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Associations of social isolation and loneliness with neurological disorders, psychiatric disorders, brain structures and behavioural phenotypes among UK Biobank participants

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Abstract:

Social isolation and loneliness are increasingly recognized as detrimental risk factors for brain health. Here, utilizing data from 383,421 participants in the UK Biobank, we identify significant associations between social isolation, loneliness, and the incidence of 11 neurological and psychiatric disorders, including major depressive disorder (MDD), schizophrenia, bipolar disorder, anxiety disorders, sleep disorders, dementia, Alzheimer's disease, Parkinson's disease, stroke, multiple sclerosis, and epilepsy employing Cox regression models. Furthermore, using Mendelian randomization analysis we find evidence for putative relationships from social isolation and loneliness to MDD, schizophrenia, sleep disorders, and epilepsy. We also observe significant associations between social isolation, loneliness, and worse cognitive and emotional performance, as well as alterations in brain structures. Additionally, mediation analyses indicate that peripheral inflammatory and biochemical markers partially mediated the links from social isolation and loneliness to neurological and psychiatric disorders.

Introduction

Social isolation refers to the lack of sufficient quantity and frequency of relationships and interactions within a community or network[1-3]. Loneliness is defined as a subjective experience of distress stemming from perceived unsatisfactory social relationships, independent of actual social isolation[1,4]. These two concepts are intertwined yet distinct[1,3]. Social isolation and loneliness are widespread, but their adverse health effects are still underrecognized[5-7]. Research has documented links between social isolation, loneliness, and heightened risks of cardiovascular disease[8], diabetes[1], and earlier mortality[9,10]. However, the effects of social isolation and loneliness on brain health remain inadequately understood. Notably, there has been a reported increase in loneliness among adolescents[11], a critical period for brain development characterized by heightened vulnerability to social stress. Brain health, defined by the absence of neurological and psychiatric disorders as well as the preservation of cognitive, emotional, and other complex functions, is fundamentally connected to quality of life[12-14]. Moreover, these neurological and psychiatric disorders pose an increasing global societal challenge due to the rising population and extended life expectancy[12,15,16]. Therefore, elucidating the link between social isolation, loneliness, and brain health is imperative, as it may inform the development of targeted interventions to reduce the morbidity and mortality associated with social isolation and loneliness, thereby enhancing public health.

Previous studies have linked social isolation and loneliness to several neurological disorders such as dementia[17,18] and stroke[8], and to various psychiatric disorders like major depressive disorder (MDD)[19], anxiety disorders[20], sleep disorders[21], as well as to major psychiatric disorders such as bipolar disorder (BD)[22] and schizophrenia[4]. Social isolation and loneliness may impact brain health through mechanisms such as the activation of the hypothalamic-pituitary-adrenal (HPA) axis[23], changes in neurotransmission and neural

circuitry[24], glial cells dysfunctions[24], and increased neuroinflammation[25], potentially leading to neurological and psychiatric disorders. Still, the mechanisms underlying the association between social isolation, loneliness and these disorders are poorly understood. Although prior observational studies have substantially advanced our comprehension of the association between social isolation, loneliness, and neurological and psychiatric disorders, the findings exhibited inconsistencies[19,26,27], and some of them were constrained by methodological limitations such as cross-sectional study designs and small sample sizes[20,22,28]. Furthermore, it remains unclear whether social isolation and loneliness have distinct associations with various neurological and psychiatric disorders across different populations. Research has also suggested links between social isolation, loneliness, and brain-related behavioral phenotypes, including cognitive function and mental health[20]; however, these findings generally lacked longitudinal evidence[20]. Additionally, few studies have explored the connection between social isolation, loneliness, and brain structures[29,30], which is essential for advancing our understanding of their impact on brain health.

In this work, we aim to conduct an extensive study with the UK Biobank (UKB) cohort to better understand the relationship between social isolation, loneliness, and brain health. First, we performed a longitudinal study on the associations between social isolation, loneliness, and the risk of 13 neurological and psychiatric disorders, employing the Cox proportional hazards model. The bidirectional Mendelian randomization (MR) analysis was further utilized to investigate possible causal and reverse causal relationships. Second, we explored the links between social isolation, loneliness, and various behavioral phenotypes, including cognitive and emotional functions, alongside changes in cortical and subcortical brain regions and white matter indictors, to better understand their impact on brain health. In addition, this study explored the mediating effects of blood inflammatory and biochemical markers on the relationship between social isolation, loneliness, and neurological

and psychiatric disorders, to propose potential mechanisms (Figure 1).

Results

Baseline characteristics of the participants

The primary analyses of neurological and psychiatric disorders included 383,421 participants. They consisted predominantly of self-identified White ethnicity (94.7 %), with an average age of 56.5 (SD = 8.1), and 53.7% were female (Table 1). Of the total, 32,206 individuals (8.4%) were identified as socially isolated, while 15,488 (4.0%) were considered lonely. Over an average follow-up of 14.2 years, 167 to 13,588 participants were diagnosed with various neurological and psychiatric disorders. Table 1 and Supplementary Table S1 present the demographic characteristics of participants with various incident neurological and psychiatric disorders.

Social isolation, loneliness, and incident neurological and psychiatric disorders

Significant associations between social isolation, loneliness, and the risk of neurological and psychiatric disorders were found using Cox proportional hazards models, with *P* values corrected for false discovery rate (FDR) using the Benjamini–Hochberg method (Figure 2). First, social isolation and loneliness exhibited distinct patterns of association with neurological and psychiatric disorders. Both social isolation and loneliness were significantly associated with the incidence of 6 neurological and psychiatric disorders (social isolation: FDR-Q < 0.001 for dementia, MDD, anxiety disorders, and schizophrenia, FDR-Q = 0.002 for sleep disorders, and FDR-Q = 0.008 for stroke; loneliness: FDR-Q < 0.001 for dementia, stroke, sleep disorders, MDD, anxiety disorders, and schizophrenia). Additionally, evidence also supported the association between social isolation with Alzheimer's disease (AD) (FDR-Q = 0.002), MS (FDR-Q = 0.009), Parkinson's disease (PD) (FDR-Q = 0.016), and BD (FDR-Q = 0.021), and between loneliness with epilepsy (FDR-Q = 0.005). Second, the effect sizes of these associations varied across different neurological and psychiatric disorders. The associations were generally

stronger for psychiatric than for neurological disorders. For loneliness, the hazard ratios (HRs) were highest for schizophrenia (HR = 2.62, 95% CI = 1.58–4.32), MDD (HR = 2.12, 95% CI = 1.98–2.27), anxiety disorders (HR = 1.67, 95% CI = 1.55–1.80), and sleep disorders (HR = 1.66, 95% CI = 1.49–1.85), and more modest for epilepsy (HR = 1.37, 95% CI = 1.12–1.69), dementia (HR = 1.36, 95% CI = 1.20–1.54), and stroke (HR = 1.24, 95% CI = 1.13–1.36). For social isolation, the strongest associations were observed for schizophrenia (HR = 3.58, 95% CI = 2.48–5.16), followed by MS (HR = 1.68, 95% CI = 1.17–2.41) and BD (HR = 1.68, 95% CI = 1.10–2.57), then dementia (HR = 1.37, 95% CI = 1.26–1.50), MDD (HR = 1.36, 95% CI = 1.28–1.44), AD (HR = 1.26, 95% CI = 1.10–1.43), PD (HR = 1.21, 95% CI = 1.05–1.41), with the smallest increases for sleep disorders (HR = 1.17, 95% CI = 1.07–1.29) and stroke (HR = 1.11, 95% CI = 1.03–1.18).

Stratified analyses were conducted based on age (> 60 vs ⩽ 60 years), sex, educational attainment, socioeconomic status (SES), longstanding illness, and physical activity. Our findings indicate that the risks of social isolation and loneliness for neurological and psychiatric disorders differ among various demographic groups (Supplementary Figure S1). Social isolation was significantly associated with four disorders (dementia, MDD, anxiety disorders, and schizophrenia) across most subgroups. Loneliness was significantly associated with three psychiatric disorders (sleep disorders, MDD, and anxiety disorders) in all stratified populations, and with other three disorders (dementia, stroke, and schizophrenia) in most subgroups. Nonetheless, there was heterogeneity in statistical significance across specific subgroup analyses. Notably, the association between social isolation and dementia, AD, and stroke, and between loneliness and dementia, stroke, and epilepsy were observed in older adults, individuals with lower educational attainment, and individuals with lower SES. Conversely, the relationships of social isolation, loneliness, and MS were significantly found in individuals with higher SES. Among males, the significant associations between social isolation and AD, epilepsy, and sleep

disorders, as well as between loneliness and epilepsy was identified. In contrast, the association between social isolation and MS was primarily found in females.

Sensitivity analyses were performed: (1) incorporating additional adjustments for behavioral confounders (Model 2), (2) further adjusting for comorbidity confounders beyond those in Model 2 (Model 3), and (3) excluding populations with comorbidities. The significant associations between social isolation with dementia, MS, schizophrenia, and MDD, and between loneliness with dementia, stroke, sleep disorders, anxiety disorders, and MDD remained significant across all analyses (Supplementary Figures S2 and S3). Furthermore, within a subset of 157,398 participants possessing primary care records, a consistent association with incident dementia was observed (social isolation: HR = 1.32, 95% CI = 1.15–1.5, $P < 0.001$; loneliness: HR = 1.45, 95% CI = 1.19–1.76, $P < 0.001$). Additionally, analyses utilizing a single-item measure of loneliness corroborated the previously mentioned associations between loneliness and neurological and psychiatric disorders (Supplementary Figure S4).

Causal effects of social isolation, and loneliness on neurological and psychiatric disorders

Bidirectional MR analyses were conducted to evaluate the causal relationships between social isolation, loneliness, and neurological and psychiatric disorders. Initially, a genome-wide association study (GWAS) was performed to explore the genetic underpinnings of social isolation ($N = 374,346$) and loneliness ($N = 363,192$), utilizing data on these variables from the present study and genotype information from UKB participants (Figure 3A, 3B). The analysis identified four genome-wide significant loci for loneliness ($P < 5\times10^{-8}$) (Supplementary Table S2). These include the replication of two known loci (mapped to *PHF2* and *TCF4*) and the identification of two previously unreported loci (mapped to *TRPC7* and *EFCAB11*). Both genes are involved in the regulation of calcium signaling[31] and have been associated with multiple neuropsychiatric disorders. Specifically, *TRPC7*

has been linked to insomnia[32], BD[33], and status epilepticus[34], whereas *EFCAB11* has been implicated in schizophrenia[35] and AD[36].

Subsequent MR analyses were conducted, employing the aforementioned GWAS data for social isolation, and loneliness. Detailed GWAS information for neurological and psychiatric disorders is provided in Supplementary Table S3. The study identified a significant causal link from loneliness to MDD, corroborated by the following four methods: Inverse Variance Weighted (IVW) (OR = 1.29, 95% CI = 1.16–1.43, $P < 0.001$), Weighted Median (WM) (OR = 1.31, 95% CI = 1.16–1.48, $P < 0.001$), Weighted Mode (WM) (OR = 1.31, 95% CI = 1.04–1.65, $P = 0.035$), and Simple Mode (SM) (OR = 1.32, 95% CI = 1.04–1.68, $P = 0.036$) (Figure 3C; Supplementary Table S4). Importantly, there was no statistically significant indication of horizontal pleiotropy. Despite significant heterogeneity detected by the IVW method ($Q = 28.80$, df = 16, $P = 0.025$), the robustness of the main finding was confirmed by leave-one-out sensitivity analysis after iteratively removing each instrumental variable (Supplementary Table S5). Conversely, the association between loneliness and schizophrenia was deemed unreliable, as only a significant finding was observed using the IVW method (OR = 1.19, 95% CI = 1.00–1.42, $P = 0.046$). Although no statistically significant evidence of horizontal pleiotropy was detected, significant heterogeneity was present (IVW-$Q = 58.18$, df = 13, $P < 0.001$), and the result of leave-one-out sensitivity analysis was not robust (Supplementary Table S5). No statistically plausible evidence was found for other causal associations (Figure 3C; Supplementary Table S4). Furthermore, to validated our findings, we utilized published multi-trait analysis of GWAS (MTAG) summary statistics for social isolation and loneliness, derived from the UKB cohort ($N = 452{,}302$) as reported by Day et al. (2018)[37]. MR analysis revealed significant causal associations from multi-trait social isolation and loneliness to epilepsy, schizophrenia, sleep disorders, and MDD (Figure 3C; Supplementary Table S4). While significant heterogeneity and horizontal

pleiotropy were observed across these associations, leave-one-out sensitivity analysis statistically confirmed the consistency of all causal estimates, with the exception of epilepsy (Supplementary Table S5). The robustness of these findings was further corroborated by MR-PRESSO, which, after correcting for outliers, affirmed that all reported causal associations remained statistically significant (Supplementary Table S5). In reverse MR analyses, we also identified significant causal associations from sleep disorders, schizophrenia, BD, and MDD to multi-trait social isolation and loneliness (Supplementary Table S6). Despite the presence of significant heterogeneity in these analyses, the leave-one-out sensitivity analysis statistically supported the robustness of the causal estimates (Supplementary Table S7).

Associations of social isolation, loneliness, and behavioral phenotypes of brain

Cognitive and emotional behavior are key phenotypes relevant to brain health[12], closely linked to neurological and psychiatric disorders and may be altered even before clinical onset. Following the exclusion of participants lacking baseline information, our analysis comprised a sample size ranging from 47,362 to 462,936 individuals to investigate the relationships between social isolation, loneliness, and cognitive and emotional behavioral phenotypes (Figure 4A; Supplementary Table S8). Social isolation was significantly linked to declines in all five cognitive phenotypes studied, while loneliness was associated with declines in two cognitive phenotypes. Notably, both social isolation and loneliness were negatively associated with all assessed emotional phenotypes, with loneliness exhibiting more pronounced effects (Figure 4A). Additionally, we performed sensitivity analyses on participants who were free from neurological and psychiatric disorders for a period of 3 years from baseline, and the results remained consistent (Supplementary Table S9). Furthermore, utilizing a cross-lagged model at two-time points, we found that both baseline social isolation and loneliness significantly affected subsequent emotional phenotypes, including general mental status, PHQ-4, and life satisfaction, within a subgroup of 16,026

to 48,340 participants after excluding those with incomplete baseline and follow-up data (Figure 4B; Supplementary Table S10).

Associations of social isolation, loneliness, and brain structures

Furthermore, we analyzed the associations between social isolation, loneliness, and brain structures to better understand their relationship with brain health (Figure 5; Supplementary Table S11-S13). Our study included a subgroup of 38,384 to 42,539 participants for whom relevant imaging data were available. Following FDR correction, significant associations were found between social isolation and reduced cortical surface area in the left lateral occipital (unstandardized regression coefficient (*b*) = -0.05; FDR-*Q* = 0.044), right lateral occipital (*b* = -0.05; FDR-*Q* = 0.046), and the left lingual cortex (*b* = -0.06; FDR-*Q* = 0.044) regions. Additionally, we observed volume changes in six subcortical structures, reductions in the left and right nucleus accumbens (*b* = -0.05; FDR-*Q* = 0.021; *b* = -0.07; FDR-*Q* < 0.001), left thalamus (*b* = -0.04; FDR-*Q* = 0.019), and the left hippocampus (*b* = -0.04; FDR-*Q* = 0.019), alongside increases in the left and right lateral ventricle (*b* = 0.05; FDR-*Q* = 0.019; *b* = 0.04; FDR-*Q* = 0.042). Notably, the association with reduced right nucleus accumbens volume (*b* = -0.06; FDR-*Q* = 0.019) remained significant in the analysis of 32,252 participants who were free from neurological and psychiatric disorders. No statistically significant association was observed among the 8,527 participants with pre-existing neurological and psychiatric disorders at the time of imaging data collection.

Moreover, After FDR correction, loneliness was associated with a reduced grey matter volume in the right inferior parietal region (*b* = -0.08; FDR-*Q* = 0.049). Additionally, we found that loneliness was significantly associated with increased white matter hyperintensities (WMH) (*b* = 0.07, *P* = 0.01). However, there was no statistically significant association between loneliness and brain structures in subgroups with or without neurological and psychiatric disorders during imaging collection. Furthermore, no statistically significant

association was identified between social isolation, loneliness, with white matter tract indictors (Supplementary Table S13).

Mediation roles of blood inflammatory and biochemical markers in the associations of social isolation, loneliness, and neurological and psychiatric disorders

After fully adjusting for confounders, significant cross-sectional associations were found between social isolation, loneliness, and 12 out of 16 blood inflammatory markers, and 24 out of 29 biochemical markers, in a cohort of 448,092 participants with available baseline data (Supplementary Table S14). Moreover, many of these markers demonstrated significant longitudinal associations with increased risks of neurological and psychiatric disorders in a cohort of 368,137 population initially free from theses disorders at baseline and during the first three years of follow-up (Supplementary Table S15-16). Our mediation analyses focused on neurological and psychiatric disorders that showed significant associations in the fully-adjusted model (Model 3). Accordingly, we assumed minimal or no confounding between exposure and outcome, exposure and mediator, and mediator and outcome, with the exposure presumed to precede the mediators[38,39]. Our mediation analyses indicated that leukocyte count, gamma-glutamyl transferase (GGT), and sex hormone-binding globulin (SHBG) significantly mediated 0.2% to 2.9% of the association between social isolation and three of the five neurological and psychiatric disorders (Figure 6; Supplementary Table S17). Additionally, inflammatory markers including neutrophil count, leukocyte count, lymphocyte percentage, systemic immune-inflammation index (SII), and neutrophil-to-lymphocyte ratio (NLR), along with biochemical markers including cystatin C and albumin significantly mediated 0.2% to 3.9% of the association between loneliness and at least four out of five neurological and psychiatric disorders (Figure 6; Supplementary Table S18). Moreover, other additional biomarkers were identified as mediators in the association between social isolation and loneliness with

neurological and psychiatric disorders (Supplementary Table S17-18).

Discussion

This study provides comprehensive evidence linking social isolation and loneliness to brain health. In our large-scale longitudinal analyses, both social isolation and loneliness were significantly associated with elevated risks of dementia, stroke, sleep disorders, schizophrenia, anxiety disorders, and MDD; additionally, social isolation was linked to AD, PD, MS, and BD, and loneliness was associated with epilepsy. MR analyses supported a putative causal association from loneliness to MDD, as well as from multi-trait social isolation and loneliness to MDD, schizophrenia, sleep disorders, and epilepsy. Moreover, reverse-causation MR indicated the association from schizophrenia, sleep disorders, BD, and MDD to multi-trait social isolation and loneliness. Besides, we found that social isolation and loneliness were significantly associated with worse cognitive and emotional performance, alterations in cortical and subcortical structures, and higher WMH load. Mediation analyses further suggested that peripheral inflammatory and biochemical markers may partly underlie the relationship between social isolation, loneliness, and the investigated neurological and psychiatric disorders.

Social isolation and loneliness are intertwined with psychiatric disorders[4,26,40]. Previous research has explored the link between social isolation, loneliness, and depression and anxiety, though majority of these studies were cross-sectional in nature[19,41-44]. Several longitudinal studies were limited by small, unrepresentative samples, short follow-up periods[19,45,46]. Recently, three large longitudinal studies from the English Longitudinal Study of Ageing (ELSA, $N = 4,211$)[47], the National Social Life, Health, and Aging Project (NSHAP, $N = 3,005$)[40], and the Irish Longitudinal Study on Ageing (TILDA, $N = 5,066$)[46] have demonstrated a link between loneliness and symptoms of depression and anxiety. Also, the TILDA ($N = 5,066$) demonstrated a link between social isolation and both MDD and generalized anxiety disorders over a follow-up duration of 2-4 years[46]. Using a

large cohort comprising 383,421 individuals and an extended follow-up duration of 14.2 years, our findings revealed a significant longitudinal link between social isolation, loneliness, and the incidence of MDD and anxiety disorders. Notably, the links between loneliness and both MDD and anxiety disorders were consistently observed across various subgroups. Moreover, MR analyses revealed significant putative causal association from loneliness to MDD. When analyzing a larger MTAG-derived dataset for the multi-trait social isolation and loneliness, a bidirectional causal relationship with MDD was observed. This finding was consistent with previous genetically informed studies which reported bidirectional evidence between loneliness and depressive disorders[48]. MR analysis did not reveal statistically significant causal association with anxiety here, aligning with prior research[49]. The anxiety disorder group may include various anxiety disorder diagnoses, potentially leading to considerable phenotypical and genetical heterogeneity. This heterogeneity, combined with the relatively small sample size of the anxiety GWAS (N = 17,310), is likely to affect the performance of MR analyses and may contribute to negative results[50]. Additionally, we identified significant longitudinal associations between social isolation, loneliness, and schizophrenia. MR analysis suggested a weak causal link from loneliness to schizophrenia; nonetheless, while a plausible causal and reverse causal relationship with schizophrenia was found when utilizing a larger dataset of MTAG for combined loneliness and social isolation. This may be attributed to the enhanced correlation between the exposure and genetic instruments[51]. Our result was similar to prior research, which has demonstrated the genetic influence of combined loneliness and social isolation on schizophrenia and suggested the plausible causal relationship[4]. Furthermore, we found a longitudinal link between social isolation and BD; MR analysis did not reveal a significant causal association from social isolation or loneliness to BD. However, a significant reverse causal association was identified from BD to multi-trait social isolation and loneliness. A previous study has reported a non-significant genetic correlation between

bipolar disorder and loneliness, despite a substantial genetic overlap, indicating a pattern of mixed allelic effect directions that may negate each other, thereby resulting in no genome-wide genetic correlation[52]. This pattern of genetic overlap may suggest the presence of subgroups within bipolar disorder that display a different genetic liability to loneliness[52]. The same may also apply to the other psychiatric disorders, and this complexity cannot be captured by the MR analyses. Further investigation requires sufficiently powers GWASs of subtypes of the psychiatric disorders to elucidate this hypothesis.

Research has investigated the link between social isolation, loneliness, and dementia[53], though findings have been inconsistent[54,55]. Cohort studies conducted in the UK (UKB, N = 462,619)[56], and the USA (the National Health and Aging Trends Study, N = 5,022)[57], which employed composite measure of social isolation encompassing multiple social domains, indicated a significant association between social isolation and dementia. Another cohort from Japan (N = 13,984)[58] showed specific social relationships domains that were associated with dementia among elders. Nonetheless, two cohorts from the longitudinal German study(AgeCoDe/AgeQualiDe, N = 1,161)[59] and the Amsterdam Study of the Elderly (AMSTEL, N = 2,173)[60] did not report statistically significant associations, possibly due to their relatively small sample sizes and short follow-up period. Also, longitudinal studies from the UKB (N = 492,322)[17] and the population-based Framingham Study (N = 2,308)[61] with a single-item loneliness question revealed a significant link between loneliness and dementia, while the other study (UKB, N = 462,619)[56] with a aggregate of loneliness items did not find significant association, which may be due to the differing loneliness assessments[17]. Our study is notable for its extended follow-up period and the use of composite measures of social isolation and loneliness, demonstrating a strong association between both social isolation and loneliness and dementia. In addition, the mixed findings may also relate to differences in adjustment for potential covariates, such as depression[56,62]. Our

study excluded participants with depressive and other psychiatric disorders at both baseline and the three-year follow-up. Also, we accounted for multiple potential confounders in our sensitivity analyses, resulting in consistently significant findings. Furthermore, in stratified analyses, we observed the significant associations in older adults, individuals with lower educational attainment, and individuals with lower SES. We also identified a link between social isolation and AD. There is limited research on the link between social isolation loneliness, and other neurodegenerative diseases[63]. Our study revealed a significant correlation between social isolation with PD and MS, with the association with MS remaining robust across all sensitivity analysis.

Several studies have explored the link between social isolation, loneliness, and stroke[26,64]. The Atherosclerosis Risk Communities study (ARIC, N = 13,686) indicated a link between social isolation and the incidence of stroke, but not between loneliness and stroke[65]. Conversely, a comprehensive UK cohort study (UKB, N = 479,054) indicated initial associations between social isolation, loneliness, and stroke, but these associations lost significance after adjusting for confounding factors[8]. Our extended follow-up and comprehensive study design revealed that both social isolation and loneliness were longitudinally linked to an increased risk of stroke. These associations were observed in subgroups of older adults, individuals with lower educational attainment, and individuals with lower SES. After adjusting for potential confounders, the link between social isolation and stroke was no longer statistically evident, whereas the connection between loneliness and stroke persisted, albeit in a weakened form. Our MR analyses did not reveal any statistically significant causal association between social isolation, loneliness and stroke.

Prior research has investigated the connections between social isolation, loneliness and sleep quality among the elderly[28,66]. Although most of them reported significant associations with poor sleep, the quality of these studies was mostly limited by the cross-sectional design[21,67,68]. This study longitudinally investigates the

associations between social isolation, loneliness, and sleep disorders. We identified significant links between social isolation, loneliness, and sleep disorders, with loneliness consistently exhibiting a significant correlation with sleep disorders across all subgroups. Furthermore, MR analyses identified a significant bidirectional association between the multi-trait social isolation and loneliness and sleep disorders. In addition, our longitudinal study found that loneliness was significantly associated with epilepsy. MR analysis further supported a putative causal effect of the multi-trait social isolation and loneliness on epilepsy. Moreover, we identified significant cross-sectional associations between social isolation, loneliness, and brain-related behavioral phenotypes including cognition and emotion in a large population, consistent with prior research[20,69]. Complementing this, we employed cross-lagged models in a subsample to demonstrate that social isolation and loneliness could predict subsequent negative changes in emotional states. However, as the overall model fit indices were suboptimal, these longitudinal findings should be interpreted with caution.

The underlying mechanisms through which social isolation and loneliness impact brain health remain unclear[24,70], potentially involving multiple factors. Firstly, our study revealed that blood inflammatory markers, including leukocyte and neutrophil count, lymphocyte percentage, SII, and NLR, partially mediated the links between social isolation, loneliness, and neurological and psychiatric disorders. The mediation was particularly pronounced in the associations between social isolation and both dementia and MDD, as well as between loneliness and conditions such as dementia, stroke, sleep disorders, and MDD. Social isolation and loneliness were associated with HPA axis hyperactivation[71], and reduced lymphocyte sensitivity to glucocorticoids[72], potentially leading to heightened oxidative stress[71], increased peripheral and central inflammation[25,73], and decreased anti-inflammatory responses[74,75], culminating in brain pathology[76]. Besides, our findings suggested that blood biochemical markers including AST, GGT, cystatin C, albumin, HbA1c, SHBG, and vitamin D played

a mediating effect on the relationship between social isolation, loneliness, and neurological and psychiatric disorders. Nevertheless, there is a paucity of research in this area, necessitating further investigation[77-80]. Moreover, animal studies of social isolation have revealed widespread neurobiological alterations at both functional[81-86] and cellular[87,88] levels, all of which necessitate further experimental validation. Additionally, our study found that social isolation and loneliness are linked to brain structures. Notably, our study found that social isolation was strongly linked to a reduced nucleus accumbens volume, even in individuals without neurological and psychiatric disorders. Previous research has partially corroborated our findings[24,29]. The nucleus accumbens, involved in reward processing and addiction[89], is linked to psychiatric disorders[90], supporting our longitudinal findings on connection between social isolation and conditions like MDD, anxiety disorders, BD, and schizophrenia. Regarding loneliness, significant associations were identified with reduced surface area in the right inferior parietal region and increased WMH in all population. WMH is recognized as a marker of poor brain health, which is linked to an increased risk of neurological and psychiatric disorders such as stroke, dementia, and depression[91,92]. Also, previous studies have identified a link between loneliness and increased functional connectivity in the default network[93]; however, this aspect was not examined in our research. Thus, more studies are needed in the future.

This study possesses multiple strengths. First, this extensive population-based prospective study features a long-term follow-up and covers a wide range of outcomes related to neurological and psychiatric disorders, phenotypes, and structures of brain. Second, we sought to assess the putative causal nature of these associations using MR analysis. Furthermore, supplementary investigations into blood biological markers have contributed to a comprehensive and multifaceted interpretation of the findings. Nonetheless, there are several limitations to this study. First, although our measures of social isolation and loneliness have been used in prior studies[1,7,94,95],

they have limitations. Social isolation was assessed using three questions focusing on the frequency of social interactions. While these items offer a partial reflection of social connectedness and support, they do not capture the multidimensional nature. And since the UKB did not include the validated UCLA loneliness scale[96,97], loneliness was evaluated using two simplified questions which could not assess critical dimensions such as duration, frequency, or intensity of lonely experiences. Nevertheless, the UKB remains the primary source for large-scale GWAS data on these complex traits, necessitating the use of these available measures despite their limitations. Secondly, social isolation and loneliness, as behavioral phenotypes, have complex genetic etiologies. The MR approach may be less effective in identifying causal associations, necessitating larger sample sizes and more robust genetic instruments to achieve sufficient statistical power[98]. Thirdly, as an observational study, there remains a possibility of residual confounding despite attempts to control for various covariates. Fourthly, the associations with behavioral phenotypes, brain structures, and biological markers were predominantly cross-sectional, necessitating caution in the interpretation of these findings. Also, our research was confined to individuals of European ancestry lacking cross-ancestry data. The generalizability of our findings may be restricted due to the relatively healthy and affluent nature of the study population.

In conclusion, our study demonstrated the associations between social isolation, loneliness, and risks of neurological and psychiatric disorders, notably dementia, stroke, sleep disorders, schizophrenia, anxiety disorders, and MDD. Furthermore, our findings indicated that social isolation and loneliness were associated with poorer cognitive and emotional performance. The correlations with altered brain structures were observed, and the mediating effects of blood inflammatory and biochemical markers might suggest potential mechanisms. These findings underscore the necessity of interventions to reduce social isolation and loneliness for enhancing brain health.

Methods

Participants

Our study utilized data from the UKB, a longitudinal cohort comprising over 500,000 participants aged 37–73 years, enrolled between 2006 and 2010. The assessments included touchscreen and interview questionnaires, physical measurements, and blood samples to gather health and genetic information at baseline and during multiple follow-ups. The database is connected to national primary care, hospital inpatient, mortality, and cancer registration records. The UKB study was approved by the North West Multicenter Research Ethical Committee (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics), and all participants gave written informed consent. This study was conducted under UKB application number 19542.

Social isolation and loneliness

In the UKB study, social isolation was assessed through three questions. One of them inquired about the number of individuals residing in the participant's household, including themselves. A score of 1 point was assigned for living alone. The frequency of visiting friends or family, or having them visit, was also assessed. For responses suggesting social interaction less frequently than once a month, including “once every few months,” “never or almost never,” or “no friends or family outside the household,” a score of 1 point was given. The third question asked about the leisure or social activities in which the participants engaged at least once a week. Participants could choose multiple options such as sports clubs or gyms, pubs or social clubs, religious groups, adult education classes, or other group activities. A score of 1 point was given for not engaging in any social activities on a weekly basis. Participants with 2 or 3 points on the three questions were defined as socially isolated[7]. Loneliness was assessed using two questions. Firstly, “Do you often feel lonely?” A “yes” response to this question earned a score of 1 point. Secondly, regarding the frequency of confiding in a close individual, a

response of "never or almost never" was also given a score of 1 point. The participants with 2 points on the two questions were defined as feeling lonely[7]. In the sensitivity analysis, loneliness was evaluated using a single-item question ("Do you often feel lonely?" Yes or no), which shows a high correlation with the UCLA Loneliness Scale[4].

Our study analyzed 466,706 individuals from the UKB, excluding 35,709 participants (7.10%) due to incomplete baseline data or non-responses regarding social isolation and loneliness[95]. The Pearson correlation coefficient for the relationship between social isolation and loneliness is 0.12 ($P < 0.001$). Higher percentages of social isolation and loneliness were observed among males, non-white populations, and individuals with lower educational attainment, especially those with lower SES. Additionally, we found the prevalence of social isolation and loneliness initially increased with age, reaching a peak in middle age, before subsequently declining (Supplementary Figure S5-6).

Neurological and psychiatric disorders

Incidence of neurological (dementia, AD, PD, dystonia, stroke, MS, epilepsy, encephalitis) and psychiatric disorders (sleep disorders, BD, schizophrenia, anxiety disorders, MDD) was primary outcome in our study. The case was identified from UKB health outcome datasets, specifically the first occurrences of health outcomes (category 1712), which include primary diagnoses or causes of death derived from hospital inpatient records, Hospital Episode Statistics, Morbidity Record data, and death register data provided by the National Health Service Digital and the Information and Statistics Division, as well as algorithmically defined outcomes (category 42). Diagnoses were categorized using the three-character codes from the International Classification of Diseases. Supplementary Table S19 provides the detailed information. The follow-up period spanned from the recruitment date to the earliest of the following events: onset of neurological and psychiatric disorders, loss

to follow-up, death, or the latest date available from general practitioner or inpatient records.

Initially, our study included 466,706 participants with complete available information on social isolation and loneliness. Participants with incident neurological and psychiatric disorders at baseline (N = 71,200) and follow-up duration less than 3 years until September 2023 (N = 12,085) were excluded to avoid reverse causality. Ultimately, the primary analysis of neurological and psychiatric disorders included 383,421 participants, with a mean age of 56.5 years, 53.7% of whom were women. Their demographic characteristics stratified by incident disorder group are detailed in Table 1.

Assessment of covariates

The analyses accounted for fundamental demographic covariates, including age (continuous, calculated from date of birth), sex (female vs. male, as recorded or self-reported in the database), and self-reported race and ethnicity (white vs. not white), level of educational attainment (college degree vs. other degree), and average household income, all of which are closely linked to social isolation, loneliness[6,99], and neurological and psychiatric disorders[16]. Average household income served as a proxy for SES, and was categorized into three levels: low (< £18,000), middle (£18,000-£51,999), and high (⩾ £52,000). Additional covariates included the Townsend Deprivation Index (TDI, continuous), body mass index (BMI, continuous), C-reactive protein (CRP, continuous), recent major life events (illness, injury, bereavement, the stress in the last 2 years, yes vs. no), long-standing illness, disability or infirmity (yes vs. no), smoking status (previous or current smoking vs. never smoking), alcohol consumption (frequency of never or special occasions only vs. other frequencies), reduced physical activity (less than six days/week of walking 10+ minutes and moderate to vigorous physical activity less than three times a week vs. others), and comorbidities (history of diabetes, hypertension, hyperlipidemia, atherosclerotic heart disease, respiratory disease, chronic kidney disease, chronic liver disease, anemia), all

considered potential confounders[1,7]. Sociodemographic, behavioral, and physical confounders were gathered at baseline in the UKB assessment center using a touchscreen questionnaire, anthropometric measurements, and hematological assays, while comorbidities were determined from self-reported data and medical records.

Behavioral phenotypes of brain

Cognitive and emotional assessments were evaluated in UKB to trace the brain functional trajectories prior to the onset of neurological and psychiatric disorders. We selected relevant variables with a baseline population of more than 100,000 or with longitudinal follow-up data[100,101]. Five cognitive tests were optimized for large-scale use and administered in a standardized sequence using a computerized touchscreen. These tests included fluid intelligence, reaction time, pairs matching, prospective memory (categorized by incorrect response on the first attempt versus others), and numeric memory with all except prospective memory measured on a continuous scale. Seven emotional assessments were conducted using a range of online questionnaires, encompassing general mental health (binary), life satisfaction (continuous), subjective well-being (continuous), the 4-item Personal Health Questionnaire depressive scale (PHQ-4) (continuous), the 9-item Personal Health Questionnaire depressive scale (PHQ-9) (continuous), the Composite International Diagnostic Interview depressive scale (CIDI) (continuous), and the Generalized Anxiety Disorder (GAD-7) scale (continuous). The detailed information of the assessments was supplied in Supplementary Table S20. All the above assessments were conducted at baseline (during 2009–2010), and second assessments at the imaging visit from 2014 to 2019 were performed for the 5 cognitive tests, general mental status, PHQ-4, and life satisfaction. All the continuous variables were logit-transformed and scaled for analysis, with higher score indicating worse function.

Brain imaging

Between 2014 and 2019, the UKB brain imaging team acquired brain magnetic resonance imaging (MRI) data

using a Siemens Skyra 3T scanner equipped with a standard Siemens 32-channel head coil. Details of the protocol and sequence parameters are accessible in the open-source document (https://biobank.ctsu.ox.ac.uk/crystal/ukb/docs/brain_mri.pdf). High-quality T1-weighted neuroimaging data were processed using the FreeSurfer aparc and aseg atlas to obtain imaging data from 68 cortical and 16 subcortical regions. The data comprised of surface areas, volumes, and average thickness of cortical regions, as well as volumes of subcortical regions. The FMRIB Software Library (FSL) version 6.0's diffusion Toolbox was employed to analyze diffusion tensor imaging (DTI) data, mapping 27 white matter through diffusion and tractography analysis[102]. In 27 white matter tracts, diffusion directionality and overall diffusivity were assessed using tract-averaged fractional anisotropy (FA) and mean diffusivity (MD) as DTI.

WMH volume was quantified utilizing the T2-weighted fluid-attenuated inversion recovery (FLAIR) images with the Brain Intensity Abnormality Classification Algorithm. The WMH load underwent logit transformation and scaling to achieve normalization and variance stabilization.

Inflammatory and biochemical markers

Inflammatory and biochemical indicators were collected from blood cell counts (category 100081) and biochemical examinations (category 17518) during the participant' initial visit. The comprehensive procedures for processing and examining blood samples are available in the UKB data sources (https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100080). We collected data on neutrophil, monocyte, and lymphocyte counts and percentages, along with CRP concentration levels. Additionally, we computed four ratios derived from the counts of these blood cells. This includes the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and lymphocyte-to-monocyte ratio (LMR). Moreover, we extracted data from biochemical biomarkers, including glucose, cholesterol, and 29 other

markers. The variables were logit-transformed and scaled for analysis.

GWAS of social isolation and loneliness

We conducted a GWAS on social isolation and loneliness, derived from three and two questionnaire items, respectively. The study initially excluded participants based on several criteria: non-white British ancestry, mismatches between self-reported and genetically determined sex, suspected sex chromosome aneuploidy, outliers in heterozygosity, absence from principal component analysis, and a genotype missing rate over 5%. We applied GCTA (http://cnsgenomics.com/software/gcta/) to the imputed variants supplied by UKB (with a call rate exceeding 0.95, minor allele frequency above 0.005, imputation quality score over 0.8, and Hardy-Weinberg P greater than 1×10^{-6}) and examined their correlations with social isolation and loneliness. The adjusted covariates included age, sex[37], genotype array type, and the top ten genetic principal components. Genetic functional mapping was performed using the FUMA platform (http://fuma.ctglab.nl/), with all parameters set to their default values. Briefly, independent significant single nucleotide polymorphisms (SNPs) were identified through LD clumping ($r^2 < 0.6$, $P < 5 \times 10^{-8}$). Among them, a set of lead SNPs were defined as those mutually independent at a stricter threshold ($r^2 < 0.1$). Finally, genomic risk loci were formed by merging lead SNPs that were within 250 kb of each other. We mapped variants to the nearest genes using ANNOVAR annotations. In addition, significant variants were classified as 'known-position', 'known-loci' (previously unreported variants associated with loneliness[37,103,104] but within 500 kb of a known locus), or 'not previously reported'[105]. In the end, we determined the heritability based on single nucleotide polymorphism through the use of linkage disequilibrium score regression[106].

Statistical analysis

Participants' initial attributes were summarized using mean and standard deviation (SD) for continuous

variables, and count and proportion for categorical variables. We utilized Cox proportional hazards models to investigate the relationship between social isolation, loneliness, and neurological and psychiatric disorders. The proportional hazards assumption was assessed using Schoenfeld residuals and the Kaplan-Meier survival curve. The analysis, adjusted for baseline age, sex, ethnicity, educational attainment, and SES (Model 1), revealed no breaches except for the association between loneliness and MS. FDR corrections ($\alpha = 0.05$) were used to adjust multiple comparisons. We conducted subgroup analyses based on sex, age (< 60 years vs ≥ 60 years), educational attainment, SES, long-standing illness, and physical activity to explore relationships within specific demographics. What's more, we performed a range of sensitivity analyses to verify the robustness of the associations. we further modified the baseline covariates in two models. Model 2 included adjustments for TDI, BMI, CRP, long-term illness, physical activity, smoking habits, and alcohol intake, alongside the covariates from Model 1. Model 3 was further adjusted for a history of diabetes, hypertension, hyperlipidemias, atherosclerotic heart disease, respiratory disease, chronic kidney disease, chronic liver disease, and anemia, along with the covariates included in Model 2. We also excluded the populations with any comorbidity in Model 3 to further control for potential confounders. Moreover, given that majority of dementia cases in the UKB are sourced from primary care records, we performed a sensitivity analysis on participants with available primary care data.

We performed bidirectional MR analyses to explore the causal association between social isolation, loneliness, and various neurological and psychiatric disorders. Summary statistics for social isolation and loneliness were derived from our internally conducted GWAS. In contrast, genetic associations for neurological and psychiatric disorders, including dementia[107], PD[108], dystonia[107], stroke[109], encephalitis[107], MS[107], epilepsy[107], sleep disorders[107], schizophrenia[110], BD[111], anxiety disorders[112], MDD[113] were sourced from extensive independent consortia with no sample overlap with the current study. Notably, summary statistics for AD[114] were

derived from a dataset that partially overlaps with the UKB participants included in our analysis (see Supplementary Table S3). Additionally, we validated our findings using a larger, publicly available multi-trait GWAS summary statistic from UKB that integrated a composite measure of loneliness and social isolation. This measure incorporated responses to the direct loneliness question (Do you often feel lonely?) along with items about the ability to confide in someone, the frequency of visiting or having family or friends visit, and the living situation[37]. Instrumental variables were chosen based on genome-wide significance ($P < 5\times10^{-6}$) and independence from linkage disequilibrium ($r^2 < 0.01$, window size = 10,000 kilobases [kb]). Following the harmonization of exposure and outcome datasets, a critical process to ensure all genetic associations correspond to the same effect allele and that strand ambiguities are resolved[115], the IVW method was employed as the primary approach for pooling MR estimates, with additional support from weighted median, weighted mode, simple mode and MR Egger methods[115]. When results from more than two of these analytical tools converge, they are deemed more reliable for causal relationships. The findings were displayed using OR and 95% CI. Cochran's *Q* test, MR-Egger intercept, and MR-PRESSO were utilized to assess the heterogeneity and horizontal pleiotropy[116,117].

Linear regression models were conducted to examine the relationship between social isolation, loneliness, and behavioral phenotypes, controlling for age at baseline, sex, ethnicity and educational attainment, and SES. To further test the reliability, we conducted the above analyses in the participants without any neurological and psychiatric disorder within 3 years from baseline. Moreover, the cross-lag model was used to examine the association with behavioral phenotypes at two-time points. In addition, we also employed linear regression models to examine the relationship between social isolation, loneliness, and brain structures, adjusting for age at baseline, sex, ethnicity, educational attainment, SES, imaging scanning sites, and intracranial volume.

Additionally, we performed a sensitivity analysis on participants both with and without neurological and psychiatric disorders.

Mediation analyses were conducted to examine the influence of inflammation and biochemical markers on the association between social isolation, loneliness, and neurological and psychiatric disorders. Linear regression models were initially employed to evaluate the relationships between social isolation, loneliness, and blood inflammatory and biochemical markers. Then, the associations of these blood markers with neurological and psychiatric disorders were analyzed using the Cox regression model. Each regression was controlled for variables including age, sex, ethnicity, educational attainment, SES, TDI, BMI, long-standing illness, physical activity, smoking status, and alcohol consumption. Mediation analyses were conducted for those variables related to both social isolation or loneliness and neurological and psychiatric disorders.

The R statistical software (version 4.3.2) (http://www.r-project.org/) was used to conducted the statistical analyses (Cox proportional hazards models were fitted using the 'survival' package (version 3.5-7); Mendelian Randomization analyses were performed with 'TwoSampleMR' (version 0.5.6) and 'MRPRESSO' (version 1.0) for main and sensitivity analyses, respectively; mediation analyses utilized the 'mediation' package (version 4.5.0); and cross-lagged panel models were specified and estimated using the 'lavaan' package (version 0.6-16)). Statistical significance was assessed with a two-tailed P value threshold of < 0.05. An FDR correction was employed when appropriate.

Data availability

The primary data used in this study are individual-level records from the UK Biobank, accessed under application number 19542. These data are available under restricted access due to UK Biobank's data governance and participant consent procedures. Researchers can apply for access via the UK Biobank Access Management

System (https://ams.ukbiobank.ac.uk/ams/). Access is granted for approved research purposes following protocol review by UK Biobank. The authors cannot publicly share the raw individual-level data. The GWAS summary statistics for neurological and psychiatric disorders were obtained from the following publicly available sources: dementia (https://gwas.mrcieu.ac.uk/datasets/finn-b-F5_DEMENTIA/), AD (https://pgc.unc.edu/for-researchers/download-results/), PD (https://gwas.mrcieu.ac.uk/datasets/ieu-a-812/), dystonia (https://r8.risteys.finngen.fi/phenocode/G6_DYSTON), stroke (http://megastroke.org/download.html), encephalitis (https://r8.risteys.finngen.fi/phenocode/G6_ENCEPHOTH), MS (https://r8.risteys.finngen.fi/phenocode/G6_MS), epilepsy (https://r8.risteys.finngen.fi/phenocode/G6_EPLEPSY), sleep disorders (https://r8.risteys.finngen.fi/phenocode/SLEEP), schizophrenia (https://pgc.unc.edu/for-researchers/download-results/), BD (https://pgc.unc.edu/for-researchers/download-results/), anxiety disorder (https://pgc.unc.edu/for-researchers/download-results/), MDD (https://pgc.unc.edu/for-researchers/download-results/).

Code availability

The software tools used in this study are openly available. The custom R code supporting these analyses is available through GitHub (https://github.com/1874309276/SI_LN_Brain_Health/tree/main)[118].

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Author Contributors Statement

All authors participated in designing the study, interpreting the data, and critically reviewing the report. J.-T.Y. and L.T.designed the study. Y.-L.Z., with help from D.-D.Z., P.-Y.G., Y.F., Y.-J.G, Y.-R.Z. did the data analyses. Y.-L.Z., with help from D.-D.Z., P.-Y.G., Z.-X.G., Y.-R.Z., conducted the drawing. Y.-L.Z. drafted the manuscript. J.-T.Y., Y.-R.Z., L.T., W.C. critically revised the manuscript, and all authors approved the final version.

Competing Interests Statement

The authors declare no competing interests.

Table 1 Baseline characteristics of the study population stratified by primary disorders

Characteristics	Total	Dementia	Stroke	Sleep disorders	Schizophrenia	Anxiety disorders	MDD
Sample size, *n*	383,421	6,248	11,304	5,779	167	13,588	12,450
Age, years	56.5 (8.1)	64.4 (4.6)	61.3 (6.6)	57.0 (7.8)	57.6 (8.3)	57.5 (8.1)	56.6 (8.3)
Female, *n* (%)	206,081 (53.7%)	3,019 (48.3%)	4,900 (43.3%)	2,171 (37.6%)	74 (44.3%)	9,065 (66.7%)	7,766 (62.4%)
Race, white, *n* (%)	363,880 (95.2%)	6,004 (96.4%)	10,841 (96.2%)	5,423 (94.1%)	145 (87.3%)	12,952 (95.6%)	11,863 (95.6%)
Education, *n* (%)							
Low level	251,674 (66.1%)	4,833 (78.8%)	8,220 (73.6%)	4,134 (72.3%)	123 (75.0%)	10,012 (74.4%)	9,325 (75.7%)
High level	128,902 (33.9%)	1,298 (21.2%)	2,951 (26.4%)	1,584 (27.7%)	41 (25.0%)	3,450 (25.6%)	2,991 (24.3%)
Average household income, *n* (%)							
Low level	67,587 (20.3%)	2,120 (42.7%)	3,040 (31.7%)	1,342 (26.6%)	84 (61.8%)	3,555 (31.3%)	3,554 (33.7%)
Middel level	173,410 (52.0%)	2,383 (48.0%)	4,909 (51.3%)	2,601 (51.5%)	43 (31.6%)	5,876 (51.7%)	5,344 (50.7%)
High level	92,693 (27.8%)	460 (9.3%)	1,628 (17.0%)	1,107 (21.9%)	9 (6.6%)	1,932 (17.0%)	1,643 (15.6%)
Social isolation, *n* (%)	32,206 (8.4%)	723 (11.6%)	1,085 (9.6%)	633 (11.0%)	57 (34.1%)	1,470 (10.8%)	1,553 (12.5%)
Loneliness, *n* (%)	15,488 (4.0%)	324 (5.2%)	576 (5.1%)	413 (7.1%)	25 (15.0%)	933 (6.9%)	1,112 (8.9%)
Deprivation index	16.9 (13.5)	18.6 (14.8)	18.2 (14.5)	20.1 (15.2)	26.0 (18.3)	19.4 (14.9)	20.6 (15.6)
BMI, Kg/m^2	27.3 (4.6)	27.5 (4.8)	27.9 (4.8)	31.2 (6.8)	28.0 (5.4)	27.7 (5.1)	28.3 (5.4)
CRP, mg/L	2.53 (4.3)	2.74 (4.6)	3.02 (4.7)	3.74 (5.4)	3.61 (6.2)	2.92 (4.7)	3.14 (4.8)
Smoking status, *n* (%)	168,515 (44.1%)	3,289 (52.9%)	5,861 (52.1%)	3,135 (54.5%)	91 (55.2%)	6,707 (49.6%)	6,677 (53.9%)
Alcohol drinking, *n* (%)	315,941 (82.4%)	4,725 (75.7%)	8,987 (79.6%)	4,458 (77.2%)	107 (64.1%)	10,233 (75.4%)	9,237 (74.3%)
Less physical activity, *n* (%)	69,932 (19.7%)	847 (15.8%)	1,901 (18.7%)	1,274 (24.5%)	27 (19.1%)	2,449 (20.2%)	2,316 (21.0%)
Recent major life events, *n* (%)	163,839 (42.9%)	2,450 (39.5%)	4,804 (42.7%)	3,042 (52.9%)	93 (55.7%)	6,635 (49.1%)	6,561 (53.1%)
Long term illness, *n* (%)	106,308 (28.3%)	2,805 (46.2%)	4,554 (41.3%)	2,891 (51.5%)	95 (60.9%)	5,449 (41.4%)	5,562 (46.1%)

Values are presented as mean (standard deviation) for continuous variables and *n* (%) for categorical variables. Educational attainment is categorized as higher (college/university degree) or lower. Average household income (in British pounds, £) served as a proxy for socioeconomic status, and was categorized into three levels: low (< £18,000), middle (£18,000-£51,999), and high (≥ £52,000). MDD, major depressive disorder; BMI, body mass index; CRP, C-reactive protein.

Figure Legends

Figure 1. Study workflow

Left: the data used in the study from UKB include social isolation, loneliness, neurological and psychiatric disorders, behavioral phenotypes, brain imaging, genomics, inflammation and biochemistry. Top right: longitudinal and putative causal associations between social isolation, loneliness and neurological and psychiatric disorders. Data are presented as HR ± 95% CI for Cox regression, with two-sided *P* values derived from Wald tests. Data are presented as OR ± 95% CI for MR, with two-sided *P* values obtained using the inverse-variance weighted (IVW) method. **P* < 0.05, ***P* < 0.01, ****P* < 0.001. Middle right: cross-sectional and two-time point associations between social isolation, loneliness and behavioral phenotypes. Bottom right: potential mechanisms contributing to the associations between social isolation, loneliness and brain health. SI, social isolation; LN, loneliness; AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; MDD, major depressive disease; PF, performance.

Figure 2. Longitudinal associations between social isolation, loneliness and the risk of neurological and psychiatric disorders

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), adjusting for age at baseline, sex, ethnicity, educational attainment, and socioeconomic status (*N* = 383,421). Data are presented as HRs, and error bars represent 95% CIs. The significance of associations was assessed using Wald tests. Two-sided *P* values were corrected for multiple comparisons using the false discovery rate (FDR) method. AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; MDD, major depressive

disease.

Figure 3. The causal relationship between social isolation, loneliness and neurological and psychiatric disorders

(A and B) GWAS Manhattan plots for social isolation and loneliness (fastGWA-mlm-binary in GCTA). The red line indicates $P = 5.0 \times 10^{-8}$. (C) MR estimates (inverse-variance weighted) of putative causal effects from social isolation (N = 374,346), loneliness (N = 363,192), and their multi-trait MTAG score (N = 452,302) on neurological and psychiatric disorders. Outcome GWAS were independent (except AD; Supplementary Table S3). Instrument strength (mean F-statistics, range): SI, 22.96 (20.85–26.97); LN, 25.39 (21.45–33.10); MTAG, 26.00 (20.86–70.9). Full results (ORs, P values) are available in Supplementary Table S4-7. SI, social isolation; LN, loneliness; AD, Alzheimer's disease; PD, Parkinson's disease; MS, multiple sclerosis; BD, bipolar disorder; MDD, major depressive disease; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Figure 4. Associations between social isolation, loneliness and behavioral phenotypes

Linear regression and cross-lag panel models (CLPM) were performed to investigate the cross-sectional and longitudinal two-time point associations, respectively, with all models adjusting for baseline age, sex, ethnicity, educational attainment, and socioeconomic status. The significance of coefficients was assessed using two-sided t-tests (linear regression) and Wald z-tests (CLPM). In the cross-lagged models, the analytical samples comprised 48,340 participants for general mental status, 44,177 for the PHQ-4, and 16,026 for life satisfaction. Data are presented as unstandardized regression coefficients (b), where larger values indicate worse performance. Exact b and P values are provided in Supplementary Table S8 and S10. PHQ-4, the 4-item Personal Health

Questionnaire; PHQ-9, the 9-item Personal Health Questionnaire depressive scale; CIDI, the Composite International Diagnostic Interview depressive scale; GAD-7, the Generalized Anxiety Disorder. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Figure 5. Associations between social isolation, loneliness and brain structures

Linear regression models were used to assess the associations, adjusting for age at baseline, sex, ethnicity, educational attainment, socioeconomic status, imaging scanning sites, and intracranial volume. Data are presented as unstandardized regression coefficients (*b*). Two-sided *P* values were calculated using *t*-tests and were corrected for multiple comparisons using the false discovery rate (FDR) method. Sample sizes for each analysis were: cortical measures, $N = 40{,}779$; subcortical measures, $N = 40{,}812$; white matter hyperintensity volume, $N = 42{,}539$; and diffusion tensor imaging measures, $N = 38{,}384$. SI, social isolation; LN, loneliness.

Figure 6. The mediating role of blood inflammatory and biochemical markers in the relationship between social isolation, loneliness, and neurological and psychiatric disorders

Mediation analyses were conducted, adjusting for age, sex, ethnicity, educational attainment, socioeconomic status, index of multiple deprivations, body mass index, long-standing illness, physical activity, smoking status, and alcohol consumption ($N = 368{,}137$). Solid lines represent the associations of social isolation and loneliness with blood markers (linear regression models, two-sided *t* test), and the associations of blood markers with neurological and psychiatric disorders (Cox regression models, two-sided Wald test). The symbol "+" indicates a positive association, and "-" indicates a negative association. The dashed line represents the tested indirect effect, with b_{IE} denoting its unstandardized coefficient. Exact *P* values are available in Supplementary Table

S14-18. ns, not significant. na, not applicable. GGT, gamma-glutamyl transferase; SHBG, hormone-binding globulin; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; MS, multiple sclerosis; MDD, major depressive disorder; Schiz, schizophrenia; BD, bipolar disorder. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Editor's Summary
The authors report associations of social isolations and loneliness with neurological disorders, psychiatric disorders, brain structures and behavioural phenotypes among UK Biobank participants.

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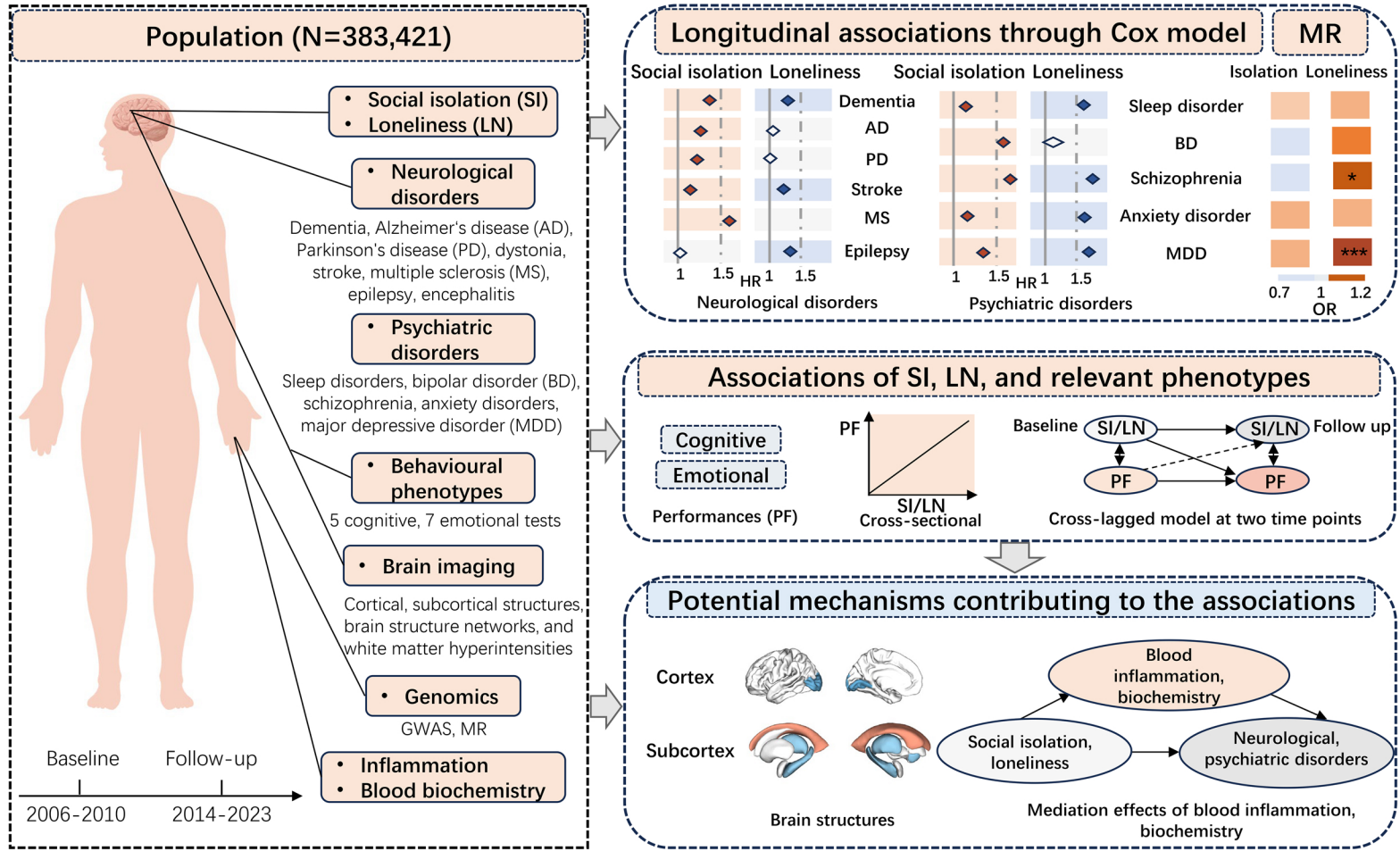
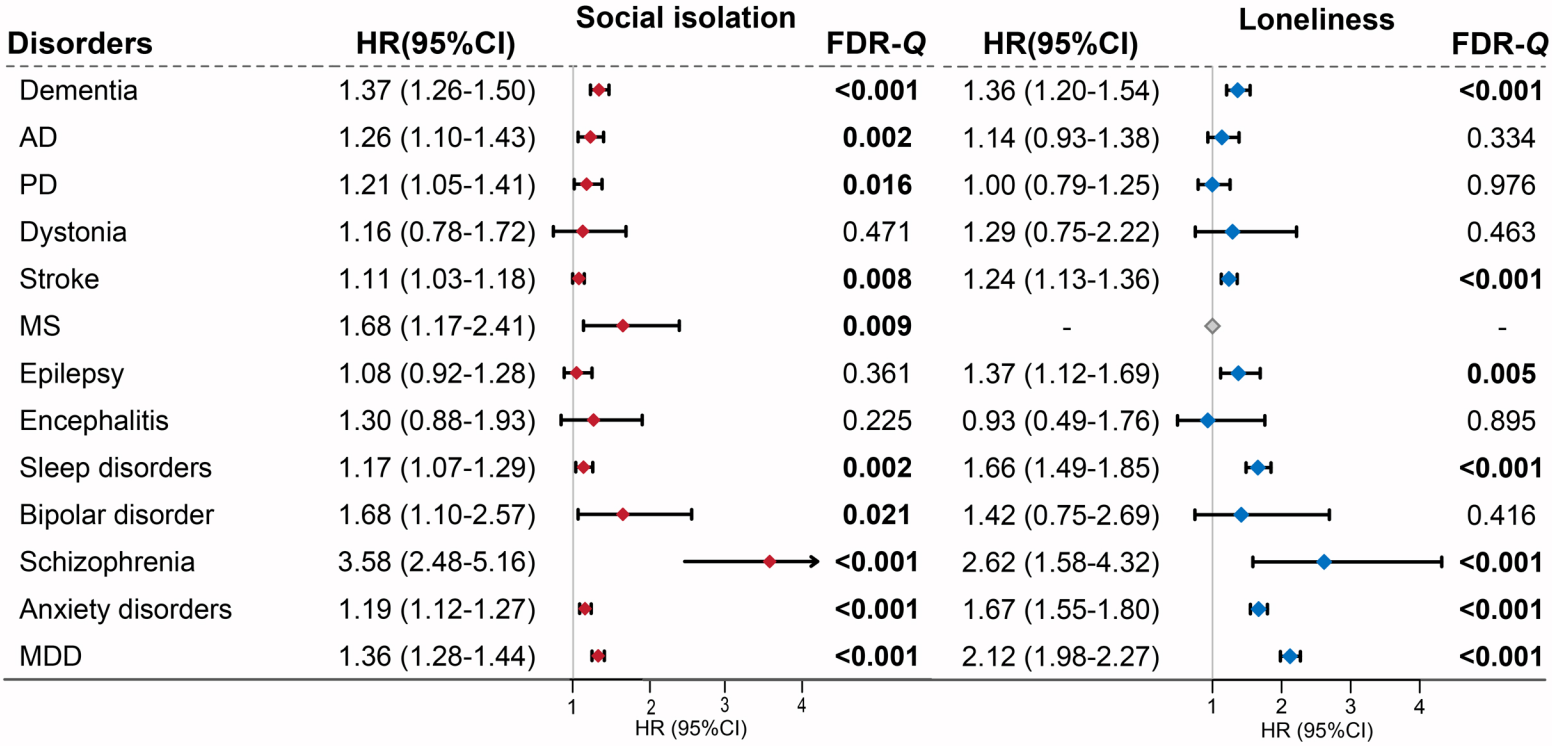
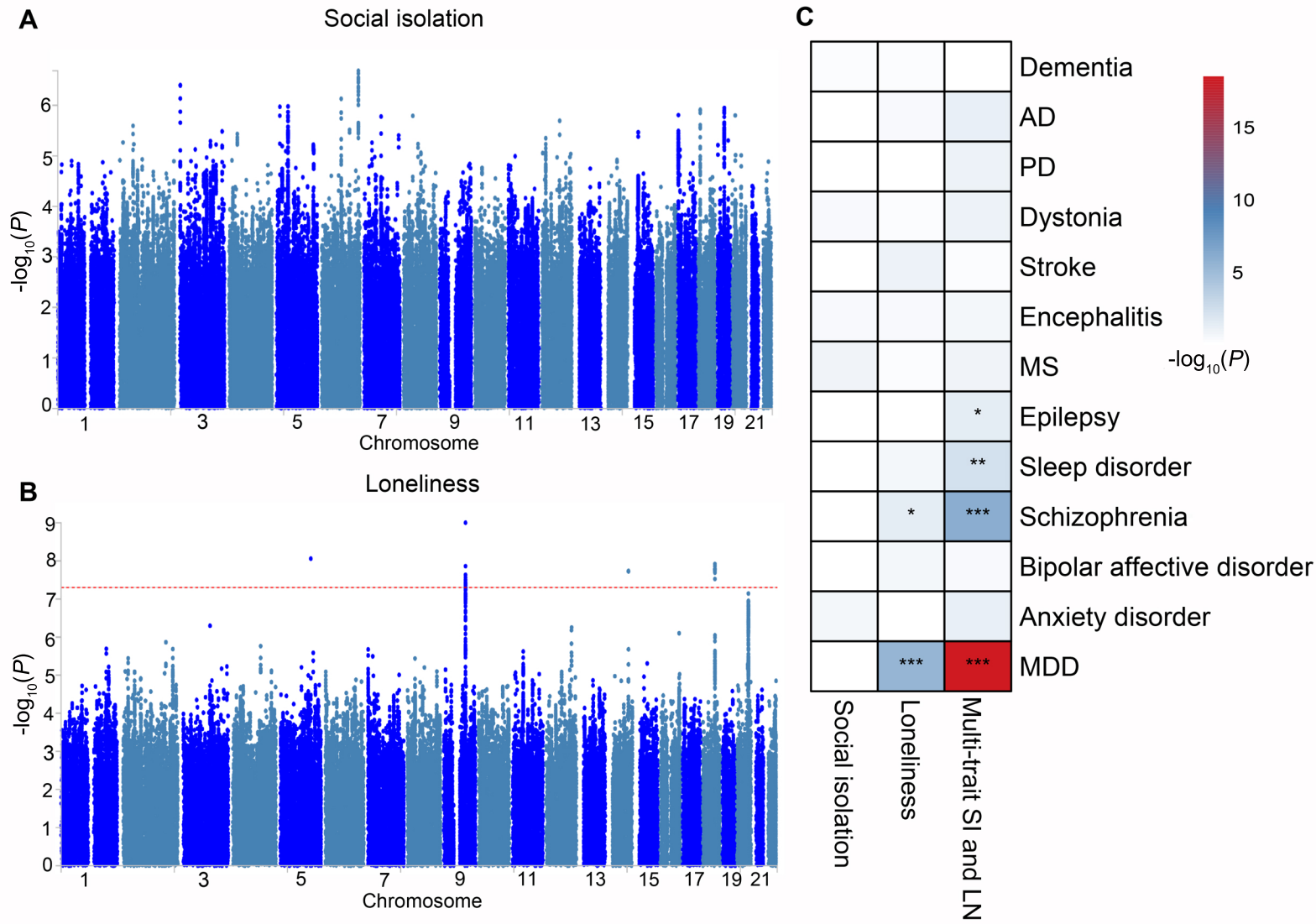
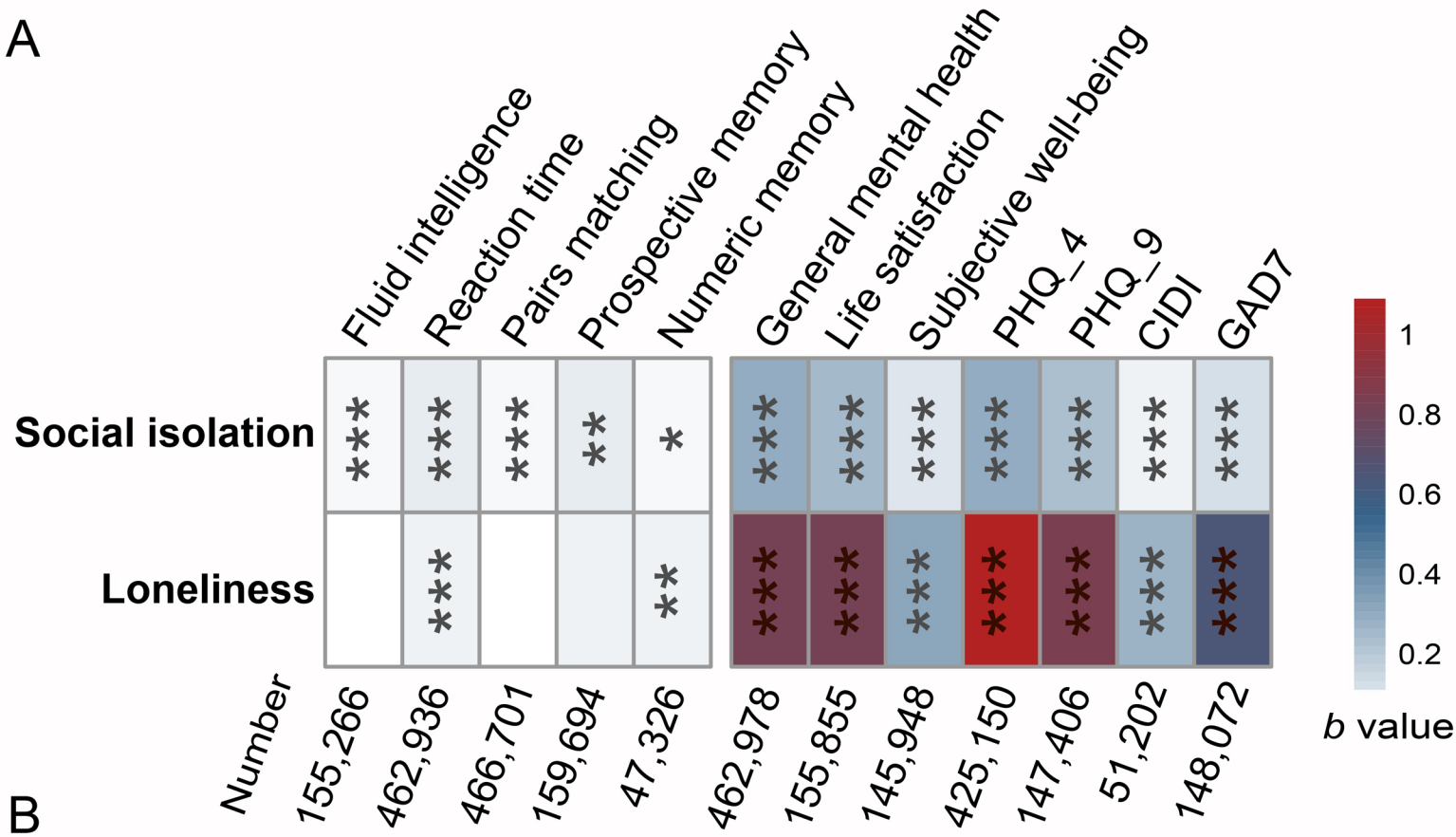
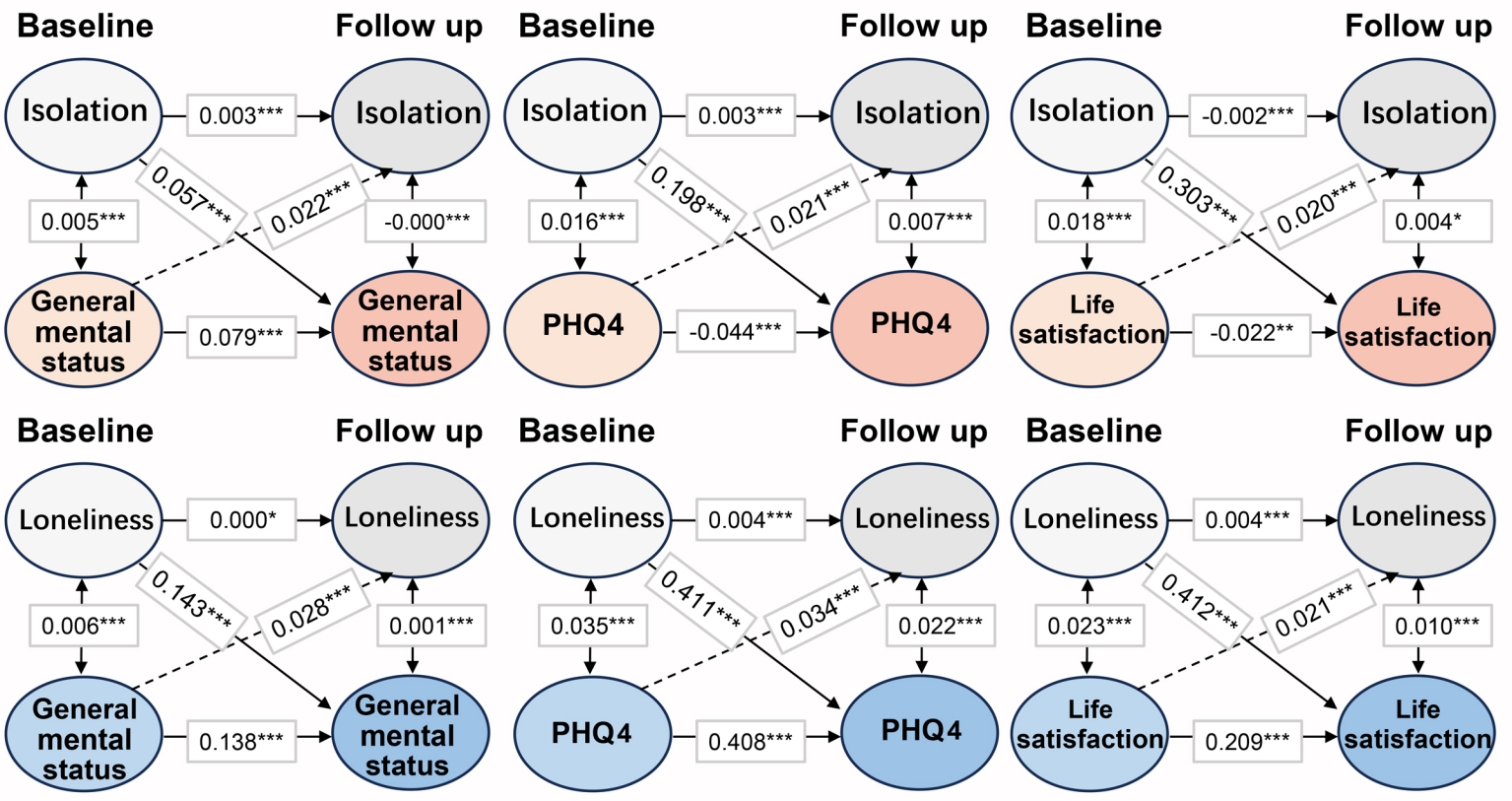
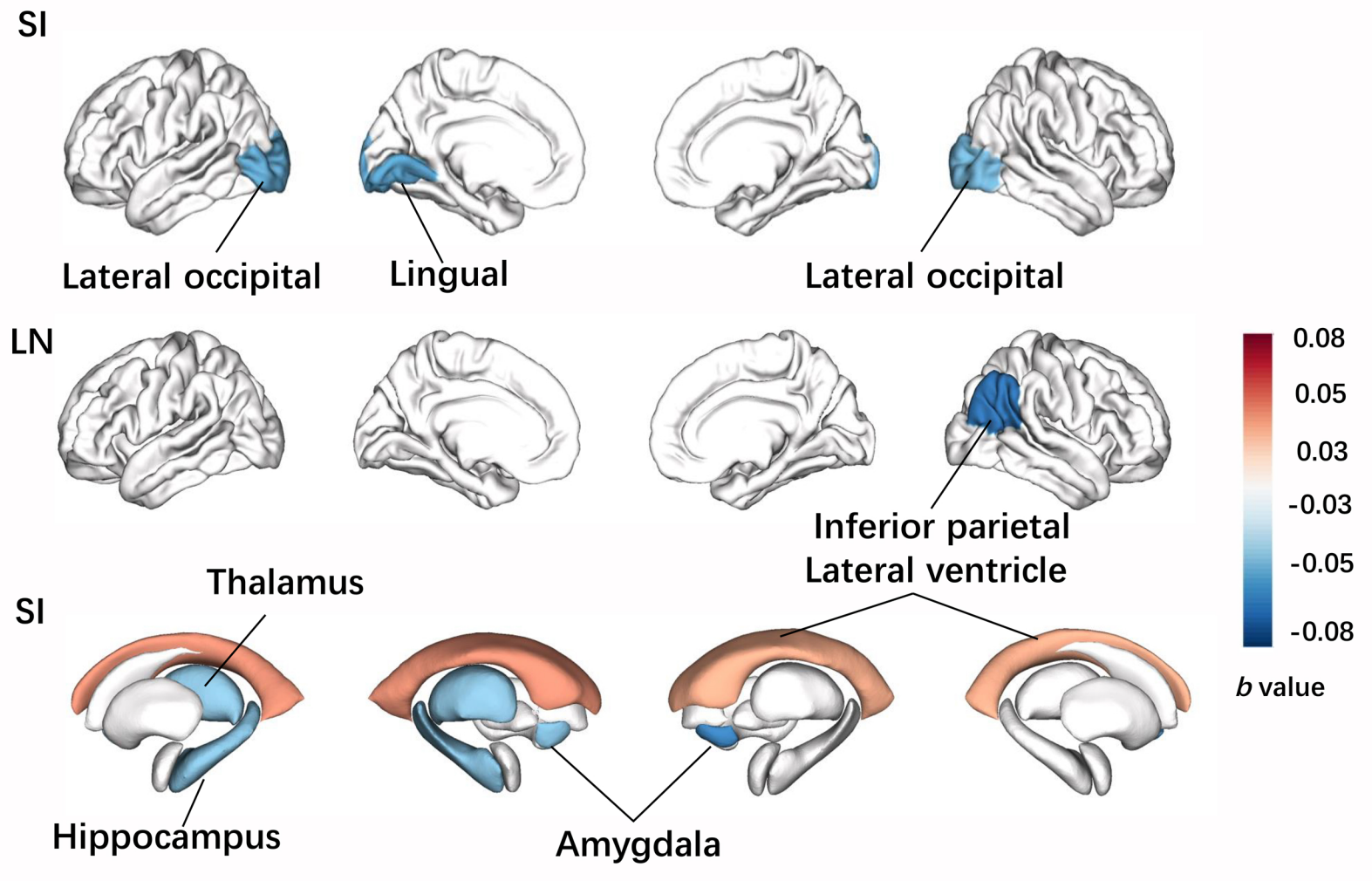

Population (N=383,421)
• Social isolation (SI)
• Loneliness (LN)
• Neurological disorders
Dementia, Alzheimer's disease (AD), Parkinson's disease (PD), dystonia, stroke, multiple sclerosis (MS), epilepsy, encephalitis
• Psychiatric disorders
Sleep disorders, bipolar disorder (BD), schizophrenia, anxiety disorders, major depressive disorder (MDD)
• Behavioural phenotypes
5 cognitive, 7 emotional tests
• Brain imaging
Cortical, subcortical structures, brain structure networks, and white matter hyperintensities
• Genomics
GWAS, MR
• Inflammation
• Blood biochemistry
Baseline
Follow-up
2006-2010
2014-2023
Longitudinal associations through Cox model
MR
Social isolation
Loneliness
Dementia
AD
PD
Stroke
MS
Epilepsy
HR
Neurological disorders
Sleep disorder
BD
Schizophrenia
Anxiety disorder
MDD
Psychiatric disorders
Isolation
OR
Associations of SI, LN, and relevant phenotypes
Cognitive
Emotional
Performances (PF)
PF
SI/LN
Cross-sectional
Baseline
SI/LN
Follow up
PF
Cross-lagged model at two time points
Potential mechanisms contributing to the associations
Cortex
Subcortex
Brain structures
Blood inflammation, biochemistry
Social isolation, loneliness
Neurological, psychiatric disorders
Mediation effects of blood inflammation, biochemistry

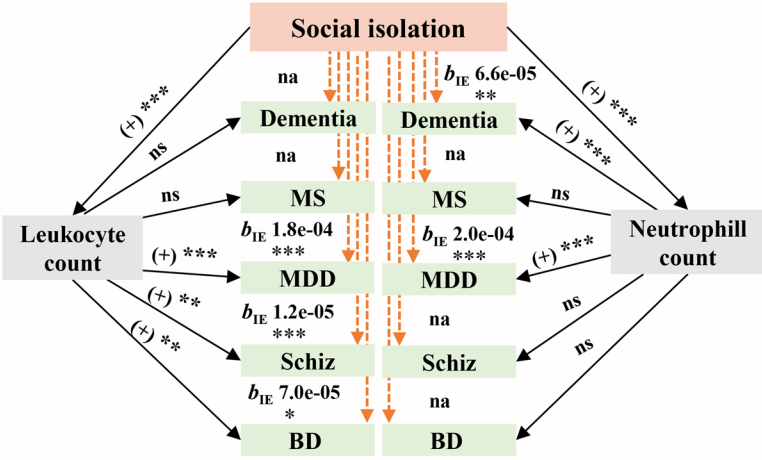

Disorders
Social isolation
HR(95%CI)
FDR-Q
Loneliness
HR(95%CI)
FDR-Q
Dementia 1.37 (1.26-1.50) <0.001 1.36 (1.20-1.54) <0.001
AD 1.26 (1.10-1.43) 0.002 1.14 (0.93-1.38) 0.334
PD 1.21 (1.05-1.41) 0.016 1.00 (0.79-1.25) 0.976
Dystonia 1.16 (0.78-1.72) 0.471 1.29 (0.75-2.22) 0.463
Stroke 1.11 (1.03-1.18) 0.008 1.24 (1.13-1.36) <0.001
MS 1.68 (1.17-2.41) 0.009 - -
Epilepsy 1.08 (0.92-1.28) 0.361 1.37 (1.12-1.69) 0.005
Encephalitis 1.30 (0.88-1.93) 0.225 0.93 (0.49-1.76) 0.895
Sleep disorders 1.17 (1.07-1.29) 0.002 1.66 (1.49-1.85) <0.001
Bipolar disorder 1.68 (1.10-2.57) 0.021 1.42 (0.75-2.69) 0.416
Schizophrenia 3.58 (2.48-5.16) <0.001 2.62 (1.58-4.32) <0.001
Anxiety disorders 1.19 (1.12-1.27) <0.001 1.67 (1.55-1.80) <0.001
MDD 1.36 (1.28-1.44) <0.001 2.12 (1.98-2.27) <0.001
1 2 3 4
HR (95%CI)
1 2 3 4
HR (95%CI)

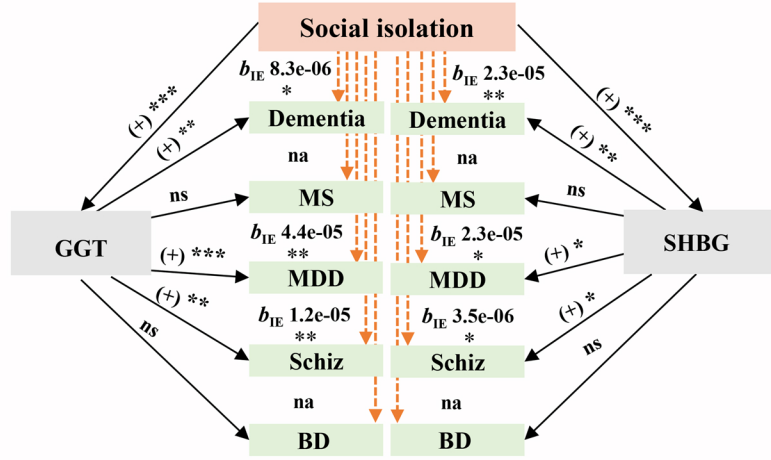

A
Social isolation
-log10(P)
Chromosome
B
Loneliness
-log10(P)
Chromosome
C
Dementia
AD
PD
Dystonia
Stroke
Encephalitis
MS
Epilepsy
Sleep disorder
Schizophrenia
Bipolar affective disorder
Anxiety disorder
MDD
Social isolation
Loneliness
Multi-trait SI and LN
-log10(P)

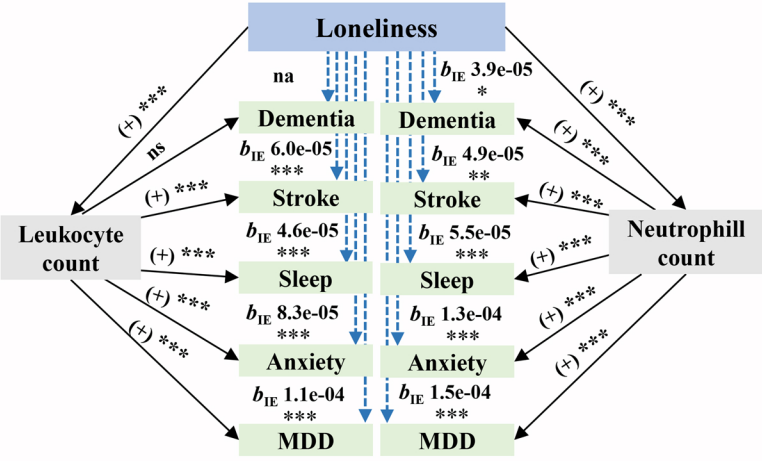

A
Fluid intelligence
Reaction time
Pairs matching
Prospective memory
Numeric memory
General mental health
Life satisfaction
Subjective well-being
PHQ_4
PHQ_9
CIDI
GAD7
Social isolation
Loneliness
Number
155,266
462,936
466,701
159,694
47,326
462,978
155,855
145,948
425,150
147,406
51,202
148,072
1
0.8
0.6
0.4
0.2
b value

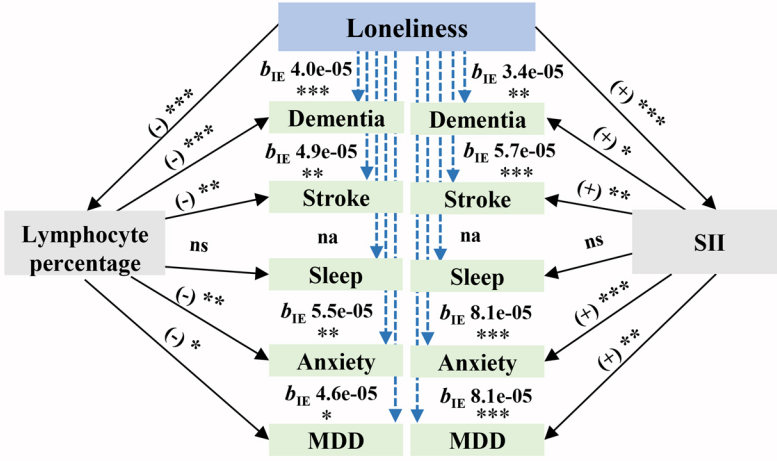

B
Baseline
Follow up
Isolation
0.003***
0.057***
0.022***
-0.000***
0.005***
General mental status
0.079***
PHQ4
0.198***
0.021***
0.007***
0.016***
-0.044***
Life satisfaction
-0.002***
0.303***
0.020***
0.004*
0.018***
-0.022**
Loneliness
0.000*
0.143***
0.028***
0.001***
0.006***
0.138***
0.004***
0.411***
0.034***
0.022***
0.035***
0.408***
0.412***
0.021***
0.010***
0.023***
0.209***

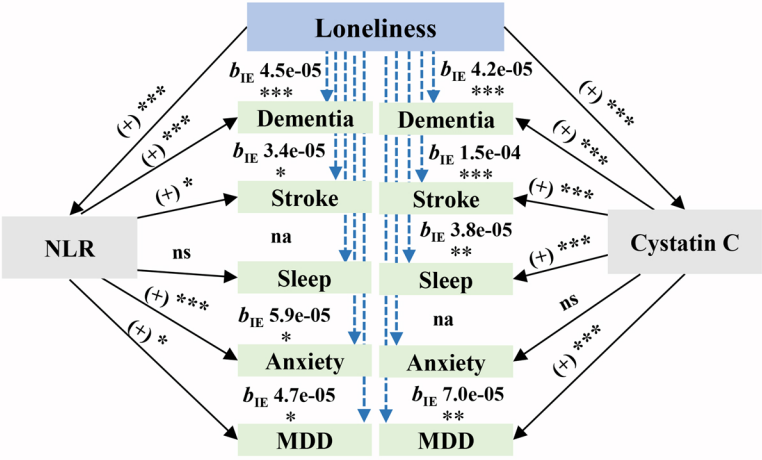

SI
Lateral occipital
Lingual
Lateral occipital
LN
Inferior parietal
Lateral ventricle
SI
Thalamus
Hippocampus
Amygdala
0.08
0.05
0.03
-0.03
-0.05
-0.08
b value

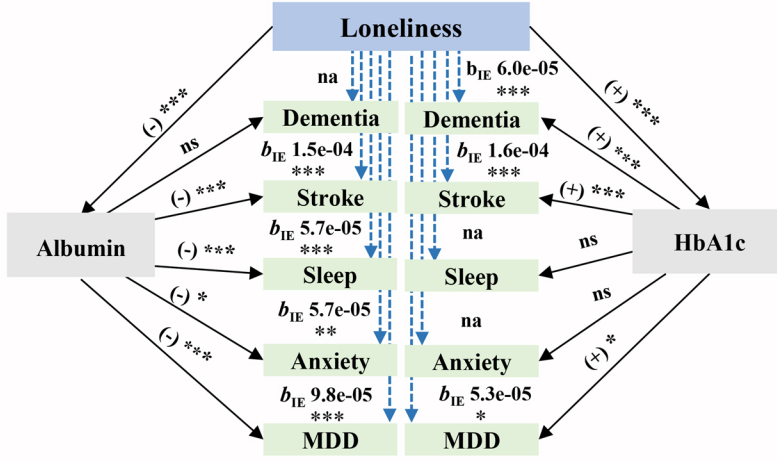

Social isolation
Leukocyte count
Neutrophill count
Dementia
MS
MDD
Schiz
BD
na
b_{IE} 6.6e-05 **
b_{IE} 1.8e-04 ***
b_{IE} 2.0e-04 ***
b_{IE} 1.2e-05 ***
b_{IE} 7.0e-05 *
(+) ***
(+) **
ns


Social isolation
GGT
SHBG
Dementia
MS
MDD
Schiz
BD
na
b_{IE} 8.3e-06 *
b_{IE} 2.3e-05 **
b_{IE} 4.4e-05 **
b_{IE} 2.3e-05 *
b_{IE} 1.2e-05 **
b_{IE} 3.5e-06 *
(+) ***
(+) **
(+) *
ns


Loneliness
Leukocyte count
Neutrophill count
Dementia
Stroke
Sleep
Anxiety
MDD
na
b_{IE} 3.9e-05 *
b_{IE} 6.0e-05 ***
b_{IE} 4.9e-05 **
b_{IE} 4.6e-05 ***
b_{IE} 5.5e-05 ***
b_{IE} 8.3e-05 ***
b_{IE} 1.3e-04 ***
b_{IE} 1.1e-04 ***
b_{IE} 1.5e-04 ***
(+) ***
ns


Loneliness
Lymphocyte percentage
SII
Dementia
Stroke
Sleep
Anxiety
MDD
na
b_{IE} 4.0e-05 ***
b_{IE} 3.4e-05 **
b_{IE} 4.9e-05 **
b_{IE} 5.7e-05 ***
b_{IE} 5.5e-05 **
b_{IE} 8.1e-05 ***
b_{IE} 4.6e-05 *
b_{IE} 8.1e-05 ***
(-) ***
(-) **
(-) *
(+) ***
(+) **
(+) *
ns


Loneliness
NLR
Cystatin C
Dementia
Stroke
Sleep
Anxiety
MDD
na
b_{IE} 4.5e-05 ***
b_{IE} 4.2e-05 ***
b_{IE} 3.4e-05 *
b_{IE} 1.5e-04 ***
b_{IE} 3.8e-05 **
b_{IE} 5.9e-05 *
b_{IE} 4.7e-05 *
b_{IE} 7.0e-05 **
(+) ***
(+) *
ns


Loneliness
Albumin
HbA1c
Dementia
Stroke
Sleep
Anxiety
MDD
na
b_{IE} 6.0e-05 ***
b_{IE} 1.5e-04 ***
b_{IE} 1.6e-04 ***
b_{IE} 5.7e-05 ***
b_{IE} 5.7e-05 **
b_{IE} 9.8e-05 ***
b_{IE} 5.3e-05 *
(-) ***
(-) *
(+) ***
(+) *
ns