187	0.084 [0.078, 0.089]
Depression	-4.24	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.263 [0.257, 0.268]
TS dep. index	-5.87	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.331 [0.325, 0.337]
Income	6.78	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.348 [0.342, 0.353]
Education	0.43	0.664	0.664	0.023 [0.017, 0.029]
Alcohol intake	3.89	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.201 [0.196, 0.207]
Physical activity	5.57	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.309 [0.304, 0.315]
BMI	-0.57	0.567	0.619	0.031 [0.026, 0.037]
Hypertension	-0.83	0.408	0.467	0.044 [0.039, 0.050]
Brain age gap	-1.99	0.047	0.087	0.109 [0.103, 0.115]

SI Table 6: Difference between individuals reporting social isolation (n = 1286) and individuals reporting both loneliness and social isolation (n = 409), based on independent sample t-tests (t) and Cohen's d effect size (d). CI = confidence interval; TS dep. index = Townsend deprivation index. P-values are reported before (p) and after (p_{corr}) FDR correction. Sex was coded 0 for women and 1 for men.

Factor	t	p	p_{corr}	$d[CI]$
Age	3.12	0.002	0.004	0.180 [0.174, 0.187]
Sex	0.86	0.390	0.467	0.049 [0.043, 0.055]
Neuroticism	-18.75	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	1.104 [1.097, 1.111]
Depression	-14.96	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	1.140 [1.133, 1.148]
TS dep. index	-1.23	0.221	0.294	0.069 [0.062, 0.075]
Income	4.32	$< 1.00 \times 10^{-3}$	$< 1.00 \times 10^{-3}$	0.234 [0.228, 0.241]
Education	3.15	0.002	0.004	0.180 [0.174, 0.186]
Alcohol intake	1.92	0.056	0.095	0.108 [0.101, 0.114]
Physical activity	1.02	0.308	0.389	0.058 [0.052, 0.065]
BMI	-1.29	0.199	0.280	0.076 [0.070, 0.083]
Hypertension	2.44	0.015	0.030	0.136 [0.130, 0.143]
Brain age gap	-1.44	0.150	0.226	0.082 [0.076, 0.089]

6. Loneliness versus social isolation: group differences using a different cut-off score for social isolation



SI Figure 1: Group differences using a cut-off score of 3 for social isolation (see Section 3.4 in the manuscript). Top left: T-values for comparisons between individuals reporting loneliness (L; N = 3164), social isolation (I; N = 59) or both (LI; N = 30) with the control group of participants who did not report loneliness or social isolation (N = 21,614). Top right: FDR-corrected -$\log_{10}(p)$ for the t-test comparisons (FDR-corrected across all tests), with p-values > 0.05 marked in red font. Bottom plot: Cohen's d effect sizes for group differences on each factor (confidence intervals for d are in the third decimal place and are not quoted). Sex was coded 0 for women and 1 for men.