Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Social Isolation, Loneliness, Polygenic Susceptibility, and Incident Major Neurological Disorders: A UK Biobank Cohort Study

Kaimin Zhang
Hangzhou Normal University
Huiwen Chen
Hangzhou Normal University
Xijie Guo
Hangzhou Normal University
Chenyu Ni
Hangzhou Normal University
Lin Zhu
zhulin@hznu.edu.cn

Hangzhou Normal University

Research Article

Keywords: Social isolation, Loneliness, Neurological disorders, Polygenic risk score, UK Biobank

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11336712/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Social Isolation, Loneliness, Polygenic Susceptibility, and Incident Major Neurological Disorders: A UK Biobank Cohort Study

Kaimin Zhang[2#], Huiwen Chen[2#], Xijie Guo[2], Chenyu Ni[2], Lin Zhu[1,2*]

1 Zhejiang Key Laboratory of Medical Epigenetics, Hangzhou Normal University, Hangzhou, Zhejiang, China.

2 College of Basic Medicine, Hangzhou Normal University, Hangzhou, Zhejiang, China.

#Co-first authors: Kaimin Zhang, Huiwen Chen

*Corresponding Author: **Lin Zhu, E-mail: zhulin@hznu.edu.cn**

Abstract

Background: Social isolation and loneliness are increasingly recognized as potentially modifiable determinants of neurological health in middle-aged and older adults, but whether their associations vary according to polygenic susceptibility remains unclear.

Methods: This prospective cohort included 370,475 UK Biobank participants. Cox models evaluated associations of social isolation and loneliness with five neurological disorders, including subgroup and interaction analyses. Disease-specific polygenic risk score (PRS) analyses assessed gene-by-social interaction.

Results: During a median follow-up of 13.7 years, social isolation was associated with dementia (HR, 1.22; 95% CI, 1.16–1.28), multiple sclerosis (MS; HR, 1.43; 95% CI, 1.14–1.78), Parkinson's disease (PD; HR, 1.18; 95% CI, 1.02–1.36), and stroke (HR, 1.13; 95% CI, 1.06–1.20). Loneliness was associated with dementia (HR, 1.39; 95% CI, 1.32–1.48), PD (HR, 1.29; 95% CI, 1.09–1.53), and stroke (HR, 1.23; 95% CI, 1.15–1.32). Neither exposure was associated with amyotrophic lateral sclerosis, and loneliness was not associated with MS. For dementia, the largest subgroup estimates were observed among never drinkers for social isolation (HR, 1.59) and non-White participants for loneliness (HR, 1.71). Concurrent social isolation and loneliness were associated with the highest hazards of dementia (HR, 1.60) and stroke (HR, 1.36), without significant multiplicative interaction between the exposures. No significant multiplicative interactions were detected between either social exposure and disease-specific PRSs. An exploratory positive HR-based RERI was observed only for social isolation and MS PRS (2.48; 95% CI, 0.17–4.68).

Conclusion: Social isolation and loneliness showed distinct associations with neurological disorders. Concurrent exposure identified higher-risk groups without evidence of synergy. These observational findings support social connection as a population-health risk marker but do not establish causality or intervention effects.

Keywords: Social isolation; Loneliness; Neurological disorders; Polygenic risk score; UK Biobank

Introduction

Major neurological disorders, including dementia [1], stroke [2], amyotrophic lateral sclerosis (ALS) [3], multiple sclerosis (MS), and Parkinson's disease (PD) [4], contribute substantially to disability and mortality. Dementia and stroke are especially prevalent and impose large societal and economic burdens [5, 6]. Although PD, ALS, and MS are less common, they often lead to progressive disability and reduced survival.

Social isolation and loneliness are distinct dimensions of social connection that are associated with health outcomes [7, 8]. Social isolation describes an objective lack of contacts or structural connection. Social isolation refers to the objective quantity of social interactions observable in behavior, whereas loneliness typically denotes the subjective emotional experience associated with the quality of social relationships[9, 10]. Prospective evidence indicates that the two exposures may be associated with morbidity and mortality through partly distinct pathways [8, 11].

Previous cohort studies, including analyses of UK Biobank data, have reported associations of social isolation or loneliness with dementia and stroke [12-15], and of loneliness with PD [16]. Residual confounding by prodromal neuropsychiatric symptoms remains a concern, particularly for dementia and PD. Evidence for ALS and MS is sparse [17]. Neurological disorders also have polygenic architectures in which many variants contribute to susceptibility [18-20]. Higher disease-specific PRS values have been associated with greater neurological disease risk [20, 21]. However, whether genetic susceptibility modifies the associations of social isolation and loneliness with major neurological disorders remains unclear.

We therefore examined the longitudinal associations of social isolation and loneliness with incident dementia, stroke, ALS, MS, and PD in the UK Biobank. We also evaluated joint exposure patterns, population-attributable fractions, and associations across disease-specific PRS strata. Additive and multiplicative interactions were tested formally, with additional analyses addressing APOE ε4 status, reverse causation, mental health symptoms, and missing data.

Materials and methods

Study population

The UK Biobank recruited 502,131 adults across the United Kingdom between 2006 and 2010. Baseline assessments included physical measurements, health and sociodemographic questionnaires, and blood collection for genomic and biochemical analyses. The North West Multi-centre Research Ethics Committee approved the UK Biobank, and all participants provided written informed consent. This study was conducted under UK Biobank application 455643. The graphical abstract summarizes the study population, exposures, genetic susceptibility, outcomes, and principal associations.

We first excluded participants with dementia, ALS, MS, PD, or stroke at baseline. We then excluded 34,798 participants with missing social isolation or loneliness data. Complete-case exclusions included missing BMI (n = 1,999), TDI (n = 573), alcohol use (n = 281), smoking (n = 1,398), physical activity (n = 7,875), education (n = 78,589), baseline depression (n = 3,366), or baseline anxiety (n = 1,939). These categories also overlapped. The final analytic sample comprised 370,475 participants (Supplemental Figure 1).

Assessment of Social Isolation and Loneliness

Baseline social isolation and loneliness were assessed using self-reported UK Biobank items [10, 22]. The social isolation index assigned one point for living alone, infrequent contact with family or friends, and no weekly group activity. Scores of 2 or 3 indicated social isolation. The loneliness index assigned one point for often feeling lonely and one point for being able to confide only once every few months or less. Only a score of 2 was classified as loneliness. Thus, the loneliness exposure was a two-item composite rather than the single direct question on feeling lonely [16, 23, 24]. Item wording and scoring are provided in Supplemental Table 1.

Outcomes

Incident dementia, stroke, ALS, MS, and PD were ascertained from linked UK Biobank records using ICD-10 codes. Dementia, stroke, ALS, multiple sclerosis (MS), and Parkinson's disease (PD) were defined using prespecified codes listed in Supplemental Table 2. For each outcome, follow-up extended from baseline until diagnosis, death, loss to follow-up, or October 31, 2022, whichever occurred first.

Covariates

Covariates included age, sex, ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, education, hypertension, diabetes, and insomnia. BMI was categorized as underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²), or obesity (≥30.0 kg/m²) [25]. Ethnicity was categorized as White or non-White. Alcohol consumption and smoking were classified as never, former, or current [26]. Household income, education level, physical activity, depression, and anxiety were assessed at baseline. Physical activity was measured as minutes per week spent walking or engaged in moderate or vigorous activity according to the International Physical Activity Questionnaire (IPAQ)[27]. Participants met the activity criterion if they reported >150 min/week of moderate-intensity activity or >75 min/week of vigorous-intensity activity. The criterion was also met by moderate-intensity activity on ≥5 days/week or vigorous-intensity activity at least once per week[28]. Education level was categorized as university degree and other qualifications. Histories of depression and anxiety were identified from self-reported medical histories or corresponding ICD-10 diagnostic codes. Hypertension was defined as blood pressure ≥130/85 mmHg or antihypertensive medication use[106]; diabetes was defined as HbA1c ≥42 mmol/mol (6.0%) or glucose-lowering treatment. Relevant UK Biobank field IDs and ICD-10 definitions are provided in Supplemental Table 2.

Polygenic Risk Scores

Genotyping, imputation, and quality control followed UK Biobank procedures described previously [29]. Disease-specific PRS values for PD, stroke, and MS were obtained from the standard PRS data released by UK Biobank. The dementia PRS was a weighted score based on 25 genome-wide significant variants with minor allele frequency >1% [30, 31]. APOE-ε4 status was examined separately because of its prominent role in genetic susceptibility to sporadic Alzheimer's disease. APOE genotype was inferred from the rs429358 and rs7412 variants. Participants were subsequently classified as APOE-ε4 carriers or non-carriers according to established criteria[32, 33]. Variant details are provided in Supplemental Table 3. Genetic analyses included 362,493 participants for dementia and 361,860 for MS, PD, and stroke.

$$PRS = \sum_{i=1}^{n} (\beta_i * SNP_i)$$

The weighted PRS was calculated as the sum of effect-allele dosages multiplied by their published effect estimates. Participants were categorized into low, intermediate, or high genetic susceptibility using disease-specific PRS tertiles. The low-PRS group served as the reference in PRS association, joint-category, and interaction analyses.

Statistical Analysis

Continuous variables are reported as mean (SD), and categorical variables as n (%). Baseline characteristics were compared by social isolation and loneliness status. Cox proportional hazards models estimated HRs and 95% CIs for each neurological outcome. Model 1 adjusted for age and sex. Model 2 additionally adjusted for ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, and education. Model 3 further adjusted for hypertension, diabetes, and insomnia. Proportional hazards assumptions were evaluated using Schoenfeld residuals.

Cumulative hazard curves were plotted by social isolation and loneliness status, and groups were compared using log-rank tests. We also examined mutual adjustment and four joint exposure categories: neither exposure, social isolation only, loneliness only, and both exposures. Population-attributable fractions (PAFs) were calculated using the formula incorporating exposure prevalence and hazard ratios. Where p denoted the prevalence of exposure in the study population and HR represented the fully adjusted hazard ratio estimate derived from regression models.

To assess potential heterogeneity in the associations of social isolation and loneliness with major neurological disorders, subgroup analyses were conducted across prespecified population groups. Stratification variables included age (<65 or ≥65 years), sex (female or male), ethnicity (White or non-White), and BMI category (underweight, normal weight, overweight, or obese). Additional analyses were stratified by TDI (low or high), alcohol consumption status (never, former, or current), and smoking status (never, former, or current). Physical activity (active or inactive) and educational attainment (college or university degree vs other levels) were also examined.

We examined associations of each disease-specific PRS with the corresponding neurological outcome and estimated the associations of social isolation and loneliness within low, intermediate, and high PRS strata. For the joint analyses, six-category variables combined each PRS stratum with the presence or absence of social isolation or loneliness. Participants with low PRS and without the corresponding social exposure served as the reference group. Multiplicative interaction was evaluated using likelihood-ratio tests comparing models with and without the relevant interaction term. Additive interaction was assessed using the relative excess risk due to interaction, calculated as $RERI = HR_{11} - HR_{10} - HR_{01} + 1$. An RERI of 0 indicated no additive interaction, whereas evidence of additive interaction was defined by a 95% CI that excluded 0. Moreover, to further validate the stability of the results, the main exposure–outcome models were additionally adjusted for the corresponding disease-specific PRS and the first 10 ancestry principal components.

Sensitivity analyses excluded participants with less than 2, 5, or 10 years of follow-up to reduce potential reverse causation. Additional models adjusted separately and jointly for depressive and anxiety symptoms. Missing covariate data were addressed using multiple imputation by chained equations with five imputed datasets. All analyses were performed in R version 4.4.3. Statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics of the 370,475 participants included in the analysis are presented in Table 1. At baseline, 8.1% of participants reported social isolation, while 5.6% were classified as lonely using the two-item loneliness index. Compared with participants without the corresponding exposure, those reporting social isolation or loneliness were more likely to be male and non-White and to have less favorable socioeconomic characteristics. Specifically, they had lower educational attainment, lower household income, and higher levels of material deprivation. Smoking, physical inactivity, and obesity were also more common, as were depression and anxiety. During a median follow-up of 13.7 years, 17,354 participants developed dementia, 13,264 developed stroke, 2,491 developed PD, 832 developed MS, and 415 developed ALS.

Associations of Social Isolation and Loneliness with Major Neurological Disorders

In fully adjusted models, social isolation was associated with dementia (HR, 1.22; 95% CI, 1.16–1.28), MS (HR, 1.43; 95% CI, 1.14–1.78), PD (HR, 1.18; 95% CI, 1.02–1.36), and stroke (HR, 1.13; 95% CI, 1.06–1.20). Loneliness was associated with dementia (HR, 1.39; 95% CI, 1.32–1.48), PD (HR, 1.29; 95% CI, 1.09–1.53), and stroke (HR, 1.23; 95% CI, 1.15–1.32). Social isolation was not associated with ALS, and loneliness was not associated with ALS or MS (Figure 1 and Supplemental Table 4). Cumulative hazard curves differed by social isolation status for dementia, MS, and stroke. Curves differed by loneliness status for dementia and stroke, but not for MS. Differences were not evident for ALS or PD with either exposure (Figure 2 and Supplemental Figure 2).

Interaction and Joint Exposure Analyses

No multiplicative interaction was detected between social isolation and loneliness for any outcome (all P for interaction > 0.05; Supplemental Table 5). Compared with neither exposure, the HRs for dementia were 1.18 for social isolation only, 1.37 for loneliness only, and 1.60 for both exposures. The corresponding stroke HRs were 1.10, 1.21, and 1.36. The joint exposure estimate for PD was not statistically significant (HR, 1.20; 95% CI, 0.83–1.75). These results describe risk accumulation across exposure categories rather than evidence of synergy (Supplemental Figure 3 and Supplemental Table 6).

Population-Attributable Fractions for Social Isolation and Loneliness

Model-based PAFs were estimated to quantify the proportion of incident cases associated with each social exposure at the population level (Supplemental Table 7). For social isolation, the largest PAF was observed for MS, at 3.4% (95% CI, 1.1%–5.9%). The corresponding PAFs were 1.8% (95% CI, 1.3%–2.2%) for dementia, 1.4% (95% CI, 0.2%–2.8%) for PD, and 1.0% (95% CI, 0.5%–1.6%) for stroke. For loneliness, the PAF was highest for dementia, at 2.1% (95% CI, 1.8%–2.6%), followed by PD at 1.6% (95% CI, 0.5%–2.9%) and stroke at 1.3% (95% CI, 0.8%–1.8%). The point estimates for loneliness were numerically higher than those for social isolation for dementia, stroke, and PD.

Subgroup and Sensitivity Analyses

For dementia, the association with social isolation was broadly consistent across subgroups,

with the largest estimate observed among never drinkers (HR, 1.59; 95% CI, 1.28–1.97). A relatively large estimate was also observed among participants with a college education (HR, 1.27; 95% CI, 1.17–1.39), but none of the subgroup interactions was significant (Supplemental Figure 4). In contrast, the association between loneliness and dementia differed by age (P for interaction = 0.0073) and smoking status (P for interaction = 0.0072). Estimates were higher among participants aged <65 years (HR, 1.43; 95% CI, 1.34–1.53) and current smokers (HR, 1.56; 95% CI, 1.39–1.75). A large estimate was also observed among non-White participants (HR, 1.71; 95% CI, 1.36–2.14), although the interaction by ethnicity was not significant (P for interaction = 0.0745) (Supplemental Figure 8). For stroke, no significant subgroup interactions were identified for either exposure. The largest social isolation estimate was observed among never drinkers (HR, 1.28; 95% CI, 1.01–1.62), whereas the largest loneliness estimates were observed among previous drinkers (HR, 1.45; 95% CI, 1.09–1.91) and non-White participants (HR, 1.44; 95% CI, 1.10–1.87) (Supplemental Figures 5 and 9). For PD, the largest social isolation estimate was observed among never drinkers (HR, 1.76; 95% CI, 1.04–2.99), with large but imprecise estimates among non-White participants and current smokers. Loneliness was associated with PD among participants aged ≥65 years (HR, 1.43; 95% CI, 1.10–1.86), those with obesity (HR, 1.40; 95% CI, 1.02–1.92), and physically active participants (HR, 1.37; 95% CI, 1.10–1.72), although no subgroup interactions were significant (Supplemental Figures 6 and 10). For MS, the largest social isolation estimate was observed among previous smokers (HR, 1.86; 95% CI, 1.30–2.64). Relatively large estimates were also observed among participants with normal weight (HR, 1.66; 95% CI, 1.16–2.36), current drinkers (HR, 1.55; 95% CI, 1.23–1.94), and physically inactive participants (HR, 1.50; 95% CI, 1.14–1.97), with no significant subgroup interactions (Supplemental Figure 7).

The main patterns were broadly similar after mutual adjustment, lag exclusions, additional mental health adjustment, and multiple imputation (Supplemental Tables 5 and 8–10). After excluding participants with less than 10 years of follow-up, associations with dementia persisted for social isolation (HR, 1.09; 95% CI, 1.01–1.19) and loneliness (HR, 1.40; 95% CI, 1.28–1.53). The social isolation estimate for PD was attenuated after 5- and 10-year exclusions, whereas the loneliness estimate remained significant (Supplemental Table 9).

Genetic Susceptibility and Associations of Social Isolation and Loneliness with Neurological Disorders

Higher disease-specific PRSs were associated with all four neurological outcomes in fully adjusted models. Compared with low PRS, high PRS was associated with dementia (HR, 1.11; 95% CI, 1.07–1.15) and stroke (HR, 1.45; 95% CI, 1.39–1.52). Larger relative associations were observed for MS (HR, 5.26; 95% CI, 4.21–6.57) and PD (HR, 2.31; 95% CI, 2.08–2.57) (Supplemental Table 11). Associations of social isolation and loneliness with dementia and stroke were broadly similar across PRS strata, whereas estimates for MS and PD varied more. For dementia, social isolation HRs ranged from 1.16 to 1.25 across strata, while loneliness HRs ranged from 1.38 to 1.41. No multiplicative interactions were detected between either social exposure and PRS for any outcome (all P for interaction >0.05). However, social isolation and MS PRS showed an exploratory positive HR-based RERI of 2.48 (95% CI, 0.17–4.68). All other RERI confidence intervals included zero (Figure 3 and Table 2).

Joint analyses used participants with low PRS and no corresponding social exposure as the reference group. For dementia, high PRS combined with social isolation or loneliness yielded HRs of 1.36 (95% CI, 1.25–1.48) and 1.53 (1.38–1.68), respectively. Joint-category estimates for all four outcomes are presented in Supplemental Table 12. Additional dementia analyses incorporated APOE ε4 status. Participants with high PRS, APOE ε4 carriage, and social isolation or loneliness had the highest observed event proportions, at 8.78% and 9.44%, respectively. Relative to low-PRS, APOE ε4 noncarriers without the corresponding social exposure, their HRs were 1.95 (95% CI, 1.70–2.24) and 2.28 (1.95–2.67), respectively. These descriptive joint-category patterns did not themselves establish effect modification (Supplemental Tables 13 and 14).

Discussion

This large prospective study based on the UK Biobank provided important insights into the associations of social isolation and loneliness with incident neurological outcomes. (1) Social isolation was associated with incident dementia, MS, PD, and stroke.

Loneliness was associated with incident dementia, PD, and stroke, but not MS or ALS. (2) We further estimated the population-level burden attributable to these social exposures. The model-based PAFs were modest. Loneliness had slightly larger PAF estimates than social isolation for dementia, PD, and stroke, whereas social isolation had the largest PAF for MS. (3) Disease-specific PRSs were associated with all four disorders included in the genetic analyses, with the strongest risk gradients observed for MS and PD. (4) We further assessed whether genetic susceptibility modified these associations. The only evidence of an additive interaction was observed between social isolation and the MS PRS, as supported by the corresponding confidence interval.

Our findings extend earlier reports linking social isolation to stroke and PD, loneliness to PD, and lower social engagement to cognitive decline and dementia[14, 16, 34]. They are also concordant with a meta-analysis of 21 longitudinal samples comprising more than 600,000 participants, in which loneliness was associated with all-cause dementia even in models accounting for depression, social isolation, or other modifiable risk factors[35]. Similarly, a longitudinal study found higher stroke risk among participants with baseline loneliness and especially among those with persistently high loneliness[36]. By contrast, evidence concerning social isolation and incident MS remains sparse; therefore, our positive MS finding should be regarded as hypothesis-generating, particularly given the smaller number of MS events.

Social isolation and loneliness capture related but non-equivalent dimensions of social connection. Our mutually adjusted models therefore suggest that each measure contributes information not fully represented by the other. The greatest hazards of dementia and stroke occurred among participants reporting both exposures. This pattern is more consistent with accumulated risk than biological synergy. A recent UK Biobank analysis also linked one or both social-connection measures to dementia, stroke, Parkinson's disease, and multiple sclerosis, although cohort overlap limits its value as independent replication[37]. Longitudinal syntheses likewise link limited social participation, infrequent contact, and loneliness with dementia and stroke risk[38-40].

These findings support social connection as a potentially modifiable risk domain, while not establishing that social interventions will prevent neurological disease[7, 41].

Several interacting pathways may explain these associations. Perceived social threat can activate the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, altering glucocorticoid and catecholamine signaling. Sustained activation may promote pro-inflammatory transcription, oxidative stress, and endothelial dysfunction, thereby increasing vascular injury and neuroimmune activation[42-44]. Neural-circuit and glial changes offer a complementary pathway. In UK Biobank imaging, loneliness correlated with default-network morphology, intrinsic connectivity, and fornix microstructure[45]. Contemporary circuit models distinguish acute social homeostatic responses from adaptations to chronic isolation, suggesting that exposure duration may shape neurological consequences[46]. Experimental studies show that juvenile isolation can impair prefrontal oligodendrocyte maturation and myelination, while chronic isolation induces a distributed Tac2/neurokinin B state[47, 48]. Social deprivation also increased astrocytic TRPA1-dependent gamma-aminobutyric acid release, suppressing hippocampal long-term potentiation and memory in mice[49]. These studies provide mechanistic plausibility, but their developmental timing and experimental intensity differ substantially from midlife human social disconnection. Behavioral and reciprocal pathways remain equally plausible. Social disconnection may reduce physical activity, disturb sleep, promote smoking, worsen diet, and delay healthcare, thereby increasing vascular and metabolic risk[7, 41]. Conversely, prodromal cognitive, motor, sensory, or mood changes may reduce social participation before diagnosis.

The PAF analyses place the relative-risk estimates in a population context. The largest estimate was observed for social isolation and MS (3.4%), whereas the PAFs for dementia, PD, and stroke ranged from 1.0% to 2.1%. The 2024 Lancet Commission includes social isolation among potentially modifiable dementia risk factors[50], supporting continued attention to social connection in brain-health research. Nevertheless, the present PAFs are conditional on exposure prevalence, model specification, covariate control, and the assumption that the fitted associations are

causal.

In subgroup analyses for dementia, the loneliness association was stronger among participants aged younger than 65 years and current smokers, with significant interaction tests for age and smoking. In contrast, the visually larger point estimates in other strata—including social isolation among never drinkers and loneliness among non-White participants—were not accompanied by significant interaction tests. No significant subgroup interaction was detected for stroke, PD, or MS. These comparisons were exploratory and numerous, so isolated patterns may reflect chance and require replication[51, 52].

Disease-specific PRSs were associated with incident neurological disorders, consistent with established genetic contributions to Alzheimer's disease, MS, PD, and stroke[53-56]. Associations were larger for MS and PD, although differences in PRS construction limit cross-disease comparisons. No significant multiplicative interactions were detected. Thus, elevated hazards among participants with high PRS and either social exposure do not establish effect modification, which depends on the analytical scale [57]. The positive HR-based RERI for social isolation and MS should be considered exploratory. Limited MS events, imprecision, and multiple comparisons warrant caution and independent replication[58]. Moreover, HR-based RERI does not directly establish absolute-risk additivity or biological synergy. Participants with high PRS, APOE ε4 carriage, and either social exposure had higher observed dementia event proportions. APOE ε4-related susceptibility to Alzheimer's disease provides relevant context[59], but these descriptive patterns do not establish genotype-dependent social exposure effects. Further evidence is needed before considering genotype-targeted interventions.

This study has several strengths, including its prospective design, large sample, linked clinical and genetic data, direct comparison of objective and subjective social connection, and formal evaluation of additive and multiplicative interaction. Several limitations remain. First, social isolation and loneliness were measured once using brief self-reported indices. Second, complete-case exclusions and the healthy-volunteer

profile of UK Biobank may have introduced selection bias. Third, residual confounding may remain from baseline cognition, hearing, functional status, household composition, and other socioeconomic or health characteristics. Depression and anxiety may also act as confounders, mediators, or prodromal manifestations, making mental-health-adjusted estimates difficult to interpret. Fourth, the predominantly White sample limits generalizability and may reduce PRS transportability. Finally, the observational design precludes causal inference.

Conclusion

Social isolation and loneliness were associated with several incident major neurological disorders, with patterns that differed by outcome. Genetic susceptibility was strongly associated with MS and PD, but formal interaction tests were mostly null. An exploratory positive HR-based RERI was observed for social isolation and MS PRS, requiring independent confirmation. These findings support considering social connection as a potential risk marker while recognizing that observational associations do not establish prevention effects. Studies with repeated exposure assessment and stronger control of prodromal disease are needed.

Funding

The current work received support from the Start-up Funding of Hangzhou Normal University, with grant number 4255C50224204010.

Declarations

Ethics approval and consent to participate: This study was conducted in accordance with the Declaration of Helsinki. The human data were obtained from the UK Biobank (Application [no.] 455643), whose original data collection was approved by the North West Multi-centre Research Ethics Committee (approval reference 21/NW/0157). As this study involved the secondary analysis of de-identified data from an ethically approved public database, no additional ethical approval or individual informed consent was required.

Consent for publication: Not applicable.

Clinical trial number: not applicable.

Author Contributions

Kaimin Zhang: conceptualization, methodology, writing - original draft. Huiwen Chen: Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing - review & editing. Xijie Guo: Data curation, Validation, Writing - original draft. Chenyu Ni: Data curation, Formal analysis, Visualization, Writing - original draft. Lin Zhu: Conceptualization, Supervision, Writing - review & editing.

Conflict of Interests

The authors declare that they have no competing interests.

References

1. Iadecola C, Anrather J: **The immunology of stroke and dementia**. *Immunity* 2025, **58**(1):18-39.
2. Hilkens NA, Casolla B, Leung TW, de Leeuw FE: **Stroke**. *Lancet* 2024, **403**(10446):2820-2836.
3. Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, Sobue G: **Amyotrophic lateral sclerosis**. *Lancet* 2022, **400**(10360):1363-1380.
4. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH: **The pathogenesis of Parkinson's disease**. *Lancet* 2024, **403**(10423):293-304.
5. Feigin VL, Vos T, Alahdab F, Amit AML, Bärnighausen TW, Beghi E, Beheshti M, Chavan PP, Criqui MH, Desai R *et al*: **Burden of Neurological Disorders Across the US From 1990-2017: A Global Burden of Disease Study**. *JAMA Neurol* 2021, **78**(2):165-176.
6. Nandi A, Counts N, Chen S, Seligman B, Tortorice D, Vigo D, Bloom DE: **Global and regional projections of the economic burden of Alzheimer's disease and related dementias from 2019 to 2050: A value of statistical life approach**. *EClinicalMedicine* 2022, **51**:101580.
7. Holt-Lunstad J: **Social connection as a critical factor for mental and physical health: evidence, trends, challenges, and future implications**. *World Psychiatry* 2024, **23**(3):312-332.
8. Holt-Lunstad J: **Social Connection as a Public Health Issue: The Evidence and a Systemic Framework for Prioritizing the "Social" in Social Determinants of Health**. *Annu Rev Public Health* 2022, **43**:193-213.

9. Christiansen J, Lund R, Qualter P, Andersen CM, Pedersen SS, Lasgaard M: **Loneliness, Social Isolation, and Chronic Disease Outcomes**. *Ann Behav Med* 2021, **55**(3):203-215.
10. Elovainio M, Hakulinen C, Pulkki-Råback L, Virtanen M, Josefsson K, Jokela M, Vahtera J, Kivimäki M: **Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study**. *Lancet Public Health* 2017, **2**(6):e260-e266.
11. Tanskanen J, Anttila T: **A Prospective Study of Social Isolation, Loneliness, and Mortality in Finland**. *Am J Public Health* 2016, **106**(11):2042-2048.
12. Chen S, Kuper H: **Tracing the temporal trends of modifiable risk factors in dementia: insights from the English Longitudinal Study of Ageing (2004-2019)**. *Lancet* 2023, **402 Suppl 1**:S34.
13. Mukadam N, Sommerlad A, Huntley J, Livingston G: **Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data**. *Lancet Glob Health* 2019, **7**(5):e596-e603.
14. Smith RW, Barnes I, Green J, Reeves GK, Beral V, Floud S: **Social isolation and risk of heart disease and stroke: analysis of two large UK prospective studies**. *Lancet Public Health* 2021, **6**(4):e232-e239.
15. Hakulinen C, Pulkki-Råback L, Virtanen M, Jokela M, Kivimäki M, Elovainio M: **Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479 054 men and women**. *Heart* 2018, **104**(18):1536-1542.
16. Terracciano A, Luchetti M, Karakose S, Stephan Y, Sutin AR: **Loneliness and Risk of Parkinson Disease**. *JAMA Neurol* 2023, **80**(11):1138-1144.
17. Khatooni M, Dehghankar L, Bahrami M, Panahi R, Hajnasiri H: **Perceived Social Isolation Among Patients With Multiple Sclerosis Suffering From Disease-Induced Pain and Disability**. *J Nurs Res* 2024, **32**(4):e341.
18. de la Fuente J, Grotzinger AD, Marioni RE, Nivard MG, Tucker-Drob EM: **Integrated analysis of direct and proxy genome wide association studies highlights polygenicity of Alzheimer's disease outside of the APOE region**. *PLoS Genet* 2022, **18**(6):e1010208.
19. Kim NJ, Mishra A, Chowdhury NF, Anderson SD, Vega OM, Chaudhari NN, Buetow KH, Thompson PM, Irimia A: **Deep neural networks and genome-wide associations reveal the polygenic architecture of local brain aging**. *Geroscience* 2025.
20. Zheng Z, Lv Y, Rong S, Sun T, Chen L: **Physical Frailty, Genetic Predisposition, and Incident Parkinson Disease**. *JAMA Neurol* 2023, **80**(5):455-461.
21. Saffie-Awad P, Grant SM, Makarious MB, Elsayed I, Sanyaolu AO, Crea PW, Schumacher Schuh AF, Levine KS, Vitale D, Koretsky MJ *et al*: **Insights into ancestral diversity in Parkinson's disease risk: a comparative assessment of polygenic risk scores**. *NPJ Parkinsons Dis* 2025, **11**(1):201.
22. Elovainio M, Komulainen K, Sipilä PN, Pulkki-Råback L, Cachón Alonso L, Pentti J, Nyberg ST, Suominen S, Vahtera J, Lipsanen J *et al*: **Association of social**

isolation and loneliness with risk of incident hospital-treated infections: an analysis of data from the UK Biobank and Finnish Health and Social Support studies. *Lancet Public Health* 2023, **8**(2):e109-e118.
23. Zhou J, Tang R, Wang X, Li X, Heianza Y, Qi L: **Improvement of Social Isolation and Loneliness and Excess Mortality Risk in People With Obesity**. *JAMA Netw Open* 2024, **7**(1):e2352824.
24. Lyu C, Siu K, Xu I, Osman I, Zhong J: **Social Isolation Changes and Long-Term Outcomes Among Older Adults**. *JAMA Netw Open* 2024, **7**(7):e2424519.
25. Kivimäki M, Strandberg T, Pentti J, Nyberg ST, Frank P, Jokela M, Ervasti J, Suominen SB, Vahtera J, Sipilä PN *et al*: **Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study**. *Lancet Diabetes Endocrinol* 2022, **10**(4):253-263.
26. Hendriks S, Ranson JM, Peetoom K, Lourida I, Tai XY, de Vugt M, Llewellyn DJ, Köhler S: **Risk Factors for Young-Onset Dementia in the UK Biobank**. *JAMA Neurol* 2024, **81**(2):134-142.
27. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, Pratt M, Ekelund U, Yngve A, Sallis JF *et al*: **International physical activity questionnaire: 12-country reliability and validity**. *Med Sci Sports Exerc* 2003, **35**(8):1381-1395.
28. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF *et al*: **Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond**. *Circulation* 2010, **121**(4):586-613.
29. Belloy ME, Eger SJ, Le Guen Y, Damotte V, Ahmad S, Ikram MA, Ramirez A, Tsolaki AC, Rossi G, Jansen IE *et al*: **Challenges at the APOE locus: a robust quality control approach for accurate APOE genotyping**. *Alzheimers Res Ther* 2022, **14**(1):22.
30. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B *et al*: **Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease**. *Nat Genet* 2013, **45**(12):1452-1458.
31. Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, Sealock J, Karlsson IK, Hägg S, Athanasiu L *et al*: **Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk**. *Nat Genet* 2019, **51**(3):404-413.
32. Bycroft C, Freeman C, Petkova D, Band G, Elliott LT, Sharp K, Motyer A, Vukcevic D, Delaneau O, O'Connell J *et al*: **The UK Biobank resource with deep phenotyping and genomic data**. *Nature* 2018, **562**(7726):203-209.
33. Zhang YP, Gao JW, Liao GH, Gao QY, Huang ZG, Zeng CR, Cai YW, Ruan YX, Chen ZT, Chen YX *et al*: **Cardiovascular-kidney-metabolic health, genetic susceptibility, and the risk of dementia: A prospective cohort study**. *J Prev Alzheimers Dis* 2026, **13**(1):100325.
34. Geng T, Li Y, Peng Y, Chen X, Xu X, Wang J, Sun L, Gao X: **Social isolation and**

the risk of Parkinson disease in the UK biobank study. *NPJ Parkinsons Dis* 2024, **10**(1):79.
35. Luchetti M, Aschwanden D, Sesker AA, Zhu X, O'Súilleabháin PS, Stephan Y, Terracciano A, Sutin AR: **A Meta-analysis of Loneliness and Risk of Dementia using Longitudinal Data from >600,000 Individuals**. *Nat Ment Health* 2024, **2**(11):1350-1361.
36. Soh Y, Kawachi I, Kubzansky LD, Berkman LF, Tiemeier H: **Chronic loneliness and the risk of incident stroke in middle and late adulthood: a longitudinal cohort study of U.S. older adults**. *EClinicalMedicine* 2024, **73**:102639.
37. Zhao YL, Zhang DD, Gao PY, Fu Y, Ge YJ, Chi HC, Guo ZX, Yu HH, Feng JF, Tan L *et al*: **Associations of social isolation and loneliness with neurological disorders, psychiatric disorders, brain structures and behavioural phenotypes among UK Biobank participants**. *Nat Commun* 2026, **17**(1).
38. Kuiper JS, Zuidersma M, Oude Voshaar RC, Zuidema SU, van den Heuvel ER, Stolk RP, Smidt N: **Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies**. *Ageing Res Rev* 2015, **22**:39-57.
39. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B: **Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies**. *Heart* 2016, **102**(13):1009-1016.
40. Mahalingam G, Samtani S, Lam BCP, Lipnicki DM, Lima-Costa MF, Blay SL, Castro-Costa E, Shifu X, Guerchet M, Preux PM *et al*: **Social connections and risk of incident mild cognitive impairment, dementia, and mortality in 13 longitudinal cohort studies of ageing**. *Alzheimers Dement* 2023, **19**(11):5114-5128.
41. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C *et al*: **Dementia prevention, intervention, and care: 2020 report of the Lancet Commission**. *Lancet* 2020, **396**(10248):413-446.
42. Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW: **The neuroendocrinology of social isolation**. *Annu Rev Psychol* 2015, **66**:733-767.
43. Cole SW: **Human social genomics**. *PLoS Genet* 2014, **10**(8):e1004601.
44. Li H, Xia N: **The role of oxidative stress in cardiovascular disease caused by social isolation and loneliness**. *Redox Biol* 2020, **37**:101585.
45. Spreng RN, Dimas E, Mwilambwe-Tshilobo L, Dagher A, Koellinger P, Nave G, Ong A, Kernbach JM, Wiecki TV, Ge T *et al*: **The default network of the human brain is associated with perceived social isolation**. *Nat Commun* 2020, **11**(1):6393.
46. Lee CR, Chen A, Tye KM: **The neural circuitry of social homeostasis: Consequences of acute versus chronic social isolation**. *Cell* 2021, **184**(6):1500-1516.
47. Makinodan M, Rosen KM, Ito S, Corfas G: **A critical period for social experience-dependent oligodendrocyte maturation and myelination**.

Science 2012, **337**(6100):1357-1360.
48. Zelikowsky M, Hui M, Karigo T, Choe A, Yang B, Blanco MR, Beadle K, Gradinaru V, Deverman BE, Anderson DJ: **The Neuropeptide Tac2 Controls a Distributed Brain State Induced by Chronic Social Isolation Stress**. *Cell* 2018, **173**(5):1265-1279.e1219.
49. Cheng YT, Woo J, Luna-Figueroa E, Maleki E, Harmanci AS, Deneen B: **Social deprivation induces astrocytic TRPA1-GABA suppression of hippocampal circuits**. *Neuron* 2023, **111**(8):1301-1315.e1305.
50. Livingston G, Huntley J, Liu KY, Costafreda SG, Selbæk G, Alladi S, Ames D, Banerjee S, Burns A, Brayne C *et al*: **Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission**. *Lancet* 2024, **404**(10452):572-628.
51. Rothwell PM: **Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation**. *Lancet* 2005, **365**(9454):176-186.
52. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM: **Statistics in medicine--reporting of subgroup analyses in clinical trials**. *N Engl J Med* 2007, **357**(21):2189-2194.
53. Kunkle BW, Grenier-Boley B, Sims R, Bis JC, Damotte V, Naj AC, Boland A, Vronskaya M, van der Lee SJ, Amlie-Wolf A *et al*: **Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing**. *Nat Genet* 2019, **51**(3):414-430.
54. **Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility**. *Science* 2019, **365**(6460).
55. Kim JJ, Vitale D, Otani DV, Lian MM, Heilbron K, Iwaki H, Lake J, Solsberg CW, Leonard H, Makarious MB *et al*: **Multi-ancestry genome-wide association meta-analysis of Parkinson's disease**. *Nat Genet* 2024, **56**(1):27-36.
56. Mishra A, Malik R, Hachiya T, Jürgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M *et al*: **Stroke genetics informs drug discovery and risk prediction across ancestries**. *Nature* 2022, **611**(7934):115-123.
57. Herrera-Luis E, Benke K, Volk H, Ladd-Acosta C, Wojcik GL: **Gene–environment interactions in human health**. *Nature Reviews Genetics* 2024, **25**(11):768-784.
58. Hunter DJ: **Gene–environment interactions in human diseases**. *Nature Reviews Genetics* 2005, **6**(4):287-298.
59. Fortea J, Pegueroles J, Alcolea D, Belbin O, Dols-Icardo O, Vaqué-Alcázar L, Videla L, Gispert JD, Suárez-Calvet M, Johnson SC *et al*: **APOE4 homozygosity represents a distinct genetic form of Alzheimer's disease**. *Nature Medicine* 2024, **30**(5):1284-1291.

596

597

598

Table 1. Baseline characteristics of study participants stratified by social isolation and loneliness status at baseline

		Social isolation			Loneliness		
Characteristic	**Overall N = 370,475**	**Not isolated N = 340,432**	**Socially isolated N = 30,043**	**P value**	**Not lonelyN = 349,839**	**Lonely N = 20,636**	**P value**
Age	55.5 (8.06)	55.6 (8.09)	55.4 (7.76)	0.0163	55.6 (8.07)	54.8 (7.89)	<0.001
Sex				<0.001			<0.001
Female	202,720 (54.72)	187,106 (54.96)	15,614 (51.97)		191,939 (54.86)	10,781 (52.24)	
Male	167,755 (45.28)	153,326 (45.04)	14,429 (48.03)		157,900 (45.14)	9,855 (47.76)	
Ethnicity				<0.001			<0.001
Non-White	18,072 (4.88)	15,932 (4.68)	2,140 (7.12)		16,474 (4.71)	1,598 (7.74)	
White	352,403 (95.12)	324,500 (95.32)	27,903 (92.88)		333,365 (95.29)	19,038 (92.26)	
BMI				<0.001			<0.001
Normal	128,507 (34.69)	118,433 (34.79)	10,074 (33.53)		122,361 (34.98)	6,146 (29.78)	
Obese	83,189 (22.45)	75,158 (22.08)	8,031 (26.73)		77,073 (22.03)	6,116 (29.64)	
Overweight	156,875 (42.34)	145,200 (42.65)	11,675 (38.86)		148,645 (42.49)	8,230 (39.88)	
Underweight	1,904 (0.51)	1,641 (0.48)	263 (0.88)		1,760 (0.50)	144 (0.70)	
TDI	-1.6 (2.91)	-1.7 (2.85)	-0.4 (3.35)	<0.001	-1.6 (2.89)	-0.9 (3.26)	<0.001
Alcohol				<0.001			<0.001
Current	347,137 (93.70)	320,130 (94.04)	27,007 (89.89)		328,256 (93.83)	18,881 (91.50)	
Never	12,673 (3.42)	11,298 (3.32)	1,375 (4.58)		11,799 (3.37)	874 (4.24)	
Previous	10,665 (2.88)	9,004 (2.64)	1,661 (5.53)		9,784 (2.80)	881 (4.27)	
Smoking				<0.001			<0.001
Current	34,070 (9.20)	29,330 (8.62)	4,740 (15.78)		31,080 (8.88)	2,990 (14.49)	
Never	211,658 (57.13)	196,042 (57.59)	15,616 (51.98)		200,677 (57.36)	10,981 (53.21)	
Previous	124,747 (33.67)	115,060 (33.80)	9,687 (32.24)		118,082 (33.75)	6,665 (32.30)	
Physical activity				<0.001			<0.001
Active	229,524 (61.95)	214,620 (63.04)	14,904 (49.61)		217,885 (62.28)	11,639 (56.40)	
Inactive	140,951 (38.05)	125,812 (36.96)	15,139 (50.39)		131,954 (37.72)	8,997 (43.60)	
Household income				<0.001			<0.001
< 18,000	53,332 (14.40)	44,267 (13.00)	9,065 (30.17)		48,226 (13.79)	5,106 (24.74)	
18,000-30,999	82,310 (22.22)	74,802 (21.97)	7,508 (24.99)		77,218 (22.07)	5,092 (24.68)	
31,000-51,999	95,702 (25.83)	89,537 (26.30)	6,165 (20.52)		91,021 (26.02)	4,681 (22.68)	
52,000-100,000	79,420 (21.44)	75,549 (22.19)	3,871 (12.88)		76,451 (21.85)	2,969 (14.39)	
> 100,000	21,688 (5.85)	20,770 (6.10)	918 (3.06)		21,091 (6.03)	597 (2.89)	
Missing	38,023 (10.26)	35,507 (10.43)	2,516 (8.37)		35,832(10.24)	2,191 (10.62)	
Education				0.9046			<0.001
College	149,054 (40.23)	136,977 (40.24)	12,077 (40.20)		142,155 (40.63)	6,899 (33.43)	
Other levels	221,421 (59.77)	203,455 (59.76)	17,966 (59.80)		207,684 (59.37)	13,737 (66.57)	
Depression	18,485 (4.99)	16,267 (4.78)	2,218 (7.38)	<0.001	16,170 (4.62)	2,315 (11.22)	<0.001
Anxiety	18,916 (5.11)	16,785 (4.93)	2,131 (7.09)	<0.001	17,029 (4.88)	1,887 (9.14)	<0.001
Hypertension				<0.001			<0.001
Yes	56,439 (15.20)	50,683 (14.90)	5,756 (19.20)		52,480 (15.00)	3,959 (19.20)	
No	292,071 (78.80)	269,632 (79.20)	22,439 (74.70)		276,651 (79.10)	15,420 (74.70)	
Missing	21,965 (5.90)	20,117 (5.90)	1,848 (6.20)		20,708 (5.90)	1,257 (6.10)	
Diabetes				<0.001			0.6107
Yes	253,991 (68.60)	232,788 (68.40)	21,203 (70.60)		239,881 (68.60)	14,110 (68.40)	
No	116,297 (31.40)	107,477 (31.60)	8,820 (29.40)		109,784 (31.40)	6,513 (31.60)	
Missing	187 (0.10)	167 (0.00)	20 (0.10)		174 (0.00)	13 (0.10)	
Insomnia				<0.001			<0.001
Yes	98,029 (26.50)	88,724 (26.10)	9,305 (31.00)		89,529 (25.60)	8,500 (41.20)	
No	272,278 (73.50)	251,559 (73.90)	20,719 (69.00)		260,157 (74.40)	12,121 (58.70)	
Missing	168 (0.00)	149 (0.00)	19 (0.10)		153 (0.00)	15 (0.10)	
New-onset	17,354 (4.68)	15,488 (4.55)	1,866 (6.21)	<0.001	15,998 (4.57)	1,356 (6.57)	<0.001
Dementia							
New-onset ALS	415 (0.11)	383 (0.11)	32 (0.11)	0.8356	393 (0.11)	22 (0.11)	0.8950
New-onset MS	832 (0.22)	736 (0.22)	96 (0.32)	<0.001	780 (0.22)	52 (0.25)	0.4352
New-onset PD	2,491 (0.67)	2,268 (0.67)	223 (0.74)	0.1312	2,337 (0.67)	154 (0.75)	0.1961
New-onset Stroke	13,264 (3.58)	11,980 (3.52)	1,284 (4.27)	<0.001	12,361 (3.53)	903 (4.38)	<0.001

Values are mean (SD) for continuous variables and n (%) for categorical variables; outcome rows report participants with incident events. Abbreviations: BMI, body mass index; TDI, Townsend deprivation index; ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; PD, Parkinson's disease.

Table 2. Associations of loneliness with major neurological disorders within polygenic risk score strata and interaction analyses

	Total N	Cases/person-years	HR (95% CI)	RERI (95% CI)[b]	P for interaction
Dementia					
Main analysis[a]	362,493	17,015/4,790,206	1.39 (1.31-1.47)		
Low	121,917	5,425/1,611,713	1.38 (1.24-1.52)	0.02 (-0.19-0.22)	0.786
Intermediate	119,900	5,559/1,585,119	1.41 (1.27-1.55)		
High	120,676	6,031/1,593,374	1.39 (1.26-1.54)		
MS					
Main analysis	361,860	806/4,837,879	0.98 (0.72-1.33)		
Low	120,621	97/1,614,237	1.42 (0.68-2.95)	-1.34 (-3.60-0.92)	0.156
Intermediate	120,620	201/1,612,798	1.06 (0.59-1.92)		
High	120,619	508/1,610,845	0.87 (0.57-1.31)		
PD					
Main analysis	361,860	2,436/4,833,873	1.30 (1.10-1.54)		
Low	120,622	496/1,613,391	1.28 (0.88-1.86)	0.04 (-0.78-0.87)	0.382
Intermediate	120,619	755/1,611,874	1.56 (1.17-2.07)		
High	120,619	1,185/1,608,608	1.15 (0.89-1.48)		
Stroke					
Main analysis	361,860	12,971/4,791,333	1.22 (1.14-1.31)		
Low	120,621	3,510/1,601,100	1.19 (1.04-1.37)	0.14 (-0.11-0.39)	0.716
Intermediate	120,619	4,250/1,598,997	1.22 (1.08-1.39)		
High	120,620	5,211/1,591,235	1.24 (1.11-1.38)		

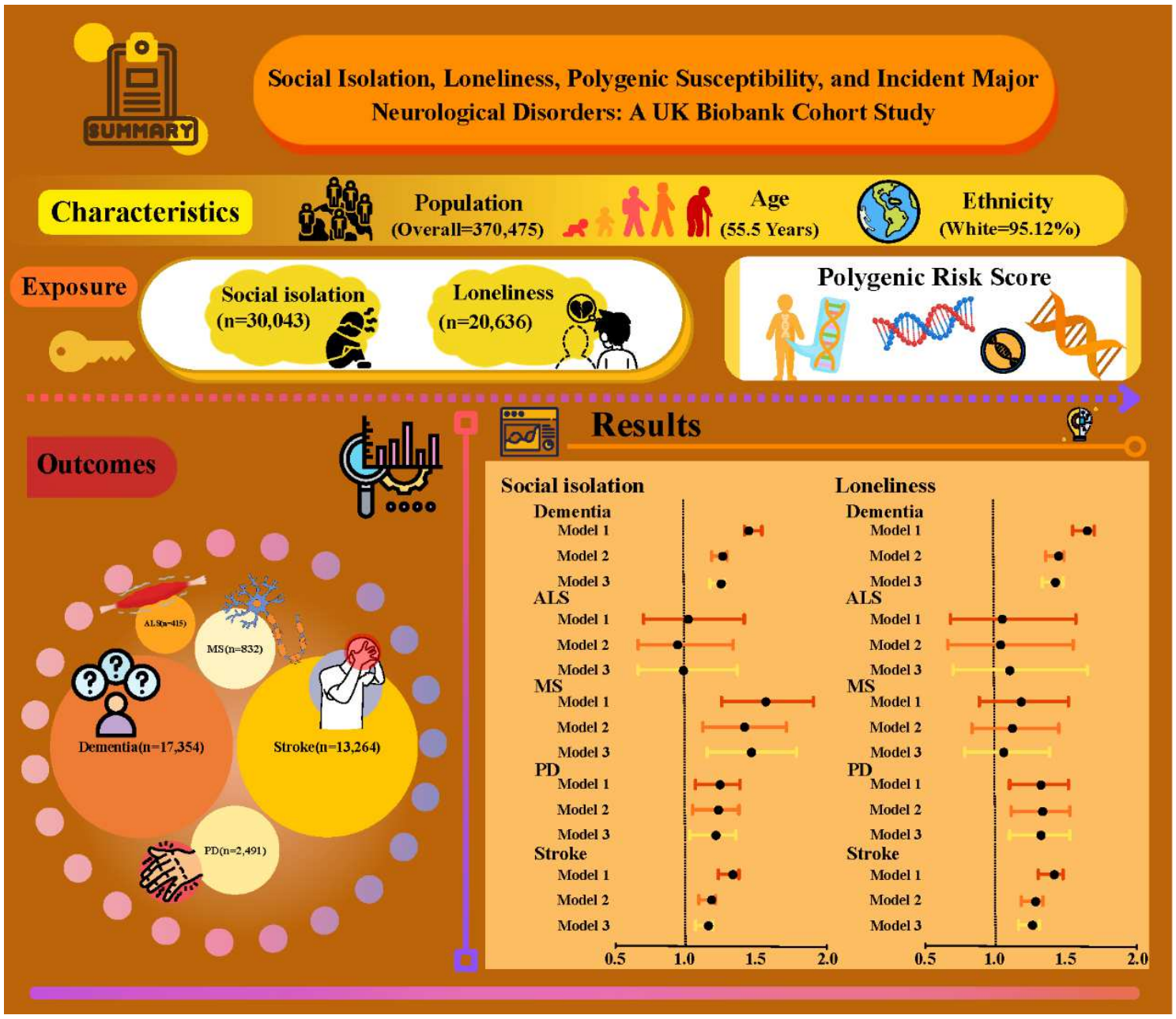
[a]Models in the main analysis row were adjusted for age, sex, ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, education, hypertension, diabetes, insomnia and first 10 principal components of ancestry.

Main analysis: On the basis of the main analysis adjusted for age, sex, ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, education, hypertension, diabetes, insomnia, further adjusted for PRS (category) and first 10 principal components of ancestry.

[b]RERI (95% CI) assessed additive interaction between the exposure and high versus low PRS; RERI = 0 indicates no additive interaction. Values are shown once per outcome.

Abbreviations: MS, multiple sclerosis; PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score; RERI, relative excess risk due to interaction.

Graphical abstract

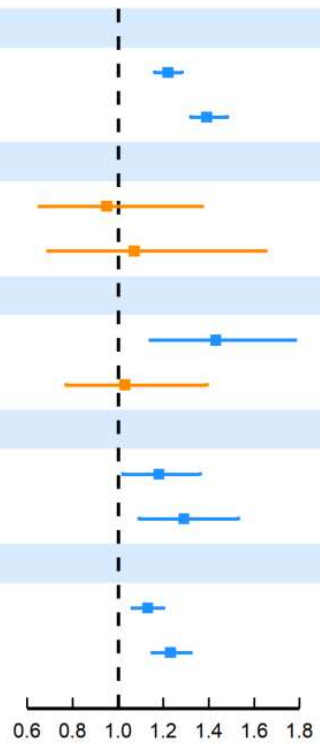


Overview of the study population, exposures, genetic risk, outcomes, and associations

Abbreviations: ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval.

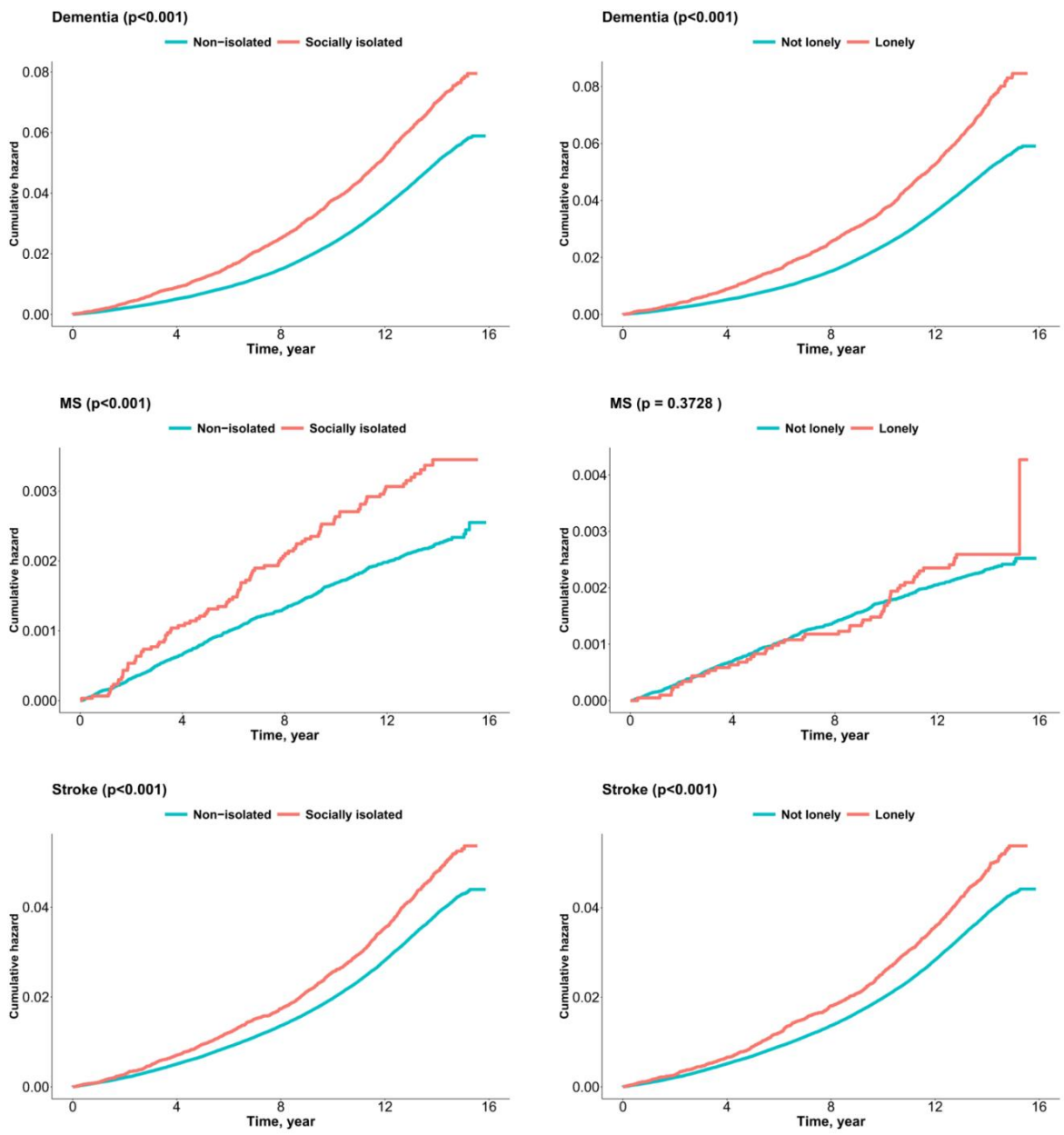
Figure 1. Forest plot of multivariable-adjusted associations of social isolation and loneliness with incident major neurological disorders

Outcomes	Case/PY	Incidence (per 1000 PY)	HR (95% CI)	P-value
Dementia				
Social isolation	17,354/4,893,251	3.55	1.22 (1.16-1.28)	<0.001
Loneliness			1.39 (1.32-1.48)	<0.001
ALS				
Social isolation	415/4,955,145	0.08	0.95 (0.65-1.37)	0.7753
Loneliness			1.07 (0.69-1.65)	0.7558
MS				
Social isolation	832/4,950,280	0.17	1.43 (1.14-1.78)	0.0018
Loneliness			1.03 (0.77-1.39)	0.8278
PD				
Social isolation	2,491/4,946,238	0.50	1.18 (1.02-1.36)	0.0259
Loneliness			1.29 (1.09-1.53)	0.0031
Stroke				
Social isolation	13,264/4,902,772	2.71	1.13 (1.06-1.20)	<0.001
Loneliness			1.23 (1.15-1.32)	<0.001



Squares indicate HRs and horizontal lines indicate 95% CIs. Nonisolated and nonlonely participants served as the reference groups. HRs were adjusted for age, sex, ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, education, hypertension, diabetes, and insomnia. Incidence rates are expressed per 1,000 person-years. Abbreviations: ALS, amyotrophic lateral sclerosis; MS, multiple sclerosis; PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; PY, person-years.

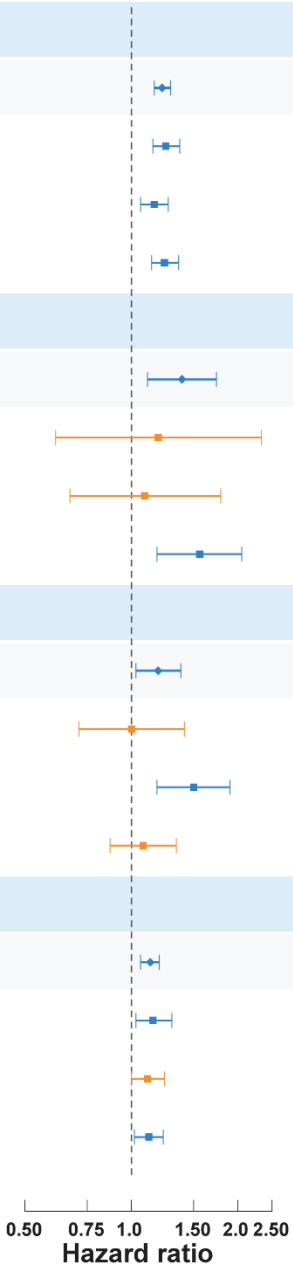
Figure 2. Cumulative hazard curves for dementia, multiple sclerosis, and stroke, stratified by social isolation and loneliness status



P values were calculated using log-rank tests.

Figure 3. Associations of social isolation with major neurological disorders within polygenic risk score and interaction analyses

Outcome	Total	Cases /person-years	Incidence	HR (95% CI)	RERI (95% CI)	P for interaction
Dementia					-0.02 (-0.18–0.13)	0.512
Main analysis	362,493	17,015/4,790,206	3.55	1.22 (1.16–1.29)		
Low PRS	121,917	5,425/1,611,713	3.37	1.25 (1.15–1.37)		
Intermediate PRS	119,900	5,559/1,585,119	3.51	1.16 (1.06–1.27)		
High PRS	120,676	6,031/1,593,374	3.79	1.24 (1.14–1.36)		
MS					2.48 (0.17–4.68)	0.372
Main analysis	361,860	806/4,837,879	0.17	1.39 (1.11–1.74)		
Low PRS	120,621	97/1,614,237	0.06	1.19 (0.61–2.33)		
Intermediate PRS	120,620	201/1,612,798	0.12	1.09 (0.67–1.79)		
High PRS	120,619	508/1,610,845	0.32	1.56 (1.18–2.05)		
PD					-0.17 (-0.45–0.80)	0.764
Main analysis	361,860	2,436/4,833,873	0.50	1.19 (1.03–1.38)		
Low PRS	120,622	496/1,613,391	0.31	1.00 (0.71–1.41)		
Intermediate PRS	120,619	755/1,611,874	0.47	1.50 (1.18–1.90)		
High PRS	120,619	1,185/1,608,608	0.74	1.08 (0.87–1.34)		
Stroke					0.02 (-0.18–0.22)	0.785
Main analysis	361,860	12,971/4,791,333	2.71	1.13 (1.06–1.20)		
Low PRS	120,621	3,510/1,601,100	2.19	1.15 (1.03–1.30)		
Intermediate PRS	120,619	4,250/1,598,997	2.66	1.11 (1.00–1.24)		
High PRS	120,620	5,211/1,591,235	3.27	1.12 (1.02–1.23)		



Models in the main analysis row were adjusted for age, sex, ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, education, hypertension, diabetes, insomnia and first 10 principal components of ancestry.

Main analysis: On the basis of the main analysis adjusted for age, sex, ethnicity, BMI, TDI, alcohol consumption, smoking, physical activity, education, hypertension, diabetes, insomnia, further adjusted for PRS (category) and first 10 principal components of ancestry. RERI (95% CI) assessed additive interaction between the exposure and high versus low PRS; RERI = 0 indicates no additive interaction.

Abbreviations: MS, multiple sclerosis; PD, Parkinson's disease; HR, hazard ratio; CI, confidence interval; PRS, polygenic risk score; RERI, relative excess risk due to interaction.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfigure20261011.docx