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Research report

# Prominent health problems, socioeconomic deprivation, and higher brain age in lonely and isolated individuals: A population-based study

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ABSTRACT

Loneliness is linked to increased risk for Alzheimer's disease, but little is known about factors potentially contributing to adverse brain health in lonely individuals. In this study, we used data from 24,867 UK Biobank participants to investigate risk factors related to loneliness and estimated brain age based on neuroimaging data. The results showed that on average, individuals who self-reported loneliness on a single yes/no item scored higher on neuroticism, depression, social isolation, and socioeconomic deprivation, performed less physical activity, and had higher BMI compared to individuals who did not report loneliness. In line with studies pointing to a genetic overlap of loneliness with neuroticism and depression, permutation feature importance ranked these factors as the most important for classifying lonely vs. not lonely individuals (ROC AUC = 0.83). While strongly linked to loneliness, neuroticism and depression were not associated with brain age estimates. Conversely, objective social isolation showed a main effect on brain age, and individuals reporting both loneliness and social isolation showed higher brain age relative to controls – as part of a prominent risk profile with elevated scores on socioeconomic deprivation and unhealthy lifestyle behaviours, in addition to neuroticism and depression. While longitudinal studies are required to determine causality, this finding may indicate that the combination of social isolation and a genetic predisposition for loneliness involves a risk for adverse brain health. Importantly, the results underline the complexity in associations between loneliness and adverse health outcomes, where observed risks likely depend on a combination of interlinked variables including genetic as well as social, behavioural, physical, and socioeconomic factors.

## 1. Introduction

Loneliness has been extensively studied in association with social, psychological, and health-related factors [1–3], and a complex interplay between genetic risk and environmental triggers likely underpins the concept of feeling lonely [4]. Loneliness has been shown to increase the risk of mortality [5] as well as developing Alzheimer's disease (AD) [6–8], and factors such as social isolation, depression, socioeconomic deprivation, cardiovascular risk, and unhealthy lifestyle behaviours may contribute to adverse health outcomes in lonely individuals [9–11]. These risk factors are also associated with neural decline in population-based studies [12–17], but the extent to which they interact with loneliness to influence brain integrity and health is largely unexplored [18].

While some studies have focused on the relative importance of known risk factors for loneliness [9] as well as excess mortality risk in lonely individuals [10], the degree to which different factors contribute to loneliness and associated health outcomes is not fully understood. Traditionally, most public health campaigns to reduce loneliness have focused on increasing social contact in the ageing population, as older adults are more susceptible to risk factors such as living alone and the loss of partners and close friends [2,19]. However, lifespan studies

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indicate that high risk for loneliness is not restricted to older age, but may also peak in early adulthood [9,20]. Furthermore, an individual can be socially contented when alone and feel lonely in the presence of others, and there are conceptual distinctions between objective measures of social isolation and self-perceived loneliness, which refers to a subjective sense of lacking desired social contact and belonging [3]. As such, loneliness and social isolation can be viewed as independent constructs that may overlap for some, but not all individuals [5], and it is unclear how each of these constructs, as well as the combination of the two, may be linked to adverse brain health [6,11,21]. Loneliness is further associated with depression [22–24] as well as the personality trait neuroticism [25–27], and the relationship between loneliness and neuroticism is largely driven by genetic factors [28]. Hence, beyond objective social isolation, intrinsic factors such as genetic risk may also contribute to a subjective sense of loneliness and associated health problems. In the wake of the COVID-19 pandemic, structural and enduring changes in social habits call for a clarification of how loneliness, social isolation, and associated risk factors may influence brain health in the general population.

In this study, we used data from 24,867 UK Biobank participants to investigate social, psychological, behavioural, cardiovascular, and socioeconomic factors in individuals reporting loneliness on a single yes/no item, and assessed how loneliness and associated risk factors were linked to estimated brain age [29] based on magnetic resonance imaging (MRI) data. Brain age estimation is frequently used to generate a marker for neural ageing processes across normative and clinical populations [30–32]. The difference between an individual's estimated brain age and chronological age provides a proxy for deviations from expected age trajectories, which has been associated with clinical risk factors and lifestyle variables [14,33–38] as well as neuropsychiatric conditions [17,39,40], supporting the use of brain age as a surrogate marker for brain integrity and health [41].

The main aims of the study were to (1) establish differences in previously described risk factors for loneliness [4,10,42] between individuals reporting loneliness and not in the current sample, (2) assess the relative importance of each risk factor for predicting loneliness, (3) test if loneliness and social, psychological, behavioural, cardiovascular, and socioeconomic factors were associated with brain age, and (4) assess the overlap between loneliness and social isolation, and investigate risk factors and brain age in groups of individuals reporting loneliness, social isolation, or both, based on previous research showing diverging findings in terms of health outcomes [8,11,21,43,44]. We first assessed group differences between individuals reporting loneliness and not, using a series of independent samples *t*-tests, calculating Cohen's *d* effect sizes for each of the risk factors in addition to age and sex. Next, we included the risk factors as input features in a binary classifier, using permutation feature importance to rank the relative contribution of each factor to the classification of lonely vs. not lonely individuals. Linear regression analyses were run for each of the risk factors vs. brain age estimates to test for main effects, and for interaction terms vs. brain age to test for effects of loneliness in combination with each risk factor. Finally, we assessed the overlap between loneliness and social isolation in the sample, and investigated risk factors and brain age estimates in groups of individuals reporting (i) loneliness but not isolation, (ii) isolation but not loneliness, and (iii) both loneliness and isolation, compared to a control group of individuals who reported neither loneliness nor social isolation.

## 2. Methods and materials

### 2.1. Sample characteristics

The initial sample was drawn from the UK Biobank MRI cohort (www.ukbiobank.ac.uk) and included a total of 42,051 participants. Participants with known brain disorders ($N$ = 3656) were excluded based on ICD10 diagnoses (chapter V and VI, field F; *mental and behavioural disorders*, including F00–F03 (Alzheimer's disease and dementia), and F06.7 (mild cognitive disorder), and field G; *diseases of the nervous system*, including inflammatory and neurodegenerative diseases (except G55-59; Nerve, nerve root and plexus disorders). An overview of the diagnoses is provided in the UK Biobank online resources (http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270), and the diagnostic criteria are listed in the ICD10 manual (https://www.who.int/classifications/icd/icdonlineversions). 503 participants were excluded based on outlier detection (see Section 2.5), yielding 37,863 participants that were included in the brain age prediction model (see Section 2.6). For further analyses, a total of 12,996 participants were excluded based on missing data on loneliness ($n$ = 409), social isolation ($n$ = 693), neuroticism ($n$ = 5360), depressive symptoms ($n$ = 1229), demographic factors ($n$ = 4), socioeconomic factors ($n$ = 2188), lifestyle behaviours ($n$ = 602), and cardiovascular risks ($n$ = 2511), yielding a final sample of 24,867 participants with complete data on MRI in addition to all other factors. Sample demographics are provided in Table 1.

**Table 1**
Sample demographics. The measurements used for loneliness, social isolation, neuroticism, depression, smoking, alcohol intake, body mass index (BMI), hypertension, Townsend deprivation index, and household income are described in Sections 2.2–2.4. GCSE = General Certificate of Secondary Education, NVQ = National Vocational Qualification.

| *N* | | 24,867 |
|---|---|---|
| Age | Mean ± SD | 63.86 ± 7.51 |
| | Range [years] | 44.57–81.83 |
| Sex | % Male | 49.97 |
| | % Female | 50.03 |
| Ethnic background | % White | 97.46 |
| | % Black | 0.55 |
| | % Mixed | 0.44 |
| | % Asian | 0.86 |
| | % Chinese | 0.25 |
| | % Other | 0.43 |
| Education | % University/college degree | 49.88 |
| | % A levels or equivalent | 13.58 |
| | % O levels/GCSE or equivalent | 21.97 |
| | % NVQ or equivalent | 5.05 |
| | % Professional qualification | 4.64 |
| | % None of the above | 4.88 |
| Assessment location | Newcastle | 5484 |
| | Cheadle | 15,725 |
| | Reading | 3658 |
| Loneliness | % yes | 12.84 |
| | % no | 87.16 |
| Social isolation | % score 0 (lowest) | 57.57 |
| | % score 1 | 35.61 |
| | % score 2 | 6.46 |
| | % score 3 (highest) | 0.35 |
| Neuroticism | Mean ± SD | 3.44 ± 2.92 |
| | Range | 0–11 |
| Depressive symptoms | Mean ± SD | 5.18 ± 1.65 |
| | Range | 4–16 |
| Smoking | % yes | 37.92 |
| | % no | 62.07 |
| Alcohol intake | % at least three times a week | 52.29 |
| | % less than three times a week | 47.71 |
| Physical activity (times per week) | Mean ± SD | 5.38 ± 3.54 |
| | Range | 0–14 |
| BMI | Mean ± SD | 26.48 ± 4.12 |
| | Range | 14.68–56.60 |
| Hypertension | % yes | 38.46 |
| | % no | 61.54 |
| Townsend deprivation index | Mean ± SD | −1.96 ± 2.65 |
| | Range | −6.26 to 10.10 |
| Household income (Annual £) | % <18,000 | 10.09 |
| | % 18,000–30,999 | 20.90 |
| | % 31,000–51,999 | 30.03 |
| | % 52,000–100,000 | 30.48 |
| | % >100,000 | 8.49 |

### 2.2. Loneliness and social isolation

Loneliness was assessed based on responses to the questions (1) "*Do you often feel lonely?*" (no = 0, yes = 1). In line with previous studies [10,45,46] a social isolation score was derived using the following questions: (1) "*Including yourself, how many people are living together in your household?*" (1 point for living alone); (2) "*How often do you visit friends or family or have them visit you?*" (1 point for friends and family visit less than once a month); and (3) "*Which of the following [leisure/social activities] do you engage in once a week or more often?*" (1 point for no participation in social activities at least weekly).

### 2.3. Neuroticism and depression

Neuroticism was derived from the Eysenck Personality Questionnaire-Revised Short Form [47,48]. 11 out of 12 available items from the neuroticism scale (excluding *loneliness*) were used, comprising the following questions: (1) *"Does your mood often go up and down?"*, (2) *"Do you ever feel 'just miserable' for no reason?"*, (3) *"Are you an irritable person?"*, (4) *"Are your feelings easily hurt?"*, (5) *"Do you often feel 'fed-up'?"* (6) *"Would you call yourself a nervous person?"* (7) *"Are you a worrier?"*, (8) *"Would you call yourself tense or 'highly strung'?"*, (9) *"Do you worry too long after an embarrassing experience?"*, (10) *"Do you suffer from 'nerves'?"*, (11) *"Are you often troubled by feelings of guilt?"* (https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=20127).

Depression was measured by a continuous score of current depressive symptoms based on the frequency of four items from the Patient Health Questionnaire [49,50]: (1) depressed mood, (2) disinterest or absence of enthusiasm, (3) tenseness or restlessness, and (4) tiredness or lethargy in the previous 2 weeks, as used in recent studies on loneliness in the UK Biobank cohort [10,43]. To test for potential variations in the results when using a measure of lifetime depressive symptoms instead of current symptoms, the group difference analyses (see Section 2.7.1) were repeated using the response to the question *"Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?"* (no = 0, yes = 1).

### 2.4. Lifestyle behaviours, cardiovascular risk, and socioeconomic factors

Lifestyle behaviours included cigarette smoking (current or previous smoker vs. never smoked), alcohol intake frequency (at least three times a week vs. twice a week or less), and physical activity (*"In a typical week, how many days did you do 10 minutes or more of moderate/vigorous physical activity?"*). Cardiovascular risk factors included body mass index (BMI) and hypertension (systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg [51]). The assessment procedures are described in the UK Biobank protocol [52]. Socioeconomic factors included education qualification (higher education including university/college degree or professional qualification vs. not higher education; see Table 1), average total household income before tax (annual income in £; see Table 1), and Townsend deprivation index [53,54], which is a measure of material deprivation within a population based on postcode of residence. The index comprises four variables: unemployment (as a percentage of those aged 16 and over who are economically active); non-car ownership (as a percentage of all households), non-home ownership (as a percentage of all households), and household overcrowding.

### 2.5. MRI data acquisition and processing

A detailed overview of the UK Biobank data acquisition and protocols is available in [55,56]. Raw T1-weighted MRI data for all participants were processed using a harmonised analysis pipeline, including automated surface-based morphometry and subcortical segmentation as implemented in FreeSurfer 5.3 [57]. In line with recent large-scale implementations [39,58,59], we utilised a fine-grained cortical parcellation scheme [60] to extract cortical thickness, area, and volume for 180 regions of interest per hemisphere, in addition to the classic set of subcortical and cortical summary statistics from FreeSurfer [57]. This yielded a total set of 1118 structural brain imaging features (360/360/360/38 for cortical thickness/area/volume, as well as cerebellar/subcortical and cortical summary statistics, respectively). The MRI variables were residualised with respect to scanning site, ethnic background, intracranial volume, and Freesurfer-derived Euler numbers [61] using linear models. To remove poor-quality data likely due to motion, participants with Euler numbers $\pm$ 4 standard deviations (SD) from the mean were excluded ($n$ = 376). In addition, participants with global MRI measures (total cortical and/or subcortical grey matter volume) $\pm$ 4 SD from the mean were excluded ($n$ = 95 and $n$ = 32, respectively), yielding a final MRI sample of 37,863 participants.

### 2.6. Brain age prediction

In line with recent brain age prediction studies [39,58,59], the *XGBoost* regression model was used to run global brain age prediction (https://github.com/dmlc/xgboost) [62]. XGboost (eXtreme gradient boosting) includes advanced regularisation to reduce overfitting, and is based on a decision-tree ensemble algorithm where the final model is based on a collection of individual models. To reduce computational time, a principal component analysis (PCA) was run and the first 700 components explaining 97.95% of the total variance were used as input. The model was run on the full MRI sample ($n$ = 37,863), and parameters were tuned in a nested cross-validation using 5 inner folds for randomised search, and 10 outer folds for model validation. The age prediction showed a mean $\pm$ standard deviation of $R^2$ = 0.45 $\pm$ 0.02, root mean square error = 5.62 $\pm$ 0.14, mean absolute error = 4.54 $\pm$ 0.08, and Pearson's $r$ (predicted vs. chronological age) = 0.67; 95% confidence interval = [0.67, 0.68], $p < 0.001$. Each participant's *brain age gap* was calculated by subtracting chronological age from predicted brain age, providing an estimation of their brain age relative to expected age trajectories [29]. The brain age gap estimates were residualised for chronological age using linear regression [63,64].

### 2.7. Statistical analyses

The statistical analyses were conducted using Python 3.7 and Scikit Learn 0.23.1. $p$-values were adjusted for multiple comparisons using false discovery rate (FDR)-correction [65].

#### 2.7.1. Group differences

To test for group differences between individuals reporting loneliness and individuals not reporting loneliness in terms of neuroticism, depression, social isolation, Townsend deprivation index, income, education, smoking status, alcohol intake, physical activity, BMI, and hypertension, a series of independent samples $t$-tests were run, and Cohen's $d$ effect sizes [66] were calculated for each factor in addition to age and sex (coded 0 for women and 1 for men).

#### 2.7.2. Classification

To assess the relative importance of each risk factor for predicting loneliness, a binary XGBoost classifier was used to classify individuals reporting loneliness vs. individuals not reporting loneliness based on the factors showing significant group differences on $t$-tests (described in Section 2.7.1). The relative contribution of each input feature was measured using permutation feature importance with 50 repetitions, indicating the decrease in model performance when a single feature value is randomly shuffled [67]. All variables were standardised (subtracting the mean and dividing by the standard deviation) before entered into the model, and the model was run with downsampling to balance the difference in group size (yielding $n$ = 3194 in each category). Parameters were tuned in a nested cross-validation using 5 inner folds for grid search, and 10 outer folds for the model validation.

#### 2.7.3. Associations with brain age estimates

To test for associations with brain age estimates, linear regressions were run for loneliness vs. *brain age gap* (described in Section 2.6) and for each of the factors showing significant group differences (see Section 2.7.1) vs. brain age gap, including age as a covariate. To assess potential interaction effects, additional linear regressions were run with interaction terms for loneliness × each of the factors vs. brain age gap.

### 2.8. Loneliness vs. social isolation: differences in risk factors and brain age gap

Pairwise *t* tests and Cohen's *d* effect sizes were used to compare groups of individuals reporting (i) loneliness but not isolation, (ii) isolation but not loneliness, and (iii) both loneliness and isolation to a control group of individuals who reported neither loneliness nor social isolation, in terms of risk factors (neuroticism, depression, Townsend deprivation index, income, education, alcohol intake, physical activity, and BMI) as well as brain age gap. An individual was classified as socially isolated if they scored $\geq 2$ on the scale of 0–3 (described in Section 2.2), and not isolated if they scored $\leq 1$.

## 3. Results

### 3.1. Group differences

Table 2 shows the differences between individuals reporting loneliness ($n = 3194$) and individuals not reporting loneliness ($n = 21{,}673$). Relative to the control group, individuals who reported loneliness scored higher on social isolation, neuroticism, and depressive symptoms, had higher Townsend deprivation index, lower income and lower education, performed less physical activity, had higher BMI, lower alcohol intake, and less hypertension. The group of individuals reporting loneliness were on average younger, and included a larger proportion of women compared to the group of individuals not reporting loneliness. No significant group differences were found for smoking status. When using the self-reported measure of lifetime depressive symptoms, the results showed similar patterns as shown in Supplementary Information (SI) Table 1.

**Table 2**
Difference between individuals reporting loneliness ($n = 3194$) and individuals not reporting loneliness ($n = 21{,}673$) 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 | $t$ | $p$ | $p_{corr}$ | $d$[CI] |
|---|---|---|---|---|
| Social isolation | 17.34 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.366 [0.365, 0.367] |
| Neuroticism | 61.82 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 1.213 [1.212, 1.214] |
| Depression | 41.54 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 1.181 [1.180, 1.182] |
| TS dep. index | 8.72 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.174 [0.174, 0.175] |
| Income | −15.28 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.294 [0.293, 0.294] |
| Education | −4.84 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.092 [0.091, 0.093] |
| Smoking status | 1.55 | 0.122 | 0.122 | 0.029 [0.029, 0.030] |
| Alcohol intake | −7.77 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.147 [0.146, 0.148] |
| Physical activity | −4.49 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.085 [0.084, 0.085] |
| BMI | 5.86 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.122 [0.121, 0.122] |
| Hypertension | −6.17 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.114 [0.113, 0.115] |
| Age | −8.81 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.165 [0.164, 0.166] |
| Sex[a] | −10.09 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ | 0.189 [0.189, 0.190] |

[a] Sex = 0 for women and 1 for men.

### 3.2. Classification

All factors except smoking status were included as features in the binary classifier. The model showed an accuracy of 0.743 (SD 0.018; Area under the ROC Curve = 0.829, SD 0.015), with 75.58% correctly identified as lonely (precision = 0.74, recall = 0.76, $f = 0.75$), and 72.98% correctly identified as not lonely (precision = 0.75, recall = 0.73, $f = 0.74$). The permutation feature importance is shown in Table 3, with neuroticism ranked as the most important contributor to the classification performance. In addition, depression, social isolation, income, and Townsend deprivation index each contributed uniquely to the classification.

### 3.3. Associations with brain age estimates

Higher scores on social isolation, Townsend deprivation index, alcohol intake, and BMI, as well as hypertension, and sex (male) were each associated with higher brain age relative to chronological age, as shown in SI Table 2. The other factors, including loneliness, did not show significant associations with brain age gap ($\beta = 0.02 \pm 0.02$ (standard error; SD), $t = 0.96$, $p = 0.337$, corrected $p = 0.368$ for loneliness). To account for the potential influence of early life factors, the analyses were repeated with birth weight as an additional covariate in a sub-sample with available data ($n = 15{,}298$). The results showed associations corresponding to the main results for all factors (SI Table 3) except loneliness, which here showed a significant association with brain age gap ($\beta = 0.06 \pm 0.03$, $t = 2.35$, $p = 0.019$ corrected $p = 0.033$).

For the interaction models, no effects of loneliness × any of the risk factors were found on brain age gap, as shown in Table 4. Interaction models including age as a covariate showed corresponding results (SI Table 4). To test for a potential interaction with early life factors, *loneliness* × *birth weigh* vs. brain age gap was run, but no significant association was found ($\beta = 0.05 \pm 0.08$, $t = 0.66$, $p = 0.507$, corrected $p = 0.609$).

### 3.4. Loneliness vs. social isolation: differences in risk factors and brain age gap

Fig. 1 shows the number of participants reporting (i) loneliness but not isolation (L), (ii) isolation but not loneliness (I), and (iii) both loneliness and isolation (LI). Fig. 2 shows the differences in risk factors and brain age gap for each of the groups compared to the control group of participants who reported neither loneliness nor social isolation ($n = 20{,}387$).

All three groups were on average more depressed, had higher Townsend deprivation index scores and lower income, performed less physical activity, had higher BMI, and lower alcohol intake relative to controls. Only the individuals who reported both loneliness and social isolation showed higher brain age gap relative to the control group, as shown in Fig. 2.

Group comparisons for L vs. LI, and I vs. LI are shown in SI Tables 5 and 6. Compared to L, LI showed a larger proportion of men, had higher Townsend deprivation index scores, had lower income and lower alcohol intake, and performed less psychical activity. Compared to I, LI were younger, showed higher neuroticism and depression, had lower income and education, and less hypertension. For brain age gap, the difference between L and LI was $t = -1.99$, $p = 0.05$, corrected $p = 0.09$, $d = 0.11$[0.10, 0.12], and the difference between L and I was $t = -1.44$, $p = 0.15$, corrected $p = 0.23$, $d = 0.08$[0.08, 0.09]. To validate the group selection criteria, $T$ scores and Cohen's $d$ effect sizes were re-calculated using a social isolation cut-off score of 3 (see Section 2.2). While the I

**Table 3**
Permutation feature importance for the classification of individuals reporting loneliness and individuals not reporting loneliness with balanced sample sizes ($n = 3194$ in each group). The features are sorted based on mean importance across 50 repetitions, with neuroticism ranked as the most prominent feature for the classification performance. TS dep. index = Townsend deprivation index.

| Variable | Mean ($\times 10^{-2}$) | SD ($\times 10^{-2}$) | $z$ | $p$ | $p_{corr}$ |
|---|---|---|---|---|---|
| Neuroticism | 13.466 | 0.524 | 25.677 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ |
| Depression | 4.310 | 0.319 | 13.517 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ |
| Social isolation | 0.926 | 0.239 | 3.869 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ |
| Income | 0.829 | 0.206 | 4.022 | $<1.00 \times 10^{-3}$ | $<1.00 \times 10^{-3}$ |
| TS dep. index | 0.345 | 0.141 | 2.438 | 0.015 | 0.035 |
| BMI | 0.291 | 0.145 | 2.014 | 0.044 | 0.088 |
| Age | 0.161 | 0.115 | 1.400 | 0.162 | 0.277 |
| Alcohol intake | 0.081 | 0.102 | 0.792 | 0.428 | 0.571 |
| Education | 0.014 | 0.017 | 0.808 | 0.419 | 0.571 |
| Physical activity | 0.002 | 0.031 | 0.061 | 0.951 | 1.000 |
| Sex | 0.000 | 0.000 | 0.000 | 1.000 | 1.000 |
| Hypertension | 0.000 | 0.000 | 0.000 | 1.000 | 1.000 |

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

| Factor | $\beta \pm SE$ | $t$ | $p$ | $p_{corr}$ |
|---|---|---|---|---|
| L × Age | 0.09 ± 0.06 | −1.37 | 0.170 | 0.702 |
| L × Sex | 0.04 ± 0.06 | 0.61 | 0.543 | 0.702 |
| L × Neuroticism | 0.04 ± 0.07 | 0.55 | 0.585 | 0.702 |
| L × Depression | 0.05 ± 0.05 | 0.94 | 0.345 | 0.702 |
| L × Social isolation | 0.10 ± 0.06 | 1.70 | 0.088 | 0.702 |
| L × TS dep. index | 0.03 ± 0.06 | 0.43 | 0.667 | 0.727 |
| L × Income | 0.08 ± 0.06 | −1.32 | 0.187 | 0.702 |
| L × Education | 0.01 ± 0.06 | 0.21 | 0.837 | 0.837 |
| L × Alcohol intake | 0.06 ± 0.06 | −0.89 | 0.374 | 0.702 |
| L × Physical activity | 0.04 ± 0.06 | 0.66 | 0.512 | 0.702 |
| L × BMI | 0.04 ± 0.06 | −0.65 | 0.514 | 0.702 |
| L × Hypertension | 0.05 ± 0.06 | 0.77 | 0.439 | 0.702 |

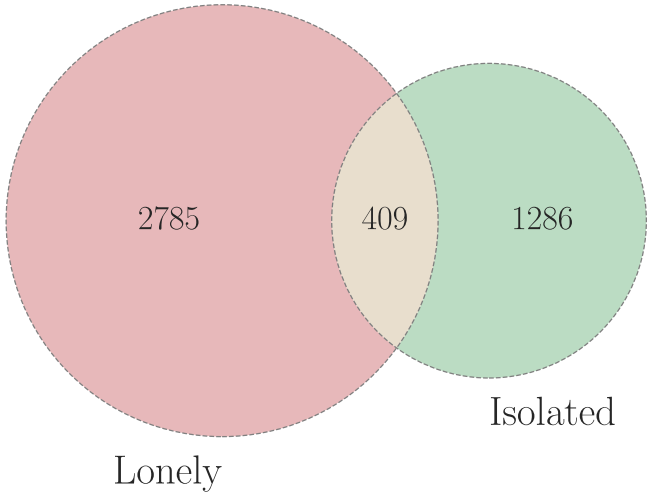


**Fig. 1.** Venn diagram showing the overlap between loneliness and social isolation, and number of participants in each of the groups; lonely = 2785, isolated = 1286, lonely and isolated = 409.

and LI groups were considerably smaller using this cut-off (N for L = 3164, I = 59, LI = 30, control group = 21,614), the results showed similar patterns, as shown in SI Fig. 1.

## 4. Discussion

In this study, we investigated social, psychological, behavioural, cardiovascular, and socioeconomic factors in relation to loneliness and estimated brain age. In summary, the results showed that individuals who reported loneliness scored higher on social isolation, neuroticism and depression, had higher Townsend deprivation index, lower income, and lower education, performed less physical activity, had higher BMI, lower alcohol intake, and less hypertension compared to the group of individuals who did not report loneliness. In line with previous studies [42], reporting loneliness was also associated with younger age and being female. Neuroticism ranked as the most prominent feature for classifying individuals reporting loneliness, followed by depression. While higher scores on social isolation, Townsend deprivation index, alcohol intake, and BMI, as well as sex (male) and hypertension were each associated with higher brain age relative to chronological age, none of the interaction terms for loneliness × the other factors showed associations with brain age estimates. Group comparisons showed that relative to controls, only individuals reporting *both* loneliness and social isolation showed on average higher brain age relative to chronological age.

### 4.1. Predictors for loneliness and associations with brain age

In line with previous studies linking loneliness to both neuroticism [26,27,25] and depression [22–24], these two factors showed the strongest contributions to the classification of lonely individuals. While social isolation also contributed significantly to the classification, the precedence of neuroticism and depression points to a considerable overlap between these traits and loneliness, which may to a large extent be driven by genetic factors [28]. However, while clearly linked to loneliness, neuroticism and depression were not associated with brain age estimates. Conversely, objective social isolation showed a significant main effect on brain age gap, and individuals reporting social isolation in addition to loneliness showed higher brain age as part of a pronounced risk profile with elevated scores on unhealthy lifestyle behaviours and socioeconomic deprivation, in addition to high neuroticism and depression. This finding may indicate that in combination with a genetic predisposition for loneliness, social isolation contributes to a risk for adverse brain health.

Loneliness has previously been associated with brain characteristics including smaller regional grey matter volume [42,68,69], and differences in structural and functional network connectivity [70–72]. While these brain characteristics are involved in both normal ageing and AD pathogenesis [73,74], the ways in which loneliness and social isolation interact to influence brain ageing in combination with other risk factors is unclear. One recent study showed that loneliness correlated with smaller grey matter volume in brain regions central to cognitive processing and emotional regulation in a sample of 319 older adults [42]. The association could not be fully explained by factors including age, sex, education, number of confidants, depressive affect, or the personality trait *openness*. Loneliness has also been shown to persist in

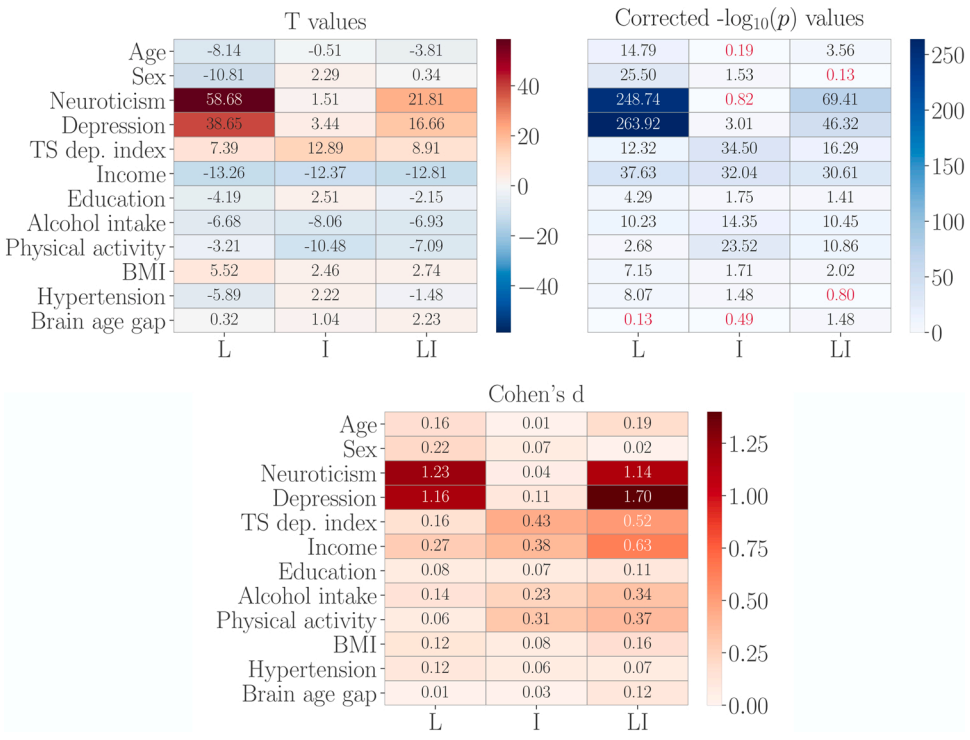


**Fig. 2.** Differences between individuals reporting loneliness (L; $n = 2785$), social isolation (I; $n = 1286$) or both (LI; $n = 409$), and the control group of participants who reported neither loneliness nor social isolation ($n = 20{,}387$). Top left: *T*-values for group comparisons on each factor. 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 comparisons 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.

predicting AD risk when measures of social contact are controlled for [44,75]. In contrast, the current results showed that social isolation, but not loneliness, was linked to brain age, and relative to controls, only individuals who reported both social isolation and loneliness showed higher brain age relative to chronological age. This finding is in line with a recent UK Biobank study showing that social isolation, but not loneliness, was associated with increased risk of dementia [43]. Similarly, social isolation has been shown to constitute a higher risk for mortality, while the effect of self-perceived loneliness on mortality risk depends on other health problems and demographic characteristics [11]. Given that unhealthy lifestyle behaviours, adverse socioeconomic conditions, and lower mental wellbeing contribute to excess mortality risk among lonely and isolated individuals [10], future studies should aim to investigate both genetic risks [95] and environmental triggers [4] to parse how loneliness and social isolation may influence brain health.

While the current results may indicate that a combination of loneliness and social isolation involves a risk for accelerated brain ageing, diverging brain age estimates could also represent one of several factors characterising individuals with a genetic predisposition for loneliness, which is linked to increased susceptibility to both mental and physical health problems [76,77,95]. Although genetic correlations between loneliness and risk factors tend to align with phenotypic correlations, there has also been some divergence; a phenotypic association between loneliness and alcohol abuse has been reported [78], but a recent study found a genetic correlation between loneliness and *lower* alcohol intake [76] – in line with the current results. This finding may be linked to a genetic association between loneliness and socioeconomic status [76], as possibly reflected in the higher Townsend deprivation index scores, lower education, and lower income observed among individuals reporting loneliness in the current sample.

### 4.2. Study limitations

In our sample of 24,867 UK Biobank participants, 12.84% reported loneliness. As statistical reports have shown a population prevalence of loneliness between 15% and 30% [79–81] (pre-coronavirus), the somewhat lower number of individuals reporting loneliness in the current sample may reflect a selection bias towards healthy or high-functioning individuals participating in comprehensive research studies. Furthermore, the loneliness prevalence in the imaging cohort was lower than what is reported for the full UK Biobank sample of >500k participants (18%; https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=2020), indicating that the imaging sub-sample likely represents a selected group of individuals. As selection or attrition bias can influence estimates of phenotypic associations [82], the current results should be interpreted with caution as they may not generalise to populations beyond those represented in the UK Biobank imaging cohort. The sample is also homogeneous in regards to ethnic background (97% white participants), preventing any conclusion about loneliness, social isolation, and risk factors across ethnic groups.

While the current measurement of loneliness has been used in previous studies [10,83], direct questions including the word *lonely* may lead to an underestimation due to low willingness of respondents to characterise themselves as lonely [84]. Comparisons with indirect measures that do not explicitly use the word *lonely*, such as the Revised UCLA Loneliness Scale [85], show that these approaches may provide variable estimations of prevalence as well as characteristics of lonely individuals. However, a relatively large overlap between classifications has also been reported, with a tendency for indirect measures to miss some of the individuals classified as lonely on direct scales [86].

The lack of association between loneliness and brain age is in contrast to some previous findings [42,68,69], which could potentially be explained by differences in brain measures used across studies. While brain age prediction combines a rich variety of brain characteristics into global estimates that can be compared to normative age trajectories, summarising measures across the brain does not provide information about regional neural networks potentially linked to loneliness. Future research may benefit from estimating regional brain ageing patterns [39,87–89] to provide more detailed measures of brain characteristics that may relate to loneliness, social isolation, and associated risk factors.

Finally, the cross-sectional nature of the current study does not allow for causal inference, and longitudinal neuroimaging studies including genetic data are required to fully understand the relationship between loneliness, social isolation, associated risk factors, and brain ageing

trajectories. Given the study limitations outlined above, future research should ideally aim for longitudinal designs including selective attrition analyses and several cohorts, as well as multiple measures of loneliness and brain characteristics. Future studies may also benefit from more advanced approaches that carefully model interactions and relationships among variables [90–92] due to the complex interplay between loneliness, social isolation, genetic and environmental risk factors, and health outcomes [4,9,10,95].

### 4.3. Conclusion

This study shows that loneliness largely overlaps with neuroticism and depression, and is further linked to social, behavioural, cardiovascular, and socioeconomic risk factors. While the results indicate that a combination of social isolation and loneliness may involve a risk for adverse brain health, longitudinal studies are required to determine causality. Recent research shows that depressive symptoms and socioeconomic factors may explain up to 66% and 44% of excess mortality risk in lonely individuals, respectively [10]. In accordance with these findings, the current results underline the complexity of associations between loneliness and adverse health outcomes [93–95], where observed risks likely depend on a combination of interlinked variables including genetic as well as social, behavioural, and socioeconomic factors. In conclusion, the results emphasise the importance of developing public-health initiatives across age groups to target mental, physical, and social health as well as socioeconomic conditions, in order to reduce risks of loneliness and adverse health outcomes in the population – both during the COVID-19 pandemic and beyond.

## Authors' contribution

A.M.G. de Lange: conceptualisation; methodology; software; formal analyses; investigation; visualisation, writing – original draft, project administration. T. Kaufmann: methodology; resources; writing – reviewing and editing. D.S. Quintana: visualisation, writing – reviewing and editing. A. Winterton: writing – reviewing and editing. O.A. Andreassen: resources; writing – reviewing and editing. L.T. Westlye: resources; methodology, writing – reviewing and editing. K.P. Ebmeier: conceptualisation; methodology; writing – reviewing and editing, project administration.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbr.2021.113510.

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