Unravelling the behavioural and genetic associations between social isolation and Alzheimer's disease risk: insights from population-scale studies

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Table of Contents

Abstract

Alzheimer's disease and related dementias (ADRD) represent a significant and growing public health burden, exacerbated by increased longevity. Recent clinical evidence suggests that social isolation may expedite dementia onset. This thesis combines findings from two population-scale studies to explore the genetic and behavioural associations between social isolation and ADRD risk. We analyzed data from 502,506 UK Biobank participants and 30,097 participants from the Canadian Longitudinal Study of Aging, revisiting traditional dementia risk factors within the context of loneliness and lack of social support. By employing a tailored Bayesian hierarchical framework, our objective was to directly quantify the probabilistic association of traditional ADRD risk to social isolation, while providing coherent estimates of associated uncertainty. Our results reveal strong links between individuals' social capital and various ADRD risk indicators. These associations replicated across both cohorts and highlighted the deep connections between daily social encounters and key aetiopathological factors of ADRD, including personal habits, lifestyle factors, physical health, mental health, and societal and external factors. Our findings underscore the importance of social lifestyle determinants as promising targets for preventive clinical action. We further investigated the genetic underpinnings of social isolation and ADRD risk using genetic data from 361,129 UK Biobank participants. Through cell-type- and tissue-specific analyses, we identified genetic variants associated with both social isolation and ADRD risk factors. By integrating genome-wide association studies (GWAS) from 80 well-established ADRD risk phenotypes and 10 GWAS on ADRD and examining gene expression in specific cell types and tissues, we uncovered overlaps between the genetic architecture underlying ADRD risk and social isolation across multiple body systems, not just the brain. This genetic interlocking suggests that social lifestyle determinants

are intertwined with ADRD-related neurodegeneration risk factors, providing crucial insights into potential intervention points. Overall, our population-scale assessments suggest that social isolation is intricately connected to ADRD risk through both behavioural and genetic pathways. These findings highlight the modifiability of social behaviours as a strategic avenue for reducing ADRD risk.

La maladie d'Alzheimer et les démences apparentées (MADA) représentent un fardeau de santé publique important et croissant, exacerbé par l'augmentation de la longévité. Des preuves cliniques récentes suggèrent que l'isolement social peut accélérer l'apparition de la démence. Cette thèse combine les résultats de deux études à grande échelle pour explorer les associations comportementales et génétiques entre l'isolement social et le risque de MADA. Nous avons analysé les données de 502 506 participants de la UK Biobank et de 30 097 participants de l'Étude longitudinale canadienne sur le vieillissement, en revisitant les facteurs de risque traditionnels de démence dans le contexte de la solitude et du manque de soutien social. En utilisant un cadre hiérarchique bayésien adapté, notre objectif était de quantifier directement l'association probabiliste des risques traditionnels de MADA avec l'isolement social, tout en fournissant des estimations cohérentes de l'incertitude associée. Nos résultats révèlent des liens étroits entre le capital social des individus et divers indicateurs de risque de MADA. Ces associations se sont reproduites dans les deux cohortes et ont mis en évidence les profondes connexions entre les rencontres sociales quotidiennes et les principaux facteurs étiopathologiques de la MADA, y compris les habitudes personnelles, les facteurs de mode de vie, la santé physique, la santé mentale, ainsi que les facteurs sociétaux et externes. Nos résultats soulignent l'importance des déterminants du mode de vie social comme cibles prometteuses pour

des actions cliniques préventives. Nous avons également étudié les bases génétiques de l'isolement social et du risque de MADA en utilisant des données génétiques de 361 129 participants de la UK Biobank. À travers des analyses spécifiques aux types de cellules et aux tissus, nous avons identifié des variantes génétiques associées à la fois à l'isolement social et aux facteurs de risque de MADA. En intégrant des études d'association génomique (GWAS) de 80 phénotypes de risque de MADA bien établis et de 10 GWAS sur la MADA, et en examinant l'expression génique dans des types de cellules et des tissus spécifiques, nous avons découvert des chevauchements entre l'architecture génétique sous-jacente au risque de MADA et l'isolement social à travers plusieurs systèmes corporels, et non seulement le cerveau. Cette intersection génétique suggère que les déterminants du mode de vie social sont imbriqués avec les facteurs de risque de neurodégénérescence liés à la MADA, fournissant des perspectives cruciales sur les points d'intervention potentiels. Dans l'ensemble, nos évaluations à l'échelle de la population suggèrent que l'isolement social est étroitement lié au risque de MADA à travers des voies comportementales et génétiques. Ces résultats mettent en lumière la modifiabilité des comportements sociaux comme une avenue stratégique pour réduire le risque de MADA.

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Contribution of Authors

Chapter 1: Social isolation is linked to classical risk factors of Alzheimer's disease-related dementias

Kimia Shafighi and Danilo Bzdok conceptualized the study. Kimia Shafighi analyzed the data and performed the statistical analyses. Kimia Shafighi and Danilo Bzdok interpreted the results. Kimia Shafighi and Vaibhav Sharma worked on data preprocessing and the design of analytic pipelines. Danilo Bzdok supervised the project. Kimia Shafighi, Sylvia Villeneuve, AmanPreet Badhwar, Pedro Rosa-Neto, Yasser Iturria-Medina, Patricia P Silveira, Vaibhav Sharma, Laurette Dube, Judes Poirier, David Glahn, and Danilo Bzdok contributed to the writing of the manuscript.

Chapter 2: Intersecting genetic mechanisms of social isolation and classic Alzheimer's disease risk factors

Kimia Shafighi and Danilo Bzdok conceptualized the study. Kimia Shafighi analyzed the data and performed the statistical analyses. Kimia Shafighi and Danilo Bzdok interpreted the results. Kimia Shafighi worked on data preprocessing. Kimia Shafighi, Sarah A. Gagliano Taliun, and Danilo Bzdok designed the genetic analytic pipelines. Danilo Bzdok supervised the project. Kimia Shafighi, Sarah A. Gagliano Taliun, Sali Farhan , Sylvia Villeneuve, AmanPreet Badhwar, Maiya Geddes, Judes Poirier, and Danilo Bzdok contributed to the writing of the manuscript.

List of Abbreviations

AD	Alzheimer's disease
ADRD	Alzheimer's disease and related dementias
APOE	Apolipoprotein E
CIHR	Canadian Institutes of Health Research
CLSA	Canadian Longitudinal Study on Aging
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
FDR	False discovery rate
FUMA	Functional Mapping and Annotation of Genome-wide association studies
GTEx	Genotype-Tissue Expression
GWAS	Genome-wide association studies
HPA	Hypothalamus-pituitary-adrenal
h^2_{SNP}	SNP-based heritability
ICT	Information and communications technology
LDSC	Linkage disequilibrium score regression
MA	Maladie d'Alzheimer
MADA	La maladie d'Alzheimer et les démences apparentées
MAGMA	Multi-marker Analysis of GenoMic Annotation
Mila	Quebec Artificial Intelligence Institute
MNI	Montreal neurological institute
NIH	National Institutes of Health
PCA	Principle component analysis
PLS	Partial least square
PLS-R	PLS-regression
PRS	Polygenic risk score
PTSD	Post-traumatic stress disorder
SE	Standard error
SNP	Single nucleotide polymorphism
s-LDSC	Stratified linkage disequilibrium score regression

UKBB	UK Biobank
WHO	World Health Organization

Introduction

Alzheimer's disease and related dementias (ADRD) represent a significant and growing public health crisis, exacerbated by increased longevity and an aging global population. With no known cure, this devastating condition incurs approximately $1 trillion in global costs annually, placing a considerable burden on patients, caregivers, and society at large [1]. Over 50 million people worldwide are currently living with dementia, and the number of ADRD cases is projected to triple by 2050, underscoring the urgency for effective prevention and treatment strategies [2]. Compounding this public health issue, there is now mounting evidence that social isolation is associated with an increased risk of ADRD, highlighting the critical role of social connections in cognitive health [3-9]. Recognizing the severity of these conditions, the World Health Organization (WHO) has identified ADRD and social isolation, separately, as global public health priorities [10, 11]. Both challenges may now be further aggravated due to chronic social deprivation as a consequence of the COVID-19 outbreak [12, 13]. The pandemic led to unprecedented levels of social isolation due to widespread lockdowns, stringent social distancing measures, and disruptions to regular social activities. This mass social isolation as a consequence of the COVID-19 mitigation strategies may have profound long-term effects on cognitive health, particularly among older adults [13].

Despite significant advances in understanding the aetiopathological antecedents of ADRD, our ability to slow the progression of this major neurodegenerative disease remains limited. A recent authoritative report on dementia prevention reported that up to 40% of ADRD risk is attributable to potentially modifiable factors [2]. These risk factors encompass a wide range of

personal, lifestyle, physical, mental, and societal dimensions. They include childhood education, physical exercise, socioeconomic status, smoking, alcohol consumption, hearing and vision loss, depression, diabetes, hypertension, sleep apnea, air pollution, and obesity. However, our understanding of how these risk factors are interrelated with social factors remains incomplete. A more comprehensive characterization of social behaviours could enable a more complete conceptualization of ADRD risk. Factors like loneliness, which reflects subjective social isolation, and regular social support, indicating objective social isolation, are often overlooked in ADRD risk models. While these social aspects have historically received less attention compared to other ADRD risk factors, they are increasingly attracting the interest of researchers, stakeholders, and policymakers. This emerging focus is imperative, as social behaviours are modifiable in principle through societal measures, unlike genetically determined risk factors [14].

Loneliness is defined as the distressing feeling that one's social needs are not being met by one's current social relationships and available social venues [15]. Loneliness is a universal human experience and a particularly significant issue among older adults. Studies in Europe [16-20] and North America [17, 21, 22] have reported a prevalence of loneliness among older adults ranging from 10% to 30%. These levels of loneliness may have escalated since the COVID-19 pandemic, with significant implications for public health. There is now emerging evidence linking loneliness to accelerated cognitive decline [23-25] and an increased risk of dementia [26, 27]. For instance, the Amsterdam Study of the Elderly found that among 2,173 older adults without dementia, those who reported experiencing subjective social isolation (e.g., feeling lonely) had a higher risk of developing dementia over a 3-year follow-up period [28]. Notably, this study controlled for demographic, somatic, and psychiatric risk factors. Still, despite these controls, individuals

experiencing social isolation remained 1.64 times more likely to develop clinical dementia compared to those who did not report loneliness. Distinct from perceived social isolation (i.e., loneliness), lack of social support – an indicator of objective social isolation – is characterized by the absence of regular interactions with members of strong and supportive social networks [29]. While a robust social network may not necessarily alleviate feelings of loneliness, and solitude does not always imply loneliness [15], these aspects of social isolation are often conflated despite being conceptually distinct. High levels of loneliness and lack of social support have both been strongly and independently [30] related to various negative health outcomes, particularly among the elderly, including immune system dysfunction [31], coronary heart disease [32], cognitive decline [33, 34], psychological distress, and shortened life expectancy [33]. This growing body of evidence underscores the urgent need for targeted interventions to reduce loneliness and enhance social support networks to mitigate the risk of cognitive decline and dementia. Studying the role of social lifestyle in ADRD onset should therefore acknowledge determinants of both subjective loneliness feelings and objective social support frequency.

To gain a holistic understanding of ADRD onset, we aimed to systematically revisit a comprehensive list of classical ADRD risk factors and explore their associations with both subjective loneliness and objective social support. Our investigation extended beyond behavioural associations, delving into the genetic underpinnings of social isolation and ADRD risk to examine how the genetic architecture of social isolation intersects with classical ADRD risk factors. The etiology of ADRD is multifaceted, involving a complex interplay of genetic, environmental, and lifestyle factors. Among these, the apolipoprotein E (APOE) gene stands out as the most explanatory genetic risk factor for ADRD [35, 36], playing a critical role in lipid transport and

immune regulation. APOE is responsible for maintaining fat homeostasis by mediating lipid transport and is highly expressed in the brain, liver, and peripheral immune cells [37, 38]. Notably, APOE exhibits an increased inflammatory response in the central nervous system and peripheral tissues, suggesting a pivotal role in the immune dysregulation observed in Alzheimer's disease pathogenesis [39, 40]. However, despite significant strides in understanding these genetic and molecular mechanisms, the field continues to grapple with controversies regarding the exact pathways driving Alzheimer's disease pathology.

The amyloid cascade hypothesis, which posits that the accumulation of amyloid-beta (Aβ) plaques in the brain is the primary cause of neurodegeneration, has long dominated research [41, 42]. Yet, the failure of numerous amyloid-targeting therapies to yield substantial clinical benefits has led to increasing scrutiny of this theory, raising questions about whether amyloid accumulation is a cause or consequence of the disease [43, 44]. Moreover, the tau hypothesis, which implicates the hyperphosphorylation of tau proteins and the formation of neurofibrillary tangles, offers an alternative or complementary pathway [45]. Recent research indicates that a more intricate interplay of genetic, cellular, and environmental factors—including neuroinflammation, vascular contributions, and mitochondrial dysfunction—may drive Alzheimer's pathology [2, 46, 47]. These controversies highlight the necessity for a broader investigative approach that considers multiple factors, including the role of social isolation and its potential impact on neuroinflammation and other neurodegenerative processes.

Previous studies have also identified a heritable component to loneliness, with genetic factors explaining a significant portion of individual differences. Twin and family studies have

estimated the genetic contribution to loneliness to be between 37% and 77% [48] , while molecular genetic variants account for 14% to 27% of individual differences [49]. These observations suggest an innate component to the propensity of feeling lonely. Given that both ADRD and loneliness have significant heritable components, understanding the genetic architecture underlying both social isolation and ADRD risk is crucial for elucidating their potential interrelationship. By integrating genetic insights with our behavioural analysis, we aim to provide a more comprehensive view of how social isolation contributes to ADRD risk from both a behavioural and genetic perspective. This approach not only deepens our understanding of ADRD risk but also elucidates the intricate interplay between genetic predispositions and the manifestation of social isolation and neurodegenerative diseases.

To address these objectives, we capitalized on the UK Biobank (UKBB) [50] and the Canadian Longitudinal Study on Aging (CLSA) [51], two of the largest and most comprehensive population-based cohort studies, providing extensive genetic, phenotypic, and health data. We utilized data from 502,506 UKBB participants and 30,097 CLSA participants for our behavioural analyses. With these extensive population cohorts [52, 53], we hypothesized that both subjective loneliness and objective social support show robust associations with major ADRD risk factors. In addition, we investigated the genetic overlap between social isolation and ADRD risk using data from 361,129 UKBB participants and 22,741 CLSA participants. The rare depth of phenotyping in these cohorts provides an exceptional opportunity to investigate the interplay between lifestyle, physical health, mental health, and societal factors, offering a comprehensive view of the classical, widely acknowledged aetiopathological factors of ADRD. By employing genome-wide association studies (GWAS) summary statistics, we explored the genetic

mechanisms that link indicators of social isolation to a range of classical ADRD risk traits. GWAS is a powerful tool that allows us to scan the entire genome for variants associated with specific traits, providing a comprehensive overview of the genetic landscape. Unlike polygenic risk scores (PRS) or Mendelian Randomization, GWAS does not rely on predefined genetic markers or assumptions about causal pathways, making it particularly useful for identifying novel genetic associations between social isolation and ADRD risk. A key component of our analysis was the use of partitioned heritability and gene-set analyses, which allowed us to assess how genetic variants contribute to social isolation and ADRD risk across different tissues, cell types, and functional genomic categories. This comprehensive analysis helps us understand the cell type- and tissue-specific genetic influences and how they might intersect between social isolation and ADRD. By leveraging over 500 cell-type and tissue-specific annotations from diverse functional genomic studies, we elucidated how genetic factors might shape the relationships between social isolation and ADRD risk, providing deeper insights into the shared genetic architecture and biological mechanisms underlying these conditions.

Overall, our research underscores the critical need to consider both subjective and objective social isolation in the context of ADRD risk. Our comprehensive investigation into the genetic and behavioural associations between social isolation and ADRD risk provides new insights into potential intervention points. We hypothesized that the findings from our population-scale studies would suggest that social isolation is intricately connected to ADRD risk through both behavioural and genetic pathways. Addressing social isolation, particularly among the elderly, through targeted interventions could significantly mitigate the burden of ADRD and improve the quality of life for affected individuals and their caregivers.

Chapter 1: Social isolation is linked to classical risk factors of Alzheimer's disease-related dementias

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Abstract

Alzheimer's disease and related dementias is a major public health burden – compounding over upcoming years due to longevity. Recently, clinical evidence hinted at the experience of social isolation in expediting dementia onset. In 502,506 UK Biobank participants and 30,097 participants from the Canadian Longitudinal Study of Aging, we revisited traditional risk factors for developing dementia in the context of loneliness and lacking social support. Across these measures of subjective and objective social deprivation, we have identified strong links between individuals' social capital and various indicators of Alzheimer's disease and related dementias risk, which replicated across both population cohorts. The quality and quantity of daily social encounters had deep connections with key aetiopathological factors, which represent 1) personal habits and lifestyle factors, 2) physical health, 3) mental health, and 4) societal and external factors. Our population-scale assessment suggest that social lifestyle determinants are linked to most neurodegeneration risk factors, highlighting them as promising targets for preventive clinical action.

Introduction

Alzheimer's disease and related dementias (ADRD) is a growing public health crisis. With no known cure, this devastating condition generates ~1 trillion global costs every year and places a considerable burden on patients, caregivers, and society [1]. The number of ADRD cases is estimated to triple by 2050 [2]. In a parallel development, there is now rapidly growing evidence that social isolation is associated with an escalated risk of ADRD [3-8]. In fact, the World Health Organization (WHO) has identified ADRD and social isolation, separately, as two global public health priorities [9, 10]. Both challenges may now be aggravating due to social deprivation as a consequence of the COVID-19 pandemic: many cities, states, and nations have imposed stringent social distancing measures – leading to probably the largest mass social isolation in recorded history.

Substantial progress has been made in delineating aetiopathological antecedents of this major neurodegenerative disease. While we have identified some biomarkers and short-term treatment of symptoms, our ability to attenuate the trajectory of neurodegenerative progression remains limited. As a source of hope, a recent consensus article [11] reported that potentially modifiable factors in ADRD amount to as much as 40% of the overall disease risk. Widely agreed upon risk factors include childhood education, exercise, socioeconomic status, smoking, alcohol consumption, hearing and vision loss, depression, diabetes, hypertension, sleep apnea, air pollution and obesity [11]. However, we still have a clouded understanding of how these risk factors are linked to social lifestyle. The relevance of subjective and objective social isolation for ADRD risk in relation to other commonly studied risk factors is only now attracting the attention of researchers, stakeholders, and policy makers. The premise of our study is that a wider

characterization of these social behaviors in late life will enable a more complete conceptualization of ADRD risk, potentially paving the way for novel treatment avenues. Such new insight is imperative given that social behaviors are modifiable in principle through societal measures [12] in contrast to genetically determined risk. Social factors like loneliness, as a measure of *subjective* social isolation, and regular social support, as a measure of *objective* social isolation, are rarely considered in risk models or authoritative surveys of ADRD aetiopathology. This knowledge gap is particularly blatant when one considers social deprivation in the elderly.

There is substantial evidence that acceleration in cognitive decline [13-15] and increased dementia risk [16, 17] co-occurs with loneliness in individuals, which is also indicated by greater ADRD-related neuropathology [13, 18]. These pointers suggest that perceived social isolation plays an important and potentially independent role from objective social isolation in normative brain aging and its aberrations in neurodegenerative disease. Different facets of social isolation – loneliness, social network, social engagement, and social support – have been associated with poor health outcomes, including hypertension and immune system dysfunction [19, 20], cognitive decline [14, 21, 22], psychological distress (e.g. depression, anxiety), increased dementia risk [5] and shortened life expectancy [23]. Studying the role of social lifestyle in ADRD onset should therefore acknowledge determinants of both subjective loneliness feelings and objective social support frequency. Here, we have systematically revisited classical, widely acknowledged aetiopathological factors closely linked to ADRD by capitalizing on two unique cohorts: 502,506 participants from the UK Biobank [24] and 30,097 participants from the Canadian Longitudinal Study of Aging [25]. Empowered by the advent of the UK Biobank and CLSA cohorts [26, 27], we have tested the hypothesis that subjective loneliness and objective social support show robust

associations with major ADRD risk factors. Narrowing this knowledge gap is particularly urgent when considering less well studied risk factors like late-life behaviors, including subjective and objective social isolation – which were recently exacerbated as a consequence of the COVID-19 pandemic.

Results

We set out to systematically explore possible links between major ADRD risk factors and rarely considered determinants of social isolation. Using a fully probabilistic approach, we carefully estimated the degree to which subjective and objective social isolation show population associations with established ADRD risk factors in the wider society. All our analyses reported in the following have been accounted for variation that can be explained by differences in participant age and sex. In the following, we present a series analysis of ADRD risk factors in four categories: 1) personal habits & lifestyle factors, 2) physical health factors, 3) mental health factors, and 4) societal & external factors, in similar measurements from the UKBB and the CLSA cohorts.

Several rich cross-associations identified between social lifestyle and ADRD risk factors

We first performed a partial least squares analysis resulting in pairs of canonical vectors. We assessed whether the social indicators, including our target variables loneliness and lack of social support, were associated with the classical risk traits of ADRD. The multivariate pattern-learning approach revealed the constellations of features that carry consistent associations within both high-dimensional variable sets (i.e., the risk traits and the social indicators). The total variance explained of the original data matrices, shown separately for risk traits and social measures in Fig 1, is mapped for 7 PLS modes in the UKBB and 6 PLS modes in the CLSA. The canonical correlation for each mode quantified the linear correspondence between the two variable sets based on Pearson's correlation between their canonical variates [40]. In other words, the PLS analysis described the relationship between the first set of variables (the social indicators) and the second

set of variables (the classical risk traits of ADRD). In both cohorts, a majority of the risk factors were linked to social lifestyle factors in at least one of the uncovered modes of joint variation.

In the UKBB cohort, the first mode, by construction, explained a larger fraction of variation than any other mode, with a canonical correlation *rho* of 0.471 between the sets of variables. For the first canonical mode, interindividual differences in social richness dominated by loneliness (0.682) and lack of social support (0.437) were strongly paired with the personality traits among the ADRD risk factors, and the neuroticism score (0.408) in particular. The neuroticism score in the UKBB is defined as a composite score of 12 neurotic behavioural domains, which includes the loneliness item. The score ranges from zero to twelve, with a higher score indicating a higher degree of neurotic behaviour. Across the 7 modes, social determinants were related to lifestyle factors (e.g., exercise), mental health factors (e.g., personality), and societal factors (e.g., income). In the CLSA cohort, the variance in the first mode (*rho*=0.500) was best explained by interindividual differences in loneliness (0.652) and lack of social support (0.512) among the social factors, and by watching TV (0.321) and getting a positive screen for depression (0.364) for the risk traits. The PLS analysis on the UKBB and the CLSA indicated that the examined social determinants reflected the risk factors of ADRD from each of the three pillars (lifestyle, mental health, and societal), in at least one of the modes of joint variation, while the associations with the physical health measures were consistently weak. Across both cohorts, the social domain of the first mode – which by construction, explains a larger fraction of variation than any other mode – was dominated by loneliness and lack of social support, which happen to be the two representative measures of subjective and objective social isolation throughout the present paper.

Bayesian regression between two determinants of social isolation and ADRD risk factors

Using a fully probabilistic approach, we next carefully estimated the degree to which subjective and objective social isolation show population associations with established ADRD risk factors in the wider society. The Bayesian framework provided a unique approach to explore relevant ADRD risk traits. The estimated posterior parameter distributions, resulting from the Bayesian analyses, implied that the social isolation measures – loneliness or lack of social support – had strong associations with target ADRD risk. The elected model was the same for all considered target risk factors. The full posterior parameter distributions – not sampling distributions – from our Bayesian modeling solutions for each variable of interest can be found in the Supporting Information (cf. S1 Figs 1-4). For brevity, we here report the mean and the 90% highest posterior density interval (HPDI) of the model parameters, after seeing the data, which contains the 90% most credible parameter solutions in Table 1, summarized in the bar plots of Figs 2 to 5. The height of each bar plot refers to the mean value and the black error bars indicate the 90% HDPI of the effects of loneliness and lack of social support.

Personal Habits & Lifestyle Factors

Taken together, our results showed statistically defensible links between both social determinants and the classical lifestyle risk factors of ADRD, which were replicated in the 502,506 UKBB and the 30,097 CLSA participants (Fig 2). Individuals who smoked more, excessively drank alcohol, experienced sleep disturbances, and failed to frequently participate in light to vigorous physical activities had greater odds of being lonely and lacking social support. In the UKBB, a higher number of cigarettes currently smoked was associated with a 19.7% increase in

the odds of feeling lonely. In addition, more frequent tobacco smoking corresponded to 10.2% increase in the odds of weak social support. In the CLSA, increasing regular participation in physical exercise with other people resulted in 20.1% decrease in the odds of feeling lonely and 26.9% decrease in having poor social support. Watching TV showed strong effects on increased feelings of loneliness and poor social support, while using the computer was linked with less loneliness and better social support. We also found that participating in religious activities was associated with reduced subjective and objective social isolation.

Physical Health Factors

We observed mutually confirmatory results between the CLSA and the UKBB among the physical health factors (Fig 3). Cardiovascular diseases were consistently associated with greater loneliness and lacking social support, with distinct stronger effects on loneliness in the UKBB. We discovered greater associations between the social determinants and vision impairments in the CLSA, and further found that CLSA participants that use specialized aids for persons who are blind or visually impaired had greater odds of feeling lonely and lacking social support. Diabetes and hearing impairment, both recognized risk factors of dementia, showed prominent links with subjective and objective social isolation across both cohorts. In the UKBB, difficulty to hear with background noise corresponded to a 29.0% increase in the odds of feeling lonely and a 9.86% increase in the odds of lacking social support. Still within the UKBB, individuals who used a hearing aid had reduced levels of loneliness and better social support. For the physical health factors in particular, the model uncertainty of our effects – indicated by wider posterior parameter

distribution – was greater in the CLSA, attributable to the smaller set of data available in the CLSA relative to the UKBB.

Mental Health Factors

Collectively, mental health factors revealed strong population associations with both subjective and objective social isolation (Fig 4). All the different measures of personality, corresponding to neurotic and depressive behaviours, showed the largest associations with both subjective and objective social determinants, across the UKBB and the CLSA cohorts. In particular, the neuroticism score in the UKBB showed the greatest effect for loneliness and lack of social support. The odds of feeling lonely and lacking social support were 3.7 and 1.4 times greater, respectively, as a function of the neuroticism score. Further, we observed in both cohorts that feelings of happiness had a strong notable link with reduced loneliness and poor social support. We also found relevant associations between an individual's social capital and determinants of mental distress such as depression and anxiety.

Societal & External Factors

Overall, our results revealed that the opportunities for social interactions and the quality of these social exchanges held strong associations with loneliness and lack of social support in both datasets (Fig 5). In both cohorts, we found that individuals who shared their home with many people, and frequently participated in family or friendship activities were less often lonely and had better social support. In the UKBB, individuals who expressed greater satisfaction with their

family relationship and their friendships revealed that the quality of social exchange also held salient effects on loneliness and lacking social support. And in the CLSA, a one unit increase in the number of close friends corresponded to 21.3% decrease in the odds of feeling lonely, and 48.8% decrease in the odds of lacking social support. However, in both the UKBB and the CLSA cohorts, we observed that having a greater number of siblings showed notable effects on increased feelings of loneliness and lacking social support. Further, we found salient links between the two measures of social isolation and socioeconomic status, measured as a combination of income, occupation, and education. In the UKBB, receiving a higher average household income corresponded to a decrease in the odds of feeling lonely and lacking social support by 33.5% and 20.6%, respectively. Finally, in both the UKBB and CLSA, living in an urban environment, as opposed to a rural setting, was associated with higher levels of loneliness and poor social support.

Discussion

The present study brings into sharp focus the multifaceted nature of inter-relationships between social isolation and major ADRD risk factors. Our collective findings suggest that both perceived and factual social capital – loneliness and lack of social support – are consistently associated with classical ADRD risk factors, after accommodating effects for age and sex differences. To the best of our knowledge, this is the first study that explicitly targeted possible links between social isolation and a comprehensive array of most studied risk factors of ADRD, which we have here demonstrated using data from two nationally representative population cohorts of older adults from two different countries.

Among the examined measures of personal habits and lifestyle factors, sleep serves as a prototypical representative that showed several, and some of the largest, associations with social isolation, which successfully replicated across the UK Biobank and the CLSA cohorts. We found that all our measures of sleep disturbance had strong associations with loneliness and lack of social support across both cohorts. Similar to our findings, objective social isolation and self-reported loneliness have previously been linked to reduced sleep efficiency and poor sleep quality [41-44]. Other investigators have hypothesized that perceived social isolation relates to hypervigilance for social threats [20], which in turn increases anxiety and reduces sleep quality. Consistent with this idea, many reports have shown that feelings of loneliness and reduced social support occur especially in individuals who report higher stress levels [45-47]. Stress pile-up and emotional coping have been argued previously to contribute to the underlying reasons why lonely people are more often smokers [48], binge drinkers [49], and binge-watchers [50, 51]. Interpersonal buffering, such as provided by subjective and objective social support, have been argued to be important

psychosocial resources to cope with stressors [48, 52]. There is a growing body of evidence that sleep disturbance [53], smoking cigarettes [54, 55], excessive alcohol consumption [56], and excessive television viewing [57, 58] are all linked to cognitive decline and the development of ADRD. Our findings across two large cohorts showed that these potentially modifiable lifestyle factors that affect the onset of dementia have large associations with both loneliness and lack of social support.

Charting a series of physical health factors, notably cardiovascular conditions, diabetes, and physical exercise, we have shown all to feature some link to social isolation status, which corroborated across both cohorts. Our results are in line with existing research showing a detrimental effect of objective social isolation on subsequent dementia through cardiovascular pathways, by increasing the risk of hypertension [59] and coronary heart disease [60]. There is accumulating evidence that associates heart disease risk factors – diabetes, hypertension, obesity, smoking cigarettes – with late-life risk of cognitive impairment and dementia [61, 62]. Moreover, participation in physical activities has been associated with better vascular health and lower risks of high cholesterol and diabetes [63] and regular physical exercise has repeatedly been shown to significantly reduce the risk of developing of dementia. Aside from the cardiovascular benefits, we explicitly showed that the social aspect of physical exercise was also important in relation to loneliness and social support. Consistent with our results, one study found that aerobic physical activities done alone did not seem to have any cognitive benefits in 754 healthy older adults [64].

Among the considered mental health factors and all our examined measures in general, we found personality traits to feature the largest associations with social isolation, replicated across

both cohorts. Our previous research has also shown a relation between personality traits and social isolation in genome-wide assessments in the UK Biobank [12]. The neuroticism score, which reflects a person's level of emotional volatility and vulnerability to stress, showed one the strongest effect size for loneliness and lack of social support, in the context of all the examined ADRD risk factors. Greater levels of late-life neuroticism have been previously associated with higher risk of developing mild cognitive impairment [65] and dementia [66-68]. Hostinar & Gunnar [69] showed that through a phenomenon termed the social buffering of stress, specific personality traits can affect an individual's susceptibility to the effects of stressors, while social support can dampen physiological stress responses [70].

By the same token, the well-established 'cognitive reserve' hypothesis claims that intellectual enrichment provides a cognitive buffer to deal with injuries to the nervous system [71], which is an overarching theme among the societal factors. In our rich datasets, we had the opportunity to concurrently examine the possible associations of numerous factors related to cognitive load, including education levels, socioeconomic status, computer use, sensory impairment, and different aspects of social interaction. Although, the relationship between social isolation and cognitive reserve is only now receiving increasing attention [72-74], we found consistently striking associations between these potentially modifiable societal factors and both loneliness and lack of social support, paralleled across two large cohorts, despite the slight difference in measures examined for the same construct between the two cohorts. Other investigators have suggested that interventions targeting social isolation and promoting a socially active lifestyle in later life may enhance cognitive reserve and reduce the risk of dementia [73].

Given the current conceptual framework of this paper, our discussion revolves around dementia more broadly rather than Alzheimer's disease in particular. In line with recent research on different biomarkers combinations in individual ADRD prognosis [75], our results also open the possibility for individual differences in the combinations of ADRD risk markers that are impacted by either or both subjective and objective social isolation. As our main contribution to the dementia literature, our study offers a comprehensive overview of the wide-ranging population-level associations between social deprivation and many ADRD risk factors.

Conclusion

Our understanding about the implications of social isolation on ADRD remains in its infancy relative to the current evidence on other classical risk factors. However, our findings show a large array of associations between these potentially modifiable risk factors and both loneliness and lack of social support. Our collective findings underscore the importance of exploring subjective and objective social isolation in depth to inform policy interventions, especially among the elderly. Compared to other ADRD risk factors, such as ApoE4 genotype, social isolation is arguably easier to modify, and therefore, particularly promising to target and alter. As the persistence of the COVID-19 pandemic continues to force imposition of social distancing measures, research on these often-neglected aspects of everyday social interaction may pave the way to address the two global public health priorities, separately recognized by the World Health Organization: ADRD and social isolation.

Methods

Population cohort 1: UK Biobank

The UK Biobank is a prospective epidemiological cohort that offers extensive behavioural and demographic assessments in 502,506 participants, recruited from across Great Britain [28]. Our study involved the full population sample including 54.4% females, aged 40-69 years when recruited (mean age 56.5, standard deviation (SD) 8.1 years). The present analyses were conducted under UK Biobank application number 25163. All participants provided written, informed consent, and the study was approved by the Review Board of the McGill University Health Centre (REC number 11/NW/0382). All analyses were performed in accordance with the relevant guidelines and regulations. Further information on the consent procedure can be found elsewhere (http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200).

Population cohort 2: Canadian Longitudinal Study of Aging

CLSA was launched in 2011 as an independent prospective epidemiological cohort and places a focus on aging trajectories and deep phenotyping [29]. This study follows a population of 30,097 individuals, including 50.9% females, aged 44-89 at enrollment (mean age 63.0, SD 10.3 years), recruited from 11 cities in 10 provinces across Canada. The acquisition of baseline data finished in 2015. All participants provided written informed consent. Ethics approval was obtained by the Research Ethics Board at McGill University (REB file #20-05-068), and the study was conducted in compliance with their guidelines and regulations.

Data availability

All used data are available to other investigators online. The UK Biobank data is available through a procedure described at http://www.ukbiobank.ac.uk/using-the-resource/. The CLSA data is accessible to researchers through data access requests at https://clsa-elcv.ca/data-access.

Social isolation target phenotypes

Studying the role of social lifestyle in ADRD onset should acknowledge determinants of both subjective feelings of loneliness and objective social support frequency. Regarding the loneliness target, we used the yes/no answer from UK Biobank participants to the question 'Do you often feel lonely?' (data field 2020). In CLSA, our loneliness target measure was based on the question 'How often did you feel lonely?', with the positive answer denoting 'all of the time (5-7 days)'. The validity of brief loneliness assessments has long been recognized, particularly for inclusion in large population-based studies [30]. Regarding the social support target, our UK Biobank analyses were based on the question 'How often are you able to confide in someone close to you?', as an objective measure of the frequency of social interactions (data field 2110). Our study modeled lack of social support as confiding less than 'daily or almost daily' (positive answer) against confiding in others more often (treated as negative answer). In CLSA, regarding lack of social support, participants were asked the question 'Someone to confide in or talk to about yourself or your problems?' and answers less than 'all of the time' or 'most of the time' were modeled as the positive case. In the UKBB and the CLSA, several items among the ADRD risk factors are defined such that the numerical encoding is different from what we used in our analysis. In all our models, we ensured that a higher value consistently meant more in a given phenotype

and that a lower value meant less. For example, 'Current tobacco consumption' in the UKBB was re-encoded so that 'occasionally' was numerically greater than 'no' and smaller than 'yes'. In the CLSA, 'Current frequency of cigarettes smoked' was reverse encoded so that 'Daily' and 'Not at all' corresponded to the highest and lowest values, respectively. Moreover, all categorical variables were treated as ordinal numeric variables. The original data-coding for all variables is available in S1 Table 1 and the entirety of our pre-processing for each item is available in our code (http://github.com/banilo/ADRISK).

Multivariate decomposition approach

We used partial least squares (PLS) correlation to examine possible cross-associations between classical ADRD risk factors and social richness indicators (cf. S1 Table 1). As used in our previous work, this technique is particularly useful when handling very large and strongly correlated datasets [31]. To analyze the relationship between the risk traits and the social factors, all input variables were systematically normalized by z-scoring across participants, and the observations (here, the participant responses) were stored in matrices, with X corresponding to the risk traits and Y representing the social indicators. The two sets of linear combinations of the original variables are obtained as follows:

$$X \in \mathbb{R}^{n \times p}$$

$$Y \in \mathbb{R}^{n \times q}$$

$$L_X = XV \qquad L_Y = YU$$

$$l_{X,l} = Xv_l \qquad l_{Y,l} = Yu_l$$

$$corr(l_{X,l}, l_{Y,l}) \propto l_{X,l}^T l_{Y,l} = max$$

where n denotes the number of participants, p is the number of risk traits, q is the number of social factors (7 in the UKBB and 6 in the CLSA), V and U denote the respective contributions of X and Y, L_X and L_Y denote the respective latent 'modes' of joint variation between patterns in X and patterns in Y, $l_{X,l}$ is the l^{th} column of L_X, and $l_{Y,l}$ is the l^{th} column of L_Y. The goal of our PLS correlation application was to find pairs of latent vectors $l_{X,l}$ and $l_{Y,l}$ with maximal correlation in the derived latent embedding and quantify the strength of the relationship between the two variable sets in the derived embedding space (the risk traits and the social indicators). Since PLS correlation was purely used as an exploratory analysis, uncertainty in effect sizes were not measured.

Bayesian regression approach

Next, to ascertain robust associations between social richness and ADRD aetiopathology in the wider society, Bayesian hierarchical regression was a natural choice of method [32], following our previous work at the population level [31, 33, 34]. In particular, classical tests for statistical significance would have only provided dichotomic statements in the form of p-values against the null hypothesis of no effect in the data [35, 36]. Instead, we aimed to directly quantify the probabilistic association of traditional ADRD risk to social isolation, while providing coherent estimates of associated uncertainty.

To this end, our analyses aimed at probabilistic answers to the question 'How certain are we that loneliness/lack of social support is linked to an ADRD risk phenotype?' Our analyses did not ask 'Is there a strict categorical answer as to whether or not a risk phenotype is linked to loneliness or lack of social support?' In this way, we aimed to directly quantify the population

uncertainty intervals of risk effects in the context of social isolation. The full Bayesian model specification took the following form:

$$y \sim Bernoulli(p)$$

$$logit(p) = alpha + x_1 * risktrait + x_2 * agebeta + x_3 * sexbeta$$

$$alpha \sim \mathcal{N}(0, 1)$$

$$risktrait \sim \mathcal{N}(\mu_{risk}, \sigma_{risk})$$

$$\mu_{risk} \sim \mathcal{N}(0, 1)$$

$$\sigma_{risk} \sim HalfNormal(1)$$

$$agebeta \sim \mathcal{N}(0, 1)$$

$$sexbeta \sim \mathcal{N}(0, 1),$$

where x_1 denotes an ADRD risk phenotype of interest (e.g., number of cigarettes smoked per day) and y denotes one of the target measures of social isolation (i.e., loneliness or lack of social support, cf. above). Details on the full list of examined risk traits (51 from the UKBB, 43 from the CLSA) can be found in S1 Table 1. The multilevel formulation of the risk trait parameter serves flexible adaptation to different data settings. Variation that could be explained by participant age or sex was accounted for as potential confounds by x_2 and x_3, respectively. In the UK Biobank or CLSA cohort, for a given risk phenotype of ADRD, we have estimated separate Bayesian models for loneliness and lack of social support. Prior to running the Bayesian models, we systematically z-scored all risk factor variables in order to make all input variables comparable.

Approximate posterior integration was achieved by means of Markov Chain Monte Carlo (MCMC), which sampled in a random walk towards the joint posterior distribution of all quantities at play [32]. In 1,000 draws, the approximate parameter distributions were improved at each step in the sense of converging to the target distribution. At each step of the MCMC chain, the entire set of parameter values were estimated to be jointly credible given the data. In the data exploration phase, we have inspected model convergence by overlap between the geometry of posterior parameter distributions from four independent MCMC chains. We obtained further evidence for proper convergence to a stable model solution based on the effect sample size and $\hat{R}$ quality criteria. In the model exploitation phase, the final solution was computed by a single MCMC chain.

Scientific computing implementation

Probabilistic hierarchical modeling and MCMC sampling [37] were implemented as symbolic computation graphs in the *PyMC3* framework (https://github.com/pymc-devs/pymc3). Posterior parameter distribution plots were generated by *Seaborn* (https://seaborn.pydata.org/). Missing data were imputed using a nonparametric method for the UK Biobank, and a Bayesian method for the CLSA. We used two different imputation methods in the CLSA and UKBB cohorts given the diverging properties of these population cohorts. The hot-deck imputation method that we have used for the UKBB is a common and computationally feasible method for imputation and involves using observed values in the sample to substitute missing values [38]. However, the hot-deck method may produce less precise model estimates for the mean and extreme quantiles than the Bayesian method [38]. The model-based Bayesian imputation is a more principled approach to handle missing data, since it entails specifying a probability model for the target variable, the covariates, and the missing data for estimation in a single modeling step [39]. Given that our study

involved the full population sample from both datasets, we could only do the more rigorous Bayesian imputation in the smaller CLSA cohort because it was not computationally expedient for the larger UKBB cohort. All analysis scripts that reproduce the results of the present study are readily accessible and open for reuse by the reader (http://github.com/banilo/ADRISK).

Figures

Fig 1. Widespread cross-associations exist between social deprivation indicators and traditional risk factors for Alzheimer's dementias. To gain a synoptic overview, we initially explored multivariable relationships between sets of social richness measures (top row) and sets of usually studied aetiopathological risk factors (lower row). In 502,506 UK Biobank participants (left column), the leading explanatory patterns ('modes') show that perceived and objective social isolation are associated with higher neuroticism scores and similar personality styles. In 30,097 CLSA participants (right column), the dominant pattern links loneliness and lacking social support to TV consumption and depression-related emotional traits. This doubly multivariate decomposition of two variable sets was obtained from partial least squares analysis (PLS; cf. Methods). Note that this cursory analysis does not attempt to single out special variables (in contrast to the analyses from Figs 2-5). Overall, this perspective makes apparent that the majority of examined risk factors may be related to some aspect of social lifestyle.

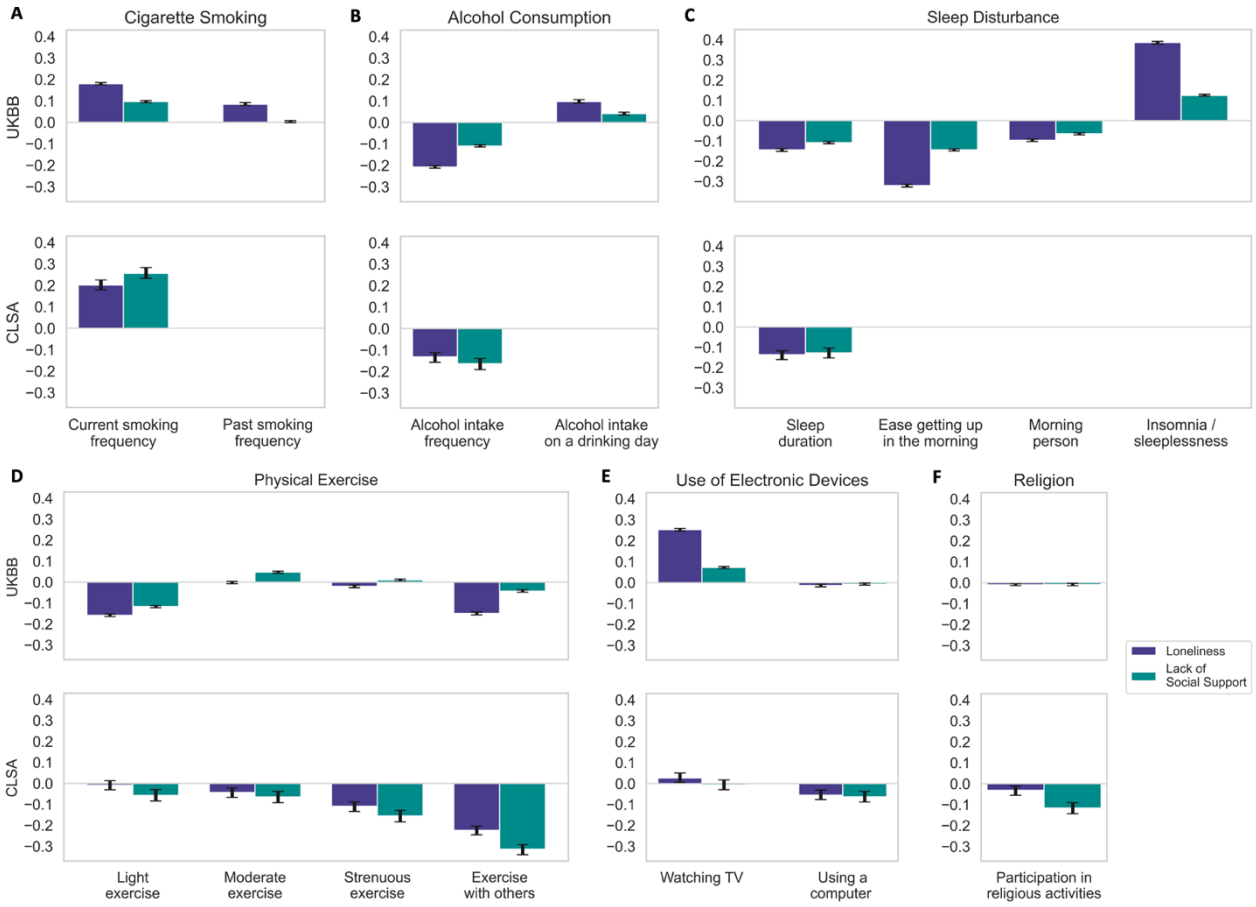


Fig 2. Various ADRD-related lifestyle factors show strong association effects with loneliness and lack of social support across both cohorts. Bayesian estimation of the posterior probability that a given risk factor relates to one of two measures of social deprivation: loneliness and lack of social support. All target risk factor variables were z-scored prior to running the Bayesian models. For simplicity, results are expressed as the mean and the 90% highest posterior density interval of the model coefficients (black error bars). In both UKBB and the CLSA, loneliness and lack of social support are robustly associated with a variety of lifestyle factors, including (A) current cigarette smoking, (B) alcohol consumption, (C) sleep duration, and (D) participation in physical activities with others. (E) Use of electronic devices and (F) participation in religious activities show smaller links to loneliness and weak social support. Both subjective and objective social isolation follow similar patterns in their associations with behavioural traits across the two cohorts. Sleeplessness has the largest association with social isolation in this category.

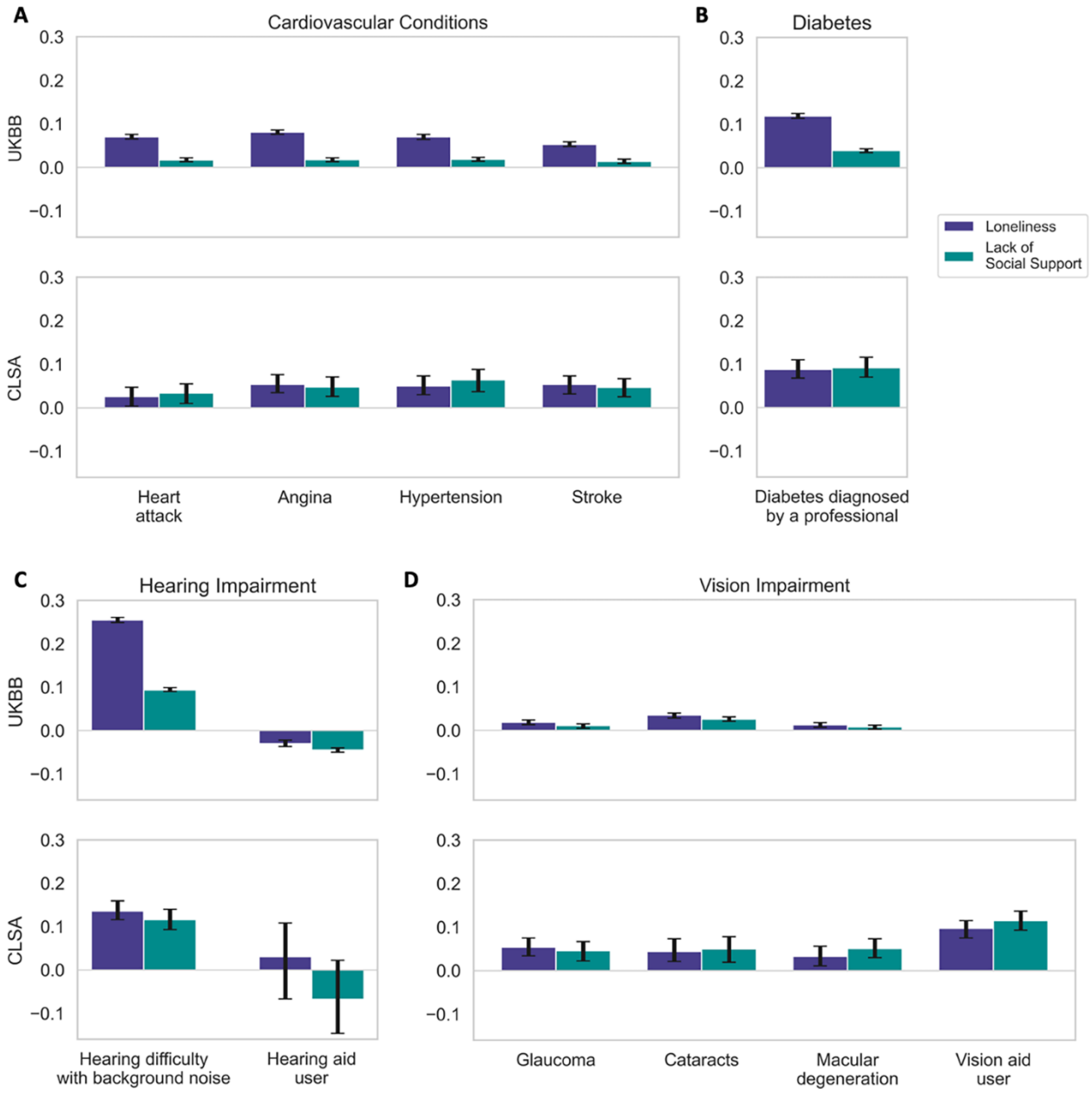


Fig 3. Physical health factors are related to social isolation. Bayesian estimation of the posterior probability that a given risk factor relates to one of two measures of social deprivation: loneliness and lack of social support. All physical health risk factor variables were standardized prior to running the Bayesian models. For simplicity, results are expressed as the mean and the 90% highest posterior density interval of the model coefficients (black error bars). In the UKBB and the CLSA cohorts, loneliness and poor social support show strong links with several physical health factors, such as (A) hypertension, (B) diabetes, (C) hearing difficulty with background noise, and (D) being a vision aid user. Across the two cohorts, hearing difficulty with background noise has the largest association with both subjective and objective social isolation in this pillar of risk traits.

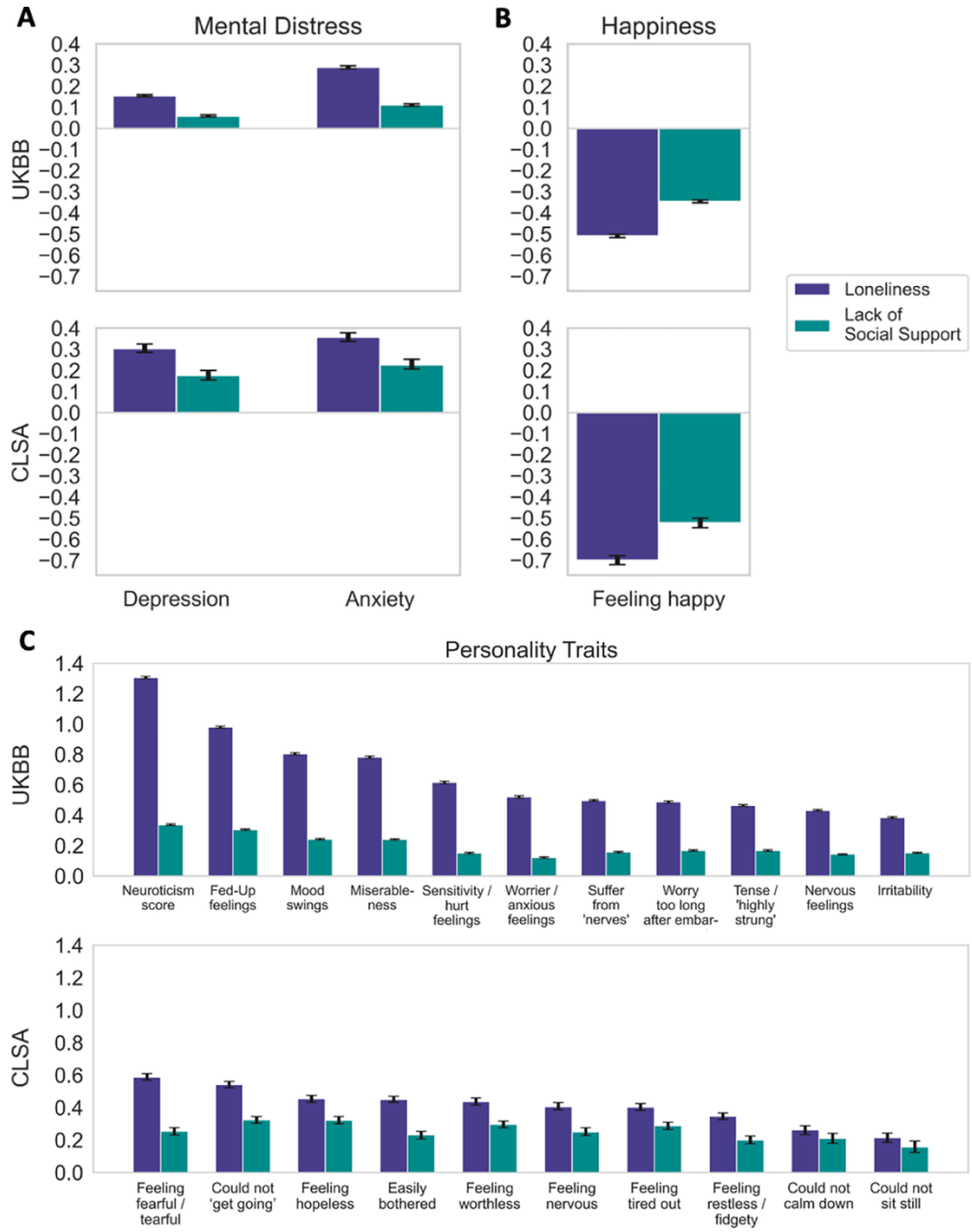


Fig 4. Mental health factors show prominent association effects with social isolation. Bayesian estimation of the posterior probability that a given risk factor relates to one of two measures of social deprivation: loneliness and lack of social support. All target risk factor variables were normalized by z-scoring across participants prior to running the Bayesian models. For simplicity, results are expressed as the mean and the 90% highest posterior density interval for the model coefficients (black error bars). In this category and across the two datasets, both loneliness and lack of social support show some of the most prominent links with (A) depression and anxiety, (B) feelings of happiness, and (C) several measures of personality that play into the stress-buffer capacity of an individual. In particular, the neuroticism score has the largest association with both subjective and objective social isolation among all the examined ADRD risk factors.

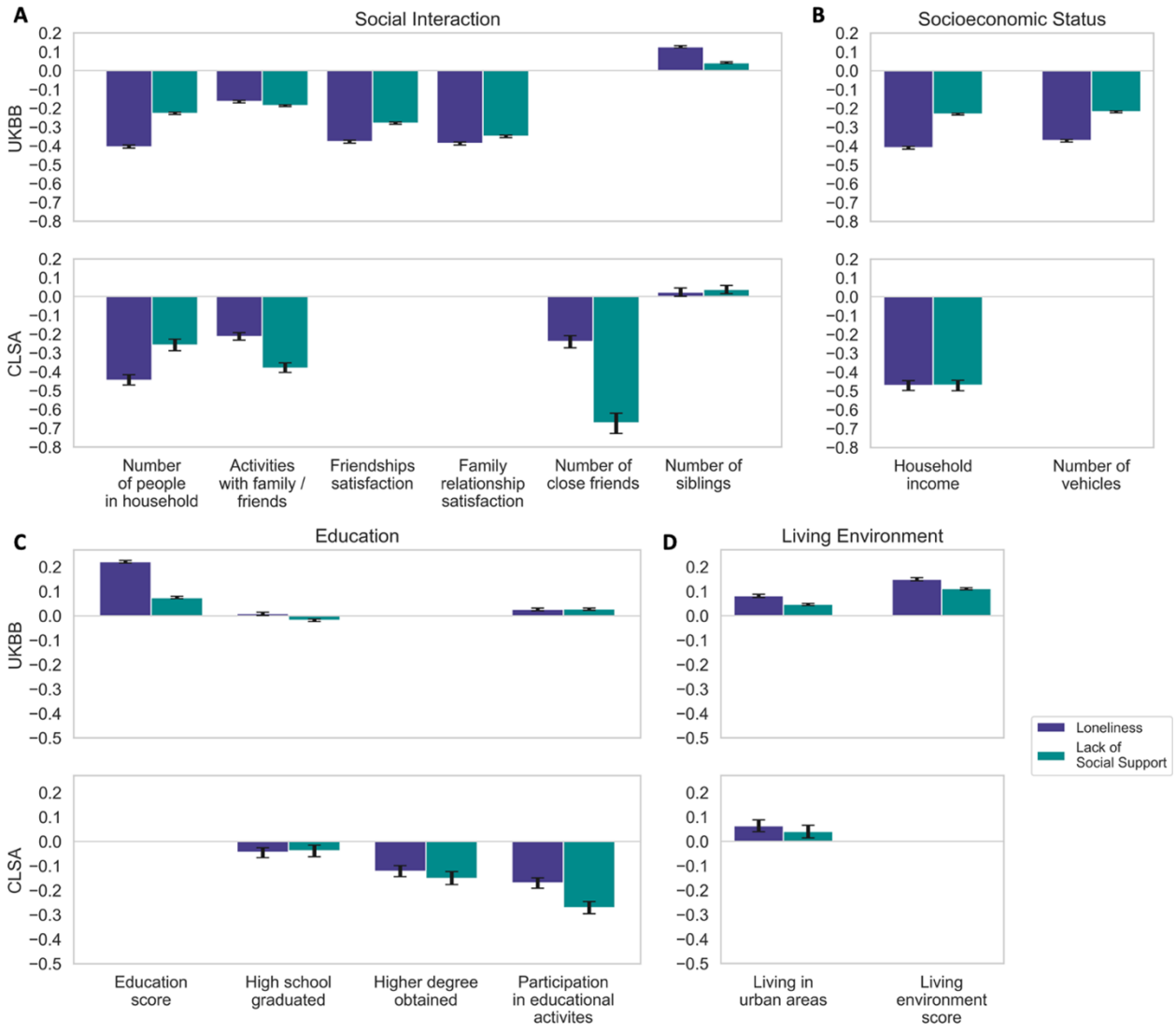


Fig 5. Societal risk factors exhibit salient association effects with social isolation. Bayesian estimation of the posterior probability that a given risk factor relates to one of two measures of social deprivation: loneliness and lack of social support. All societal risk factor variables were z-scored prior to running the Bayesian models. For simplicity, results are expressed as the mean and the 90% highest posterior density interval for the model coefficients (black error bars). In the UKBB and the CLSA datasets, loneliness and lack of social support show strong associations with several societal factors, including (A) the number of people living in the household and the number of close friends, (B) household income, and (C) graduating from high school and obtaining higher degrees. (D) Living in an urban environment is also linked with higher levels of subjective and objective social deprivation.

Tables

Personal Habits & Lifestyle Factors

UKBB		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Smoking	**Current tobacco smoking**	**0.180**	**0.175**	**0.185**	**0.097**	**0.092**	**0.101**
	Past tobacco smoking	**0.085**	**0.079**	**0.092**	**0.003**	**-0.001**	**0.008**
Alcohol	**Alcohol intake frequency**	**-0.208**	**-0.213**	**-0.202**	**-0.110**	**-0.114**	**-0.104**
	Amount of alcohol drunk on a typical drinking day	**0.097**	**0.090**	**0.106**	**0.041**	**0.035**	**0.048**
Sleep Disturbance	**Daily sleep duration**	**-0.145**	**-0.152**	**-0.139**	**-0.109**	**-0.114**	**-0.104**
	Difficulty getting up in the morning	**-0.321**	**-0.328**	**-0.315**	**-0.145**	**-0.150**	**-0.140**
	Morning person	**-0.097**	**-0.103**	**-0.091**	**-0.065**	**-0.070**	**-0.060**
	Insomnia or sleeplessness	**0.386**	**0.379**	**0.392**	**0.125**	**0.121**	**0.130**
Physical Exercise	**Light – walking for pleasure**	**-0.158**	**-0.164**	**-0.152**	**-0.117**	**-0.122**	**-0.112**
	Moderate – swimming, cycling, keep fit, bowling	**-0.001**	**-0.007**	**0.004**	**0.048**	**0.043**	**0.052**
	Strenuous – strenuous sports	**-0.020**	**-0.027**	**-0.014**	**0.011**	**0.006**	**0.015**
	Attending sports club or gym	**-0.149**	**-0.156**	**-0.143**	**-0.043**	**-0.048**	**-0.037**
Digital Technology	**Time spent watching television**	**0.253**	**0.247**	**0.259**	**0.073**	**0.068**	**0.077**
	Time spent using the computer	**-0.014**	**-0.020**	**-0.007**	**-0.007**	**-0.012**	**-0.002**
Religious Activities	**Attending a religious group**	**-0.009**	**-0.015**	**-0.003**	**-0.010**	**-0.014**	**-0.005**

CLSA		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Smoking	**Current frequency of cigarettes smoked**	**0.202**	**0.179**	**0.225**	**0.256**	**0.233**	**0.283**
Alcohol	**Alcohol drinking frequency in past 12 months**	**-0.132**	**-0.157**	**-0.112**	**-0.164**	**-0.191**	**-0.139**
Sleep Disturbance	**Number of sleep hours during past month**	**-0.137**	**-0.161**	**-0.117**	**-0.129**	**-0.153**	**-0.104**
Physical Exercise	**Light – bowling, shuffleboard, badminton, fishing**	**-0.009**	**-0.030**	**0.013**	**-0.057**	**-0.083**	**-0.029**
	Moderate – hunting, skating, softball	**-0.043**	**-0.067**	**-0.022**	**-0.065**	**-0.092**	**-0.038**
	Strenuous – jogging, swimming, cycling, skiing	**-0.109**	**-0.134**	**-0.088**	**-0.155**	**-0.184**	**-0.128**
	Participation in physical activities with others	**-0.224**	**-0.245**	**-0.203**	**-0.314**	**-0.340**	**-0.291**
Digital Technology	**Participation in watching television**	**0.027**	**0.006**	**0.051**	**-0.006**	**-0.029**	**0.018**
	Participation in computer activities	**-0.055**	**-0.076**	**-0.030**	**-0.063**	**-0.088**	**-0.037**
Religious Activities	**Participation in religious activities**	**-0.032**	**-0.055**	**-0.012**	**-0.116**	**-0.143**	**-0.091**

Physical Health Factors

UKBB		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Cardiovascular Conditions	**Heart attack**	**0.070**	**0.065**	**0.076**	**0.017**	**0.013**	**0.022**
	Angina	**0.081**	**0.076**	**0.086**	**0.018**	**0.013**	**0.022**

	High blood pressure	**0.070**	**0.064**	**0.076**	**0.019**	**0.014**	**0.023**
	Stroke	**0.053**	**0.048**	**0.059**	**0.014**	**0.009**	**0.019**
Diabetes	**Diabetes diagnosed by a professional**	**0.119**	**0.114**	**0.125**	**0.040**	**0.035**	**0.044**
Hearing Impairment	**Difficulty hearing with background noise**	**0.255**	**0.249**	**0.261**	**0.094**	**0.090**	**0.099**
	Hearing aid user	**-0.030**	**-0.037**	**-0.022**	**-0.045**	**-0.050**	**-0.040**
Vision Impairment	**Glaucoma**	**0.019**	**0.013**	**0.024**	**0.011**	**0.005**	**0.015**
	Cataracts	**0.035**	**0.028**	**0.040**	**0.026**	**0.021**	**0.031**
	Macular degeneration	**0.013**	**0.007**	**0.018**	**0.008**	**0.003**	**0.012**

CLSA		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Cardiovascular Conditions	**Heart attack or myocardial infarction**	**0.026**	**0.004**	**0.047**	**0.034**	**0.010**	**0.055**
	Angina (or chest pain due to heart disease)	**0.054**	**0.035**	**0.076**	**0.048**	**0.026**	**0.071**
	High blood pressure or hypertension	**0.050**	**0.030**	**0.073**	**0.064**	**0.037**	**0.088**
	Stroke or CVA	**0.054**	**0.032**	**0.073**	**0.047**	**0.025**	**0.067**
Diabetes	**Diabetes, borderline diabetes, or high blood sugar diagnosed by a professional**	**0.088**	**0.068**	**0.110**	**0.092**	**0.070**	**0.116**
Hearing Impairment	**Difficulty hearing with background noise**	**0.136**	**0.116**	**0.159**	**0.116**	**0.093**	**0.140**
	Hearing aid user	**0.031**	**-0.067**	**0.108**	**-0.068**	**-0.146**	**0.022**
Vision Impairment	**Glaucoma**	**0.054**	**0.034**	**0.075**	**0.046**	**0.022**	**0.067**
	Cataracts	**0.044**	**0.021**	**0.073**	**0.050**	**0.019**	**0.078**
	Macular degeneration	**0.033**	**0.011**	**0.056**	**0.051**	**0.030**	**0.073**

	Vision aid user (besides glasses or contact lenses)	**0.097**	**0.075**	**0.115**	**0.115**	**0.093**	**0.137**

Mental Health Factors

UKBB		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Depression	**Diagnosed with depression by a professional**	**0.155**	**0.150**	**0.160**	**0.059**	**0.054**	**0.064**
Anxiety	**Feeling nervous, anxious, 'on-edge'**	**0.290**	**0.282**	**0.297**	**0.112**	**0.105**	**0.117**
Happiness	**Feeling happy**	**-0.509**	**-0.517**	**-0.501**	**-0.346**	**-0.352**	**-0.339**
Personality Traits	**Neuroticism score**	**1.306**	**1.298**	**1.314**	**0.337**	**0.332**	**0.343**
	Fed-up feelings	**0.980**	**0.973**	**0.987**	**0.305**	**0.301**	**0.310**
	Mood swings	**0.804**	**0.798**	**0.811**	**0.242**	**0.238**	**0.247**
	Miserableness	**0.779**	**0.772**	**0.786**	**0.241**	**0.236**	**0.246**
	Sensitivity / hurt feelings	**0.616**	**0.608**	**0.623**	**0.151**	**0.146**	**0.156**
	Worrier / anxious feelings	**0.521**	**0.514**	**0.528**	**0.122**	**0.117**	**0.127**
	Worry too long after embarrassment	**0.487**	**0.480**	**0.493**	**0.167**	**0.163**	**0.172**
	Suffer from 'nerves'	**0.497**	**0.492**	**0.503**	**0.158**	**0.153**	**0.162**
	Tense / 'highly strung'	**0.464**	**0.459**	**0.470**	**0.167**	**0.162**	**0.172**
	Nervous feelings	**0.432**	**0.427**	**0.438**	**0.143**	**0.138**	**0.147**
	Irritability	**0.385**	**0.379**	**0.390**	**0.153**	**0.148**	**0.157**

CLSA		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Depression	**Clinical depression**	**0.303**	**0.284**	**0.324**	**0.176**	**0.154**	**0.199**
Anxiety	**Sees oneself as anxious and easily upset**	**0.358**	**0.337**	**0.378**	**0.227**	**0.206**	**0.253**

Happiness	**Frequency of feeling happy**	**-0.700**	**-0.720**	**-0.678**	**-0.522**	**-0.545**	**-0.500**
Personality Traits	**Feeling fearful / tearful**	**0.587**	**0.568**	**0.609**	**0.253**	**0.230**	**0.276**
	Could not 'get going'	**0.541**	**0.521**	**0.561**	**0.324**	**0.302**	**0.345**
	Feeling hopeless	**0.454**	**0.431**	**0.475**	**0.322**	**0.300**	**0.345**
	Easily bothered	**0.450**	**0.430**	**0.469**	**0.232**	**0.205**	**0.253**
	Feeling worthless	**0.436**	**0.414**	**0.458**	**0.296**	**0.274**	**0.317**
	Feeling nervous	**0.406**	**0.385**	**0.430**	**0.250**	**0.227**	**0.275**
	Feeling tired out	**0.402**	**0.381**	**0.424**	**0.288**	**0.264**	**0.310**
	Feeling restless / fidgety	**0.346**	**0.325**	**0.367**	**0.199**	**0.176**	**0.224**
	Could not calm down	**0.263**	**0.233**	**0.288**	**0.210**	**0.179**	**0.240**
	Could not sit still	**0.214**	**0.185**	**0.243**	**0.157**	**0.123**	**0.194**

Societal & External Factors

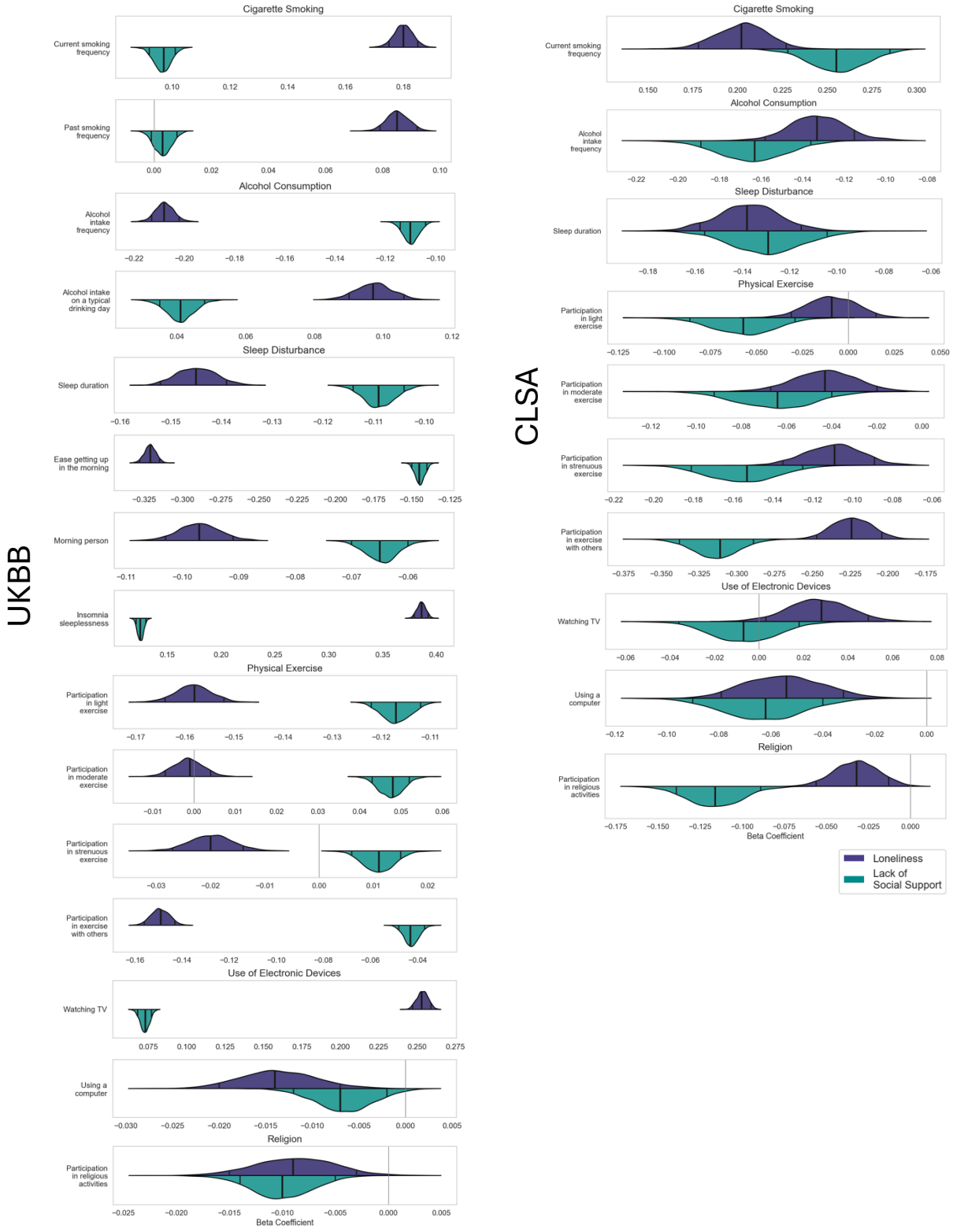
UKBB		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Social Interaction	**Number of people in household**	**-0.405**	**-0.412**	**-0.395**	**-0.227**	**-0.233**	**-0.221**
	Frequency of visits from friends / family	**-0.164**	**-0.171**	**-0.158**	**-0.186**	**-0.191**	**-0.182**
	Friendships satisfaction	**-0.377**	**-0.385**	**-0.370**	**-0.279**	**-0.285**	**-0.273**
	Family relationship satisfaction	**-0.387**	**-0.395**	**-0.379**	**-0.349**	**-0.356**	**-0.343**
	Number of full siblings	**0.127**	**0.122**	**0.133**	**0.042**	**0.038**	**0.047**
Socioeconomic Status	**Average total household income**	**-0.409**	**-0.416**	**-0.402**	**-0.230**	**-0.235**	**-0.225**
	Number of vehicles	**-0.371**	**-0.378**	**-0.365**	**-0.218**	**-0.223**	**-0.213**
Education	**Education score**	**0.222**	**0.216**	**0.227**	**0.075**	**0.071**	**0.080**
	Age completed full-time education	**0.009**	**0.002**	**0.015**	**-0.018**	**-0.023**	**-0.013**
	Attending adult education classes	**0.027**	**0.021**	**0.032**	**0.028**	**0.023**	**0.032**

Living Environment	**Living in urban areas**	**0.082**	**0.075**	**0.088**	**0.047**	**0.042**	**0.051**
	Living environment score	**0.150**	**0.143**	**0.156**	**0.111**	**0.106**	**0.115**

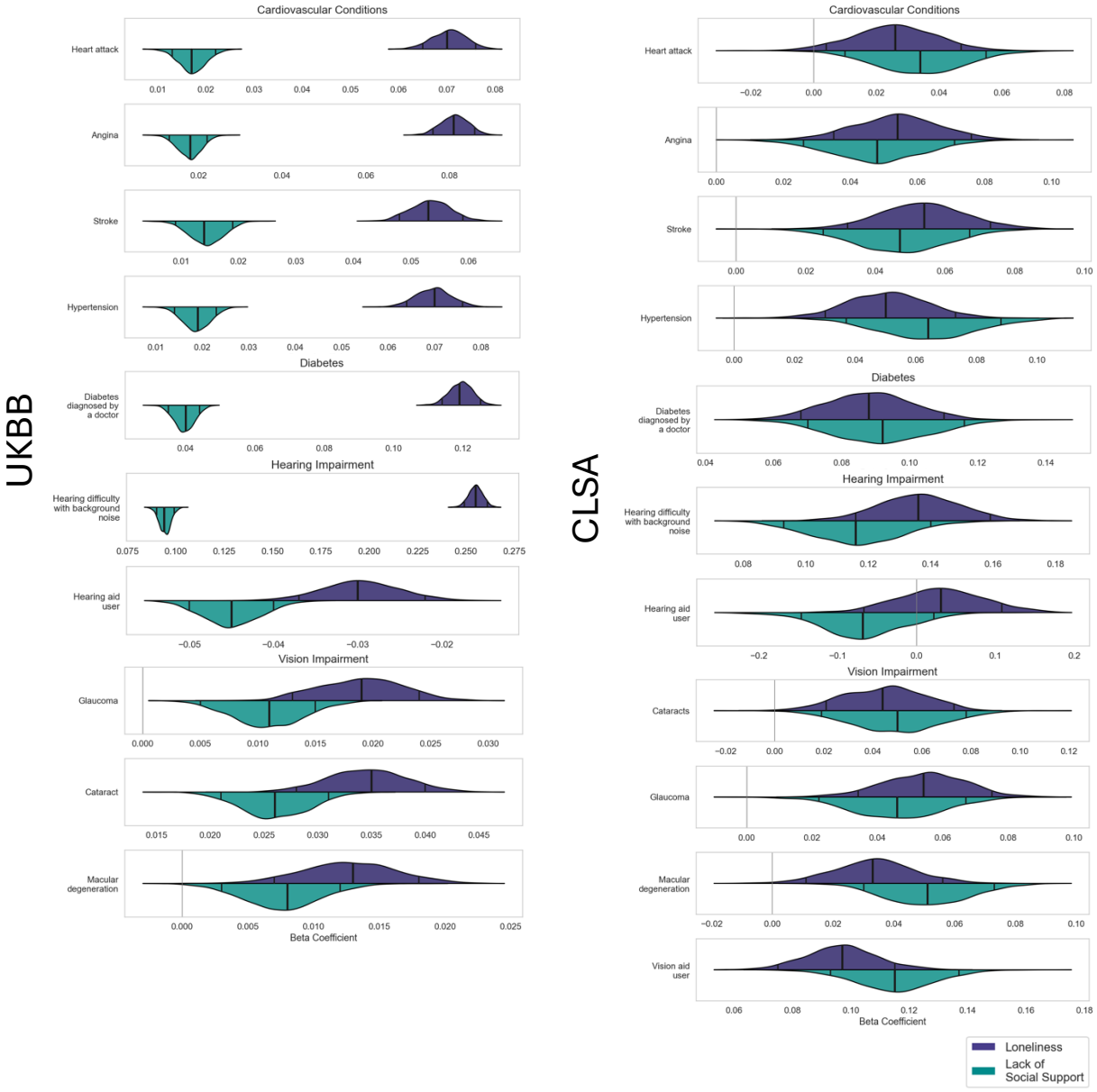
CLSA		*Loneliness*			*Lack of Social Support*		
		Mean	**5% HDPI**	**95% HDPI**	**Mean**	**5% HDPI**	**95% HDPI**
Social Interaction	**Number of people in household**	**-0.445**	**-0.470**	**-0.415**	**-0.259**	**-0.286**	**-0.227**
	Frequency of participation in friends / family activities out of household	**-0.213**	**-0.232**	**-0.192**	**-0.381**	**-0.403**	**-0.353**
	Number of close friends	**-0.239**	**-0.273**	**-0.208**	**-0.672**	**-0.728**	**-0.620**
	Number of living siblings	**0.023**	**0.001**	**0.045**	**0.038**	**0.015**	**0.059**
Socioeconomic Status	**Total household income from the past 12 months**	**-0.471**	**-0.497**	**-0.445**	**-0.469**	**-0.498**	**-0.443**
Education	**High school graduated**	**-0.044**	**-0.066**	**-0.025**	**-0.038**	**-0.062**	**-0.015**
	Higher degree obtained	**-0.122**	**-0.144**	**-0.098**	**-0.151**	**-0.176**	**-0.123**
	Participation in educational or cultural activities	**-0.169**	**-0.191**	**-0.149**	**-0.271**	**-0.295**	**-0.246**
Living Environment	**Living in urban areas**	**0.064**	**0.040**	**0.088**	**0.041**	**0.014**	**0.066**

Table 1. Mean associations between subjective and objective social isolation and ADRD risk factors in the UKBB and the CLSA.

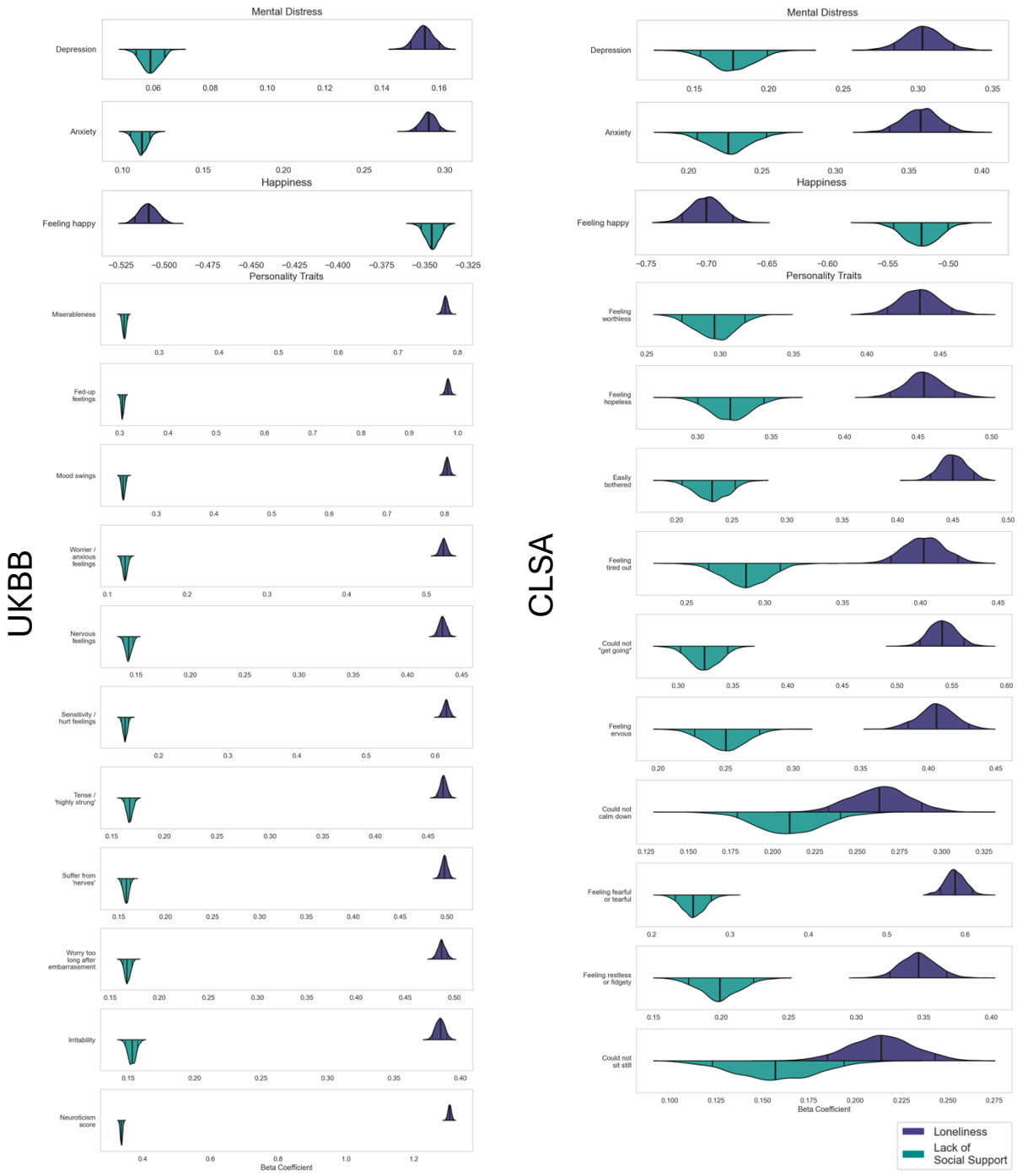
Supplementary Material



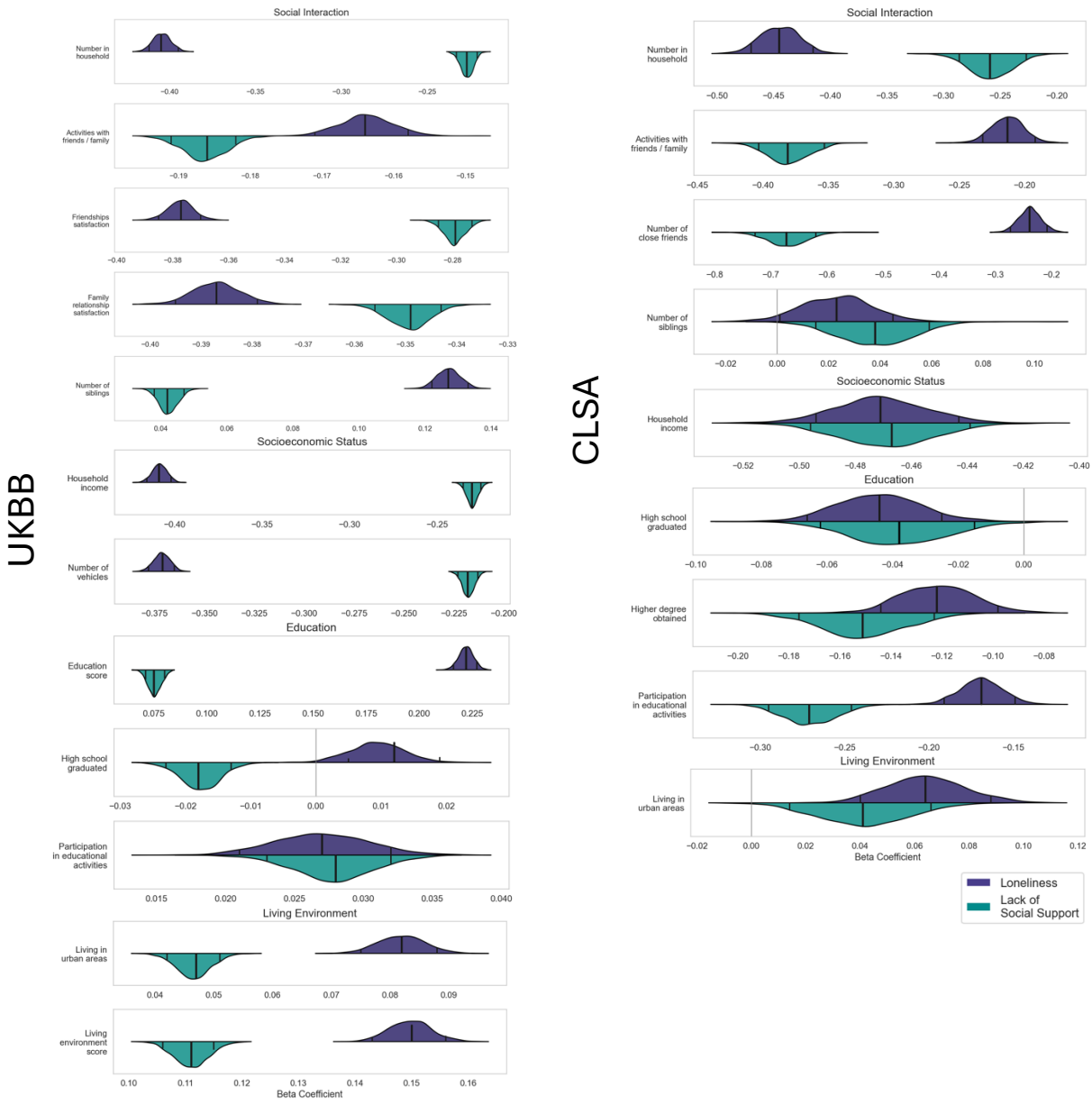
Supplementary Figure 1. Various ADRD-related lifestyle factors show strong association effects with loneliness and lack of social support across both cohorts



Supplementary Figure 2. Physical health factors are related to social isolation.



Supplementary Figure 3. Mental health factors show prominent association effects with social isolation.



Supplementary Figure 4. Societal risk factors exhibit salient association effects with social isolation.

UK BioBank	**CLSA -** Comprehensive Assessment V1_Baseline (COM)
2020 - Loneliness, isolation "Do you often feel lonely?" 0 No 1 Yes	**DEP_LONLY_COM - CES-D 10 scale: Frequency feel lonely** "How often did you feel lonely?" 1 All of the time (5-7 days) 2 Occasionally (3-4 days) 3 Some of the time (1-2 days) 4 Rarely or never (less than 1 day)
2110 - Able to confide "How often are you able to confide in someone close to you?" 0 Never or almost never 1 Once every few months 2 About once a month 3 About once a week 4 2-4 times a week 5 Almost daily	**SSA_CONFID_COM - MOS scale: Support availability if need to confide** "Someone to confide in or talk to about yourself or your problems?" 1 None of the time 2 A little of the time 3 Some of the time 4 Most of the time 5 All of the time
100347 - Current tobacco smoking "Do you smoke tobacco now?" 0 No 1 Yes, on most or all days 2 Only occasionally	**SMK_CURRCG_COM - Current frequency of cigarettes smoked** "At the present time, do you smoke cigarettes daily, occasionally or not at all?" 1 Daily (at least one cigarette every day for the past 30 days) 2 Occasionally (at least one cigarette in the past 30 days, but not every day) 3 Not at all (you did not smoke at all in the past 30 days)
100348 - Past tobacco smoking "In the past, how often have you smoked tobacco?" 1 Smoked on most or all days 2 Smoked occasionally 3 Just tried once or twice 4 I have never smoked	
1558 - Alcohol intake frequency "About how often do you drink alcohol?" 1 Daily or almost daily 2 Three or four times a week 3 Once or twice a week 4 One to three times a month 5 Special occasions only 6 Never	**ALC_FREQ_COM - Alcohol drinking frequency in past 12 months** "About how often during the past 12 months did you drink alcohol?" 1 Almost every day (incl. 6 times a week) 2 4-5 times a week 3 2-3 times a week 4 Once a week 5 2-3 times a month 6 About once a month 7 Less than once a month 8 Never
20403 - Amount of alcohol drunk on a typical drinking day "How many drinks[1] containing alcohol do you have on a typical day when you are drinking?" 1 1 or 2 2 3 or 4 3 5 or 6 4 7, 8, or 9 5 10 or more	
1160 - Sleep duration "About how many hours sleep do you get in every 24 hours? (please include naps)"	**SLE_HOUR_NB_COM - Number of sleep hours during past month** Integer
1170 - Getting up in morning	

"On an average day, how easy do you find getting up in the morning?" 1 Not at all easy 2 Not very easy 3 Fairly easy 4 Very easy	
1180 - Morning/evening person (chronotype) "Do you consider yourself to be?" 1 Definitely a 'morning' person 2 More a 'morning' than 'evening' person 3 More an 'evening' than a 'morning' person 4 Definitely an 'evening' person	
1200 - Sleeplessness / insomnia "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" 1 Never/rarely 2 Sometimes 3 Usually	
6164 - Types of physical activity in last 4 weeks "In the last 4 weeks did you spend any time doing the following? (You can select more than one answer)" 1 Walking for pleasure (not as a means of transport) 2 Other exercises (eg: swimming, cycling, keep fit, bowling) 3 Strenuous sports 4 Light DIY (eg: pruning, watering the lawn) 5 Heavy DIY (eg: weeding, lawn mowing, carpentry, digging)	**PA2_LSPRT_MCQ - PASE scale: Frequency of participation in light sports** "Over the past 7 days, how often did you engage in light sports or recreational activities such as bowling, golf with a cart, shuffleboard, badminton, fishing or other similar activities?" 1 Never 2 Seldom (1 to 2 days) 3 Sometimes (3 to 4 days) 4 Often (5 to 7 days) **PA2_MSPRT_MCQ - PASE scale: Frequency of participation in moderate sports** "Over the past 7 days, how often did you engage in moderate sports or recreational activities such as ballroom dancing, hunting, skating, golf without a cart, softball or other similar activities?" 1 Never 2 Seldom (1 to 2 days) 3 Sometimes (3 to 4 days) 4 Often (5 to 7 days) **PA2_SSPRT_MCQ - PASE scale: Frequency of participation in strenuous sports** "Over the past 7 days, how often did you engage in strenuous sports or recreational activities such as jogging, swimming, snowshoeing, cycling, aerobics, skiing, or other similar activities?" 1 Never 2 Seldom (1 to 2 days) 3 Sometimes (3 to 4 days) 4 Often (5 to 7 days)
6160 - Leisure/social activities "Which of the following do you attend once a week or more often? (You can select more than one)" 1 Sports club or gym 2 Pub or social club 3 Religious group 4 Adult education class 5 Other group activity	**SPA_SPORT_COM - Frequency of participation in sports or physical activities with others** "In the past 12 months, how often did you participate in Sports or physical activities that you do with other people?" 1 At least once a day 2 At least once a week 3 At least once a month 4 At least once a year 5 Never **SPA_CLUB_COM - Frequency of participation in clubs or fraternal organization activities**

	"In the past 12 months, how often did you participate in Service club or fraternal organization activities?" 1 At least once a day 2 At least once a week 3 At least once a month 4 At least once a year 5 Never **SPA_CHRCH_COM - Frequency of participation in religious activities** "In the past 12 months, how often did you participate in church or religious activities such as services, committees or choirs?" 1 At least once a day 2 At least once a week 3 At least once a month 4 At least once a year 5 Never **SPA_EDUC_COM - Frequency of participation in educational or cultural activities** "In the past 12 months, how often did you participate in Educational and cultural activities involving other people such as attending courses, concerts, plays, or visiting museums?" 1 At least once a day 2 At least once a week 3 At least once a month 4 At least once a year 5 Never
1070 - Time spent watching television (TV) "In a typical DAY, how many hours do you spend watching TV? (Put 0 if you do not spend any time doing it)"	**PA2_SIT_TV_MCQ - PASE scale: Participated in sitting activities - Watching TV** 0 No 1 Yes
1080 - Time spent using computer "In a typical DAY, how many hours do you spend using the computer? (Do not include using a computer at work; put 0 if you do not spend any time doing it)"	**PA2_SIT_COM_MCQ - PASE scale: Participated in sitting activities - Computer activities** 0 No 1 Yes
6150 - Vascular/heart problems diagnosed by doctor "Has a doctor ever told you that you have had any of the following conditions?" 1 Heart attack 2 Angina 3 Stroke 4 High blood pressure	**CCC_AMI_COM - Heart attack or myocardial infarction** "Has a doctor ever told you that you have had a heart attack or myocardial infarction?" 1 Yes 2 No **CCC_ANGI_COM - Angina (or chest pain due to heart disease)** "Has a doctor ever told you that you have angina (or chest pain due to heart disease)?" 1 Yes 2 No **CCC_HBP_COM - High blood pressure or hypertension** "Has a doctor ever told you that you have high blood pressure or hypertension?" 1 Yes 2 No **CCC_CVA_COM - Stroke or CVA (cerebrovascular accident)** Has a doctor ever told you that you have experienced a Stroke or CVA (cerebrovascular accident)? 1 Yes 2 No

2443 - Diabetes diagnosed by doctor "Has a doctor ever told you that you have diabetes?" 0 No 1 Yes	**DIA_DIAB_COM - Diabetes, borderline diabetes or high blood sugar** “Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?” 1 Yes 2 No
2257 - Hearing difficulty/problems with background noise "Do you find it difficult to follow a conversation if there is background noise (such as TV, radio, children playing)?" 0 No 1 Yes	**HRG_NOIS_COM - Hearing difficulty with background noise** “Do you find it difficult to follow a conversation if there is background noise, such as TV, radio or children playing, even if using a hearing aid as usual?” 1 Yes 2 No
3393 - Hearing aid user "Do you use a hearing aid most of the time?" 0 No 1 Yes	**HRG_AID_COM - Uses any type of hearing aids** “Do you use any aids, specialized equipment, or services for persons who are deaf or hard of hearing, for example, a volume control telephone or TV decoder?” 1 Yes 2 No
6148 - Eye problems/disorders "Has a doctor told you that you have any of the following problems with your eyes?” 1 Diabetes related eye disease 2 Glaucoma 3 Injury or trauma resulting in loss of vision 4 Cataract 5 Macular degeneration 6 Other serious eye condition	**ICQ_CATRCT_COM – Ever had cataracts** “Has a doctor ever told you that you have cataracts?” 1 Yes 2 No **ICQ_GLAUC_COM – Ever had glaucoma** “Has a doctor ever told you that you have glaucoma?” 1 Yes 2 No **CCC_MACDEG_COM - Macular degeneration** “Has a doctor ever told you that you have macular degeneration?” 1 Yes 2 No
	VIS_AID_COM - Vision aids use “Besides glasses or contact lenses, do you use any aids or specialized equipment for persons who are blind or visually impaired, for example, magnifiers or Braille reading materials?” 1 Yes 2 No
20544 - Mental health problems ever diagnosed by a professional "Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't have it currently?” 1 Social anxiety or social phobia 2 Schizophrenia 3 Any other type of psychosis or psychotic illness 4 A personality disorder 5 Any other phobia (eg disabling fear of heights or spiders) 6 Panic attacks 7 Obsessive compulsive disorder (OCD) 10 Mania, hypomania, bipolar or manic-depression **11 Depression** 12 Bulimia nervosa 13 Psychological over-eating or binge-eating 14 Autism, Asperger’s or autistic spectrum disorder	**DPR_CLINDEP_COM - Clinical depression** 1 Yes 2 No

15 Anxiety, nerves or generalized anxiety disorder 16 Anorexia nervosa 17 Agoraphobia 18 Attention deficit or attention deficit and hyperactivity disorder (ADD/ADHD)	
20506 - Recent feelings of nervousness or anxiety "Over the last 2 weeks, how often have you been bothered by any of the following problems? [anxiety symptoms] Feeling nervous, anxious or on edge" 1 Not at all 2 Several days 3 More than half the days 4 Nearly every day	**PER_ANX_MCQ - TIPI scale: Sees oneself as anxious and easily upset** “Has a doctor ever told you that you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?” 1 Yes 2 No
20127 - Neuroticism score This is an externally derived summary score of neuroticism, based on 12 neurotic behaviour domains. Questions included: • Does your mood often go up and down? • Do you ever feel 'just miserable' for no reason? • Are you an irritable person? • Are your feelings easily hurt? • Do you often feel 'fed-up'? • Would you call yourself a nervous person? • Are you a worrier? • Would you call yourself tense or 'highly strung'? • Do you worry too long after an embarrassing experience? • Do you suffer from 'nerves'? • Do you often feel lonely? • Are you often troubled by feelings of guilt? Participants could answer Yes, No, Do not know or Prefer not to answer. This field summarises the number of Yes answers across these twelve questions into a single integer score for each participant.	
Personality Traits	
1920 - Mood swings "Does your mood often go up and down?" 0 No 1 Yes **1930 - Miserableness** "Do you ever feel 'just miserable' for no reason?" 0 No 1 Yes **1940 - Irritability** "Are you an irritable person?" 0 No 1 Yes **1950 Sensitivity / hurt feelings** "Are your feelings easily hurt?" 0 No 1 Yes **1960 - Fed-up feelings** "Do you often feel 'fed-up'?" 0 No 1 Yes	**K10_WRTHLSS_MCQ - K10 scale: Frequency feeling worthless - past 30 days** 1 All of the time 2 Most of the time 3 Some of the time 4 A little of the time 5 None of the time **K10_HPLS_MCQ - K10 scale: Frequency hopeless - past 30 days** 1 All of the time 2 Most of the time 3 Some of the time 4 A little of the time 5 None of the time **K10_TIRED_MCQ - K10 scale: Frequency tired out - past 30 days** 1 All of the time 2 Most of the time 3 Some of the time 4 A little of the time 5 None of the time

1970 - Nervous feelings
"Would you call yourself a nervous person?"
0 No
1 Yes

1980 - Worrier / anxious feelings
"Are you a worrier?"
0 No
1 Yes

1990 - Tense / 'highly strung'
"Would you call yourself tense or 'highly strung'?"
0 No
1 Yes

2000 - Worry too long after embarrassment
"Do you worry too long after an embarrassing experience?"
0 No
1 Yes

2010 - Suffer from 'nerves'
"Do you suffer from 'nerves'?"
0 No
1 Yes

K10_NRVS_MCQ - K10 scale: Frequency nervous - past 30 days
1 All of the time
2 Most of the time
3 Some of the time
4 A little of the time
5 None of the time

K10_NRVSCLMD_MCQ - K10 scale: Frequency could not calm down - past 30 days
1 All of the time
2 Most of the time
3 Some of the time
4 A little of the time
5 None of the time

K10_RSTLS_MCQ - K10 scale: Frequency restless or fidgety - past 30 days
1 All of the time
2 Most of the time
3 Some of the time
4 A little of the time
5 None of the time

K10_RSTLSSTL_MCQ - K10 scale: Frequency can not sit still - past 30 days
1 All of the time
2 Most of the time
3 Some of the time
4 A little of the time
5 None of the time

DEP_FRFL_COM - CES-D 10 scale: Frequency feel fearful or tearful
“How often did you feel fearful or tearful?”
1 All of the time (5-7 days)
2 Occasionally (3-4 days)
3 Some of the time (1-2 days)
4 Rarely or never (less than 1 day)

DEP_BOTR_COM - CES-D 10 scale: Frequency easily bothered
“How often were you bothered by things that usually don’t bother you?”
1 All of the time (5-7 days)
2 Occasionally (3-4 days)
3 Some of the time (1-2 days)
4 Rarely or never (less than 1 day)

DEP_GTGO_COM - CES-D 10 scale: Frequency feel could not 'get going'
“How often did you feel that you could not “get going”?”
1 All of the time (5-7 days)
2 Occasionally (3-4 days)
3 Some of the time (1-2 days)
4 Rarely or never (less than 1 day)

4526 - Happiness
"In general how happy are you?"
1 Extremely happy
2 Very happy
3 Moderately happy
4 Moderately unhappy
5 Very unhappy
6 Extremely unhappy

DEP_HAPP_COM - CES-D 10 scale: Frequency feel happy
"How often were you happy?”
1 All of the time (5-7 days)
2 Occasionally (3-4 days)
3 Some of the time (1-2 days)
4 Rarely or never (less than 1 day)

709 - Number in household "Including yourself, how many people are living together in your household? (Include those who usually live in the house such as students living away from home during term, partners in the armed forces or professions such as pilots)"	**SN_LIVH_NB_COM - Number of people living in household (excluding the participant)** “How many people, not including yourself, currently live in your household?”
1031 - Frequency of friend/family visits "How often do you visit friends or family or have them visit you?" 1 Almost daily 2 2-4 times a week 3 About once a week 4 About once a month 5 Once every few months 6 Never or almost never 7 No friends/family outside household	**SPA_OUTS_COM - Frequency of participation in family / friends activities out of household** “In the past 12 months, how often did you participate in family- or friendship-based activities outside the household?” 1 At least once a day 2 At least once a week 3 At least once a month 4 At least once a year 5 Never
4570 - Friendships satisfaction "In general, how satisfied are you with your friendships?" 1 Extremely happy 2 Very happy 3 Moderately happy 4 Moderately unhappy 5 Very unhappy 6 Extremely unhappy	
4559 - Family relationship satisfaction "In general, how satisfied are you with your family relationships?" 1 Extremely happy 2 Very happy 3 Moderately happy 4 Moderately unhappy 5 Very unhappy 6 Extremely unhappy	
	SN_FRND_NB_COM - Number of close friends **“**Not counting family members, how many people do you consider close friends – that is, people you can confide in and talk over personal matters with?”
1873 - Number of full brothers "How many brothers do you have? (Please include those who have died, and twin brothers. Do not include half-brothers, step-brothers or adopted brothers)" **1883 - Number of full sisters** "How many sisters do you have? (Please include those who have died, and twin sisters. Do not include half-sisters, step-sisters or adopted sisters)"	**SN_SIBLIV_NB_COM - Number of living siblings** “How many, if any, living siblings (sisters, brothers) do you have?”
728 - Number of vehicles in household "How many cars or vans are owned, or available for use, by you or members of your household? (Please include company vehicles if available for private use)" 1 None 2 One 3 Two 4 Three 5 Four or more	
738 - Average total household income before tax "What is the average total income before tax received by your household?" 1 Less than 18,000 2 18,000 to 30,999	**INC_TOT_COM - Total household income** “What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?” 1 Less than $20,000

3 31,000 to 51,999 4 52,000 to 100,000 5 Greater than 100,000	2 $20,000 or more, but less than $50,000 3 $50,000 or more, but less than $100,000 4 $100,000 or more, but less than $150,000 5 $150,000 or more
26414 - Education score (England) This domain measures the extent of deprivation in terms of education, skills and training in an area. The indicators are structured into two sub-domains: one relating to children and young people and one relating to adult skills. These two sub-domains are designed to reflect the 'flow' and 'stock' of educational disadvantage within an area respectively.	
845 - Age completed full time education "At what age did you complete your continuous full-time education?"	**ED_HSGR_COM - Education high school graduated** “Did you graduate from high school (secondary school)?” 1 Yes 2 No
	ED_HIGH_COM – Education highest degree “What is the highest degree, certificate, or diploma you have obtained?” 1 No post-secondary degree, certificate, or diploma 2 Trade certificate or diploma from a vocational school or apprenticeship training 3 Non-university certificate or diploma from a community college, CEGEP, school of nursing, etc. 4 University certificate below bachelor’s level 5 Bachelor’s degree 6 University degree or certificate above bachelor’s degree
20118 - Home area population density - urban or rural The classification is derived by combining each participant’s home postcode with data generated from the 2001 census. 1 England/Wales - Urban - sparse 2 England/Wales - Town and Fringe – sparse 3 England/Wales - Village – sparse 4 England/Wales - Hamlet and Isolated dwelling – sparse 5 England/Wales - Urban - less sparse 6 England/Wales - Town and Fringe - less sparse 7 England/Wales - Village - less sparse 8 England/Wales - Hamlet and Isolated Dwelling - less sparse 9 Postcode not linkable 11 Scotland - Large Urban Area 12 Scotland - Other Urban Area 13 Scotland - Accessible Small Town 14 Scotland - Remote Small Town 15 Scotland - Very Remote Small Town 16 Scotland - Accessible Rural 17 Scotland - Remote Rural 18 Scotland - Very Remote Rural	**SDC_URBAN_RURAL_COM – Urban / rural classification** 0 Rural 1 Urban core 2 Urban fringe 3 Urban population centre outside CMA and CA 6 Secondary core 9 Postal code link to dissemination area

Supplementary Table 1. Details on the examined risk factors and social indicators per cohort. A "drink" is defined as one unit of alcohol.

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Bridge

Our investigation leverages extensive population-scale data to elucidate the intersecting mechanisms linking both perceived and objective social isolation—manifested as loneliness and lack of social support—with ADRD risk. By exploring these connections, we aim to inform public health strategies and interventions designed to mitigate the risk of ADRD, ultimately contributing to better health outcomes and quality of life for the aging population.

In the initial phase detailed in Chapter 1, we capitalized on two large and nationally representative cohorts – the UKBB and the CLSA – to illuminate the complex behavioural associations between social isolation and a comprehensive suite of lifestyle, physical health, mental health, and societal factors that are well-established in ADRD aetiopathology. The findings highlight that both loneliness and lack of social support are significantly associated with a range of modifiable ADRD risk factors. These include negative health behaviours such as sleep disturbances, smoking, alcohol consumption, binge-watching television and insufficient physical exercise, all of which have been consistently linked to cognitive decline and the development of dementia. The study's broad focus on various health and lifestyle ADRD risk traits reveals consistent patterns across both population cohorts and reinforces the significance of social factors in the context of ADRD risk.

In Chapter 2, building on the observed behavioural associations in Chapter 1, we aim to provide a nuanced understanding of the underlying biological mechanisms between social isolation and ADRD risk. By employing advanced genetic correlation analyses, Chapter 2 will elucidate the

shared genetic architecture between social isolation and major ADRD risk factors. Our study will investigate how loneliness and lack of social support are genetically intertwined with classical ADRD risk factors such as neuroticism, sleep disturbances, smoking, and hearing problems. Based on the 2020 report of the Lancet Commission on dementia prevention [14], we selected 51 traits from the UKBB and 43 traits from the CLSA that reflected these widely acknowledged modifiable risk factors for ADRD in Chapter 1. In Chapter 2, we will expand on those risk factors to include 27 and 15 more nuanced variables in the UKBB and the CLSA, respectively. For instance, in the UKBB, we expand our socioeconomic status factors to include "Employment Deprivation Score" and "Employment Status: Paid Employment / Retired / Unable to Work / Unemployed." Furthermore, through partitioned heritability analyses and gene-set analyses, we will identify genetic variants associated with specific tissues, cell types, and functional genomic categories, thereby offering insights into the biological pathways linking social isolation and ADRD risk. This genetic perspective will deepen our understanding of the interplay between genetic predispositions and social behaviours, ultimately contributing to more targeted and effective interventions for ADRD prevention. Given access to two of the largest and most comprehensive population-based cohort studies, providing both extensive phenotypic and genetic data, our investigation was uniquely positioned to transition from behavioural analyses to genetic analyses. This approach will enable us to gain a more holistic view of the intersections between social isolation and ADRD risk.

Chapter 2: Intersecting genetic mechanisms of social isolation and classic Alzheimer's disease risk factors

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Abstract

Loneliness and lack of social support are a growing burden on our societies; linked to various physical and psychological problems. Risk factors associated with Alzheimer's disease and related dementias (ADRD) have been investigated in separate studies yet resemble those of social isolation. We thus interrogated the relationship between social isolation and ADRD risk through the lens of pathway-, cell-type- and tissue-specific bases of risk heritability. In 361,129 UK Biobank participants, we explored the genetic variants associated with social isolation and ADRD risk factors. Integrating genome-wide association studies (GWAS) from 80 well-established ADRD risk phenotypes and 10 GWAS on ADRD and capitalizing on the gene expression of specific cell types and tissues, we identified molecular overlap between the genetic architecture underlying ADRD risk and both facets of social isolation, across several different body systems, not just the brain. Our population-scale assessment suggests that the examined social lifestyle determinants are genetically intertwined with risk factors of ADRD-related neurodegeneration. Such new insight is imperative given that social behaviours are modifiable in principle.

Introduction

Social isolation is a growing public health concern. There is now slowly compounding evidence that the quality and quantity of social relationships are important factors in the genesis of neurodegenerative diseases and early mortality [1-6]. For instance, Kuiper et al. (2015) demonstrated a robust association between poor social relationships and increased risk of dementia, highlighting the critical role of social connections in cognitive health [3]. One notable meta-analysis by Julianne Holt-Lunstad and colleagues found that social isolation increases the likelihood of mortality by 29% [4]. In fact, in 2021, the WHO identified social isolation as a growing public health priority among older people [7]. Loneliness, as a self-perceived form of social isolation, is a universal human experience and a notable issue among older adults. Studies conducted in Europe [8-12] and North America [9, 13, 14] have reported that loneliness is a frequent issue among older adults, with an overall prevalence of 10-30%. Around one in five people in the U.S. [14] and around one in four people in the UK over the age of 65 suffer from loneliness [12]. The risks of social isolation may now be aggravated due to chronic social deprivation as a consequence of the COVID-19 pandemic. After a prolonged period of social distancing restrictions imposed since the outbreak of COVID-19, studies have shown that levels of loneliness have escalated [15, 16]. According to one definition, loneliness is the distressing feeling that one's social needs are not being met by one's current social relationships and available social venues [17]. Loneliness has also been defined as the experienced discrepancy between an individual’s desired and actual social exchange with others [18]. These views acknowledge that people can live in solitude and not feel lonely. Conversely, individuals can be embedded in a tightly-knit social life and still feel lonely.

Instead, as a measure of objective social isolation, lack of social support is the factual absence of regular interactions with members of strong and supportive social networks [19]. As such, perceived social isolation (i.e., loneliness) is often considered to be distinct from objective social isolation (i.e., social support). A rich social network may not mitigate loneliness and a factually solitary lifestyle does not necessarily imply feeling lonely or disconnected [17]. Previous epidemiological studies have indeed suggested [20] that perceived and objective social isolation play important independent roles in brain aging and its aberrations seen in neurodegenerative disease. High levels of loneliness and lack of social support from friends or relatives are both strongly related to various negative health outcomes, particularly amongst the elderly [4].

The etiology and underlying genetic mechanism of social isolation have been examined in several studies. Such genetic association studies have identified a heritable component of loneliness. In twin and family studies, genetic factors explained ~37% of the individual differences in loneliness [21]. In Dutch twin studies, the genetic contribution to individual differences in loneliness was estimated at 48-77% [22, 23]; while molecular genetic variants accounted for 14–27% [24]. Together, these observations suggest that there is an innate component to the propensity to feel lonely. In addition to genetic components, loneliness and lack of social support are associated with a range of modifiable behavioural traits that are related to social engagement, including physical activity, obesity risk, and smoking habits [25-27]. Our previous work found associations between both these facets of social isolation and an extensive range of behavioural, physical, psychological, and socioeconomic risk factors of Alzheimer's disease and related dementias (ADRD) at the population level [28]. This behavioural study carefully examined classical ADRD risk factors, such as depression, hypercholesterolemia, diabetes, hearing and

vision loss, and hypertension, and explored other widely agreed upon modifiable factors, such as education, exercise, socioeconomic status, smoking, alcohol consumption, sleep apnea, and air pollution [29, 30].

Alzheimer's disease and related dementias is a major progressive neurodegenerative disease – clinically characterized by a deterioration in cognition, affect and behaviour; thus interfering with functional capacity and daily living. Among other pathological features, ADRD is commonly linked to polymorphisms in the gene apolipoprotein E (*APOE*) and the reactivity of astrocytes and microglia [31, 32]. *APOE*, the single most explanatory genetic risk factor for ADRD [33, 34], is responsible for maintaining fat homeostasis by mediating lipid transport [35, 36]. High expressions of apolipoprotein *APOE* are observed in the brain, mainly by astrocytes and microglia [37]; but also in the liver and peripheral immune cells including monocytes and macrophage cells [38]. While AD progression has previously been shown to depend on inflammation and activation of immune cells, which is consistent with the increase of systemic inflammation with old age [39], the role of adaptive immunity in AD remains poorly understood [40].

As the motivation for the present investigation, there is evidence of the widespread associations between chronic social deprivation and various health outcomes, as well as the risk factors of ADRD. Yet, the biological underpinnings shared between social isolation and ADRD risk remain unclear. While previous studies [41-43], have confirmed heritable components for both social isolation and ADRD and explored potential genetic links using methods like Mendelian Randomization and polygenic risk scores, there remains a need for further investigation into the direct genetic mechanisms that may be shared between these two public health priorities. To

address this gap, we aim to answer the following research question: What are the genetic mechanisms that intersect social isolation and ADRD risk factors? Specifically, we aim to: 1) quantify the genetic overlap between social isolation and ADRD risk factors, and 2) characterize the genetic variants associated with specific tissues, cell types, and functional genomic categories relevant to these conditions. By employing comprehensive bioinformatic analyses, we provide a full picture of the biological mechanisms contributing to these health concerns. We quantified the genetic overlap between social isolation and ADRD risk in 361,129 participants from the UK Biobank (UKBB) and 22,741 participants from the Canadian Longitudinal Study on Aging (CLSA) – two of the largest and most comprehensive population-based cohort studies, providing extensive genetic, phenotypic, and health data. We tested the hypothesis that social isolation has a shared genetic component with ADRD risk factors. For that purpose, we performed a series of analyses using genome-wide association studies (GWAS) summary statistics for each target phenotype to characterize the overlap in genetic mechanisms between social isolation indicators and complex human traits related to personality, cognition (e.g. fluid intelligence and prospective memory), substance use, social connections, and physical and mental health. We further aimed to systematically chart genetic variants associated with specific tissues, cell types, and functional genomic categories. The premise of our study is that a wider characterization of these social lifestyle determinants in mid to late-life will advance the conceptualization of ADRD risk, potentially paving the way for novel treatment avenues. Such new insight is imperative given that social behaviours are modifiable in principle through societal measures [44], in stark contrast to genetic risk such as that conferred by *APOE*.

Results

Social isolation is genetically intertwined with ADRD risk factors

We set out to systematically explore the nature and extent of shared genetic contributors between major ADRD risk factors and key aspects of social isolation. We performed GWAS on the self-reported responses to the questions about loneliness and social support, available from the UK Biobank (N = 361,129). Genome-wide significant SNPs associated with the two social isolation dimensions were mapped to corresponding genes. FUMA provides insights into the overlap of differentially expressed genes (DEGs) across various tissue types, based on GWAS summary statistics [45]. Specifically, FUMA assesses the proportion of overlapping genes between different target phenotypes, offering an overview of shared biological signalling pathways. This analysis helps identify gene sets that may be involved in multiple phenotypic traits, potentially indicating pleiotropy—where a single gene influences more than one trait. We present a FUMA plot that highlights the proportion of overlapping genes between our target phenotypes, loneliness and social support, and other traits such as "Alzheimer's disease and fasting glucose levels (pleiotropy)" and "Neuroticism" that were already previously reported in the FUMA catalog (Fig. 1). The GWAS "Alzheimer's disease and fasting glucose levels (pleiotropy)" shows a possible pleiotropic relationship, where the same set of genes might contribute to both Alzheimer's disease risk and fasting glucose levels. The plot illustrates that not only did both social traits show notable overlap with their corresponding previously reported GWAS from the FUMA GWAS Catalog, but that the genes associated with both loneliness and lack of social support show significant overlap with genes associated with neuroticism and with Alzheimer's disease and fasting glucose levels. That is, we observed sets of implicated genes that were identified as simultaneously underlying

heritability for both social isolation and ADRD, perhaps as an instance of pleiotropy (where a gene affects two or more seemingly unrelated phenotypic traits). As FUMA builds on MAGMA, FUMA was not included in our main analyses but as a confirmational gene-level analysis. Hence, the prioritized genes from the social traits are overrepresented in similar sets as the prioritized genes from Alzheimer's disease or fasting glucose levels.

Motivated by this first brick of evidence, we subsequently conducted systematic genome-wide association analyses on our collection of 80 phenotypes with known ADRD risk. To crosscheck our results, we used ten different previously published GWAS summary statistics on Alzheimer's disease from the largest-in-kind studies (cf. Methods). We used LDSC to estimate SNP-based heritability for each phenotype (Supplementary Tables 1 and 2). We estimated the SNP-based heritability of our loneliness and lack of social support phenotypes to be 7.85% (S.E. 0.0046) and 4.13% (S.E. 0.0023), respectively.

The resulting GWAS summary statistics were then used in genome-wide genetic correlation assays in LDSC (Fig. 2, left) to probe the constellation of "genetic real estate" that may be shared with known risk factors of ADRD. Indeed, we found various strong pairwise genetic correlations between the target social richness indicators and major ADRD risk traits. Loneliness exhibited significant genetic correlations with 60 complex traits, including wide-ranging genetic overlap with neuroticism ($r_g = 0.72$, $p = 0.0$), stress as measured by experiencing fed-up feelings ($r_g = 0.81$, $p = 0.0$) and depressive symptoms ($r_g = 0.74$, $p = 8.12\text{e-}7$). In contrast, loneliness phenotype showed strong negative genetic links with happiness ($r_g = -0.56$, $p = 2.46\text{e-}12$), friendship satisfaction ($r_g = -0.44$, $p = 2.81\text{e-}8$), household income ($r_g = -0.47$, $p = 5.75\text{e-}76$),

financial satisfaction (r_g = -0.46, p = 5.51e-12), and health satisfaction (r_g = -0.52, p = 4.47e-17). Objective social isolation, as examined here by lack of social support, shared significant genetic overlap with 48 traits in a similar pattern to loneliness, such as fed-up feelings (r_g = 0.43, p = 1.61e-51), family satisfaction (r_g = -0.54, p = 8.18e-10), happiness (r_g = -0.53, p = 2.35e-9). On the other hand, some of the ADRD summary statistics only showed strong genetic links with risk traits related to education, socioeconomic status, and cardiovascular health.

To probe for coherent groups of genetic correlation between phenotype pairs, we deployed hierarchical clustering to uncover overlaps among all the target traits. The phenotypes were aggregated into groups based on their respective collective genetic links with the remaining phenotypes. Both aspects of social isolation belonged to the same spectral cluster, along with the majority of the classical ADRD risk factors, including smoking, education, socioeconomic status, exercise, personality traits, hearing impairment, and diabetes. The ADRD summary statistics were highly correlated with each other but showed little significant correlations with their other classical risk factors. All genetic correlation results can be found in Supplementary Figure 2.

We investigated the genetic links between this envelope of phenotypes using MAGMA to cross-check the results on genetic overlap patterns. This platform identifies the shared genome-wide significant genes (including only protein-coding loci) between two traits, complementary to LDSC which calculates the per-SNP genetic covariance (including protein-coding and non-protein-coding loci). By analyzing the underlying genes of each phenotype, the MAGMA results showed strong genetic overlap between the social isolation dimensions, personality traits, hearing difficulty, and income (Fig. 2, right). Similar to the genetic correlations obtained by LDSC, the

ADRD summary statistics showed strong genetic overlap with themselves, and less so with their well-established risk factors in MAGMA. Note that the MAGMA heatmap in Figure 2 is asymmetric (cf. Methods), and the conclusions derived are based on the horizontal genetic overlap results. Consequently, we observed broadly similar patterns of genetic correlations in the LDSC and MAGMA analyses.

To further explore modes of mechanistic interlockings of social isolation and the ADRD risk factors, we computed the average of the genetic correlation results across all phenotypes for each complex trait in LDSC. The average here refers to the mean value of the genetic correlations. The genetic correlations were first converted to absolute values to emphasize the magnitude of genetic association, rather than directionality. Across all 90 phenotypes, loneliness and lack of social support – not ADRD – held the highest average genetic correlation magnitudes (Fig. 3, left). We repeated our analysis in MAGMA by taking the average genetic overlap across all phenotypes for each trait and found striking similar results (Fig. 3, right). In both analyses, subjective and objective aspects of social isolation, but exceptionally loneliness, maintained high average genetic overlap across all phenotypes. These findings persisted even when we excluded the personality traits, which hold the highest genetic overlaps with loneliness and lack of social support (Supplementary Fig. 3).

Partitioned heritability of social isolation and ADRD risk traits show similar patterns of enrichment

To quantitatively dissect the biological pathways underlying the phenotypes under study, we brought to bear s-LDSC to 80 quantitative traits and 20 ADRD GWAS (including and

excluding the *APOE* region). We first used s-LDSC with the full baseline model to test for the enrichment of 24 annotations that are not specific to any cell type, including coding regions, enhancers, introns, and evolutionarily conserved regions in the genome [41]. Of these 24 functional categories, the genetic signals for regions conserved in mammals were significantly enriched for the social traits and several major ADRD risk traits in LDSC (Fig. 4, left). ADRD was most significantly enriched in H3K27ac histone marks (defined as an active enhancer mark [42]) and super-enhancers. Among the classical ADRD risk traits, the ADRD summary statistics shared overlapping genetic signals with cardiovascular health and diabetes.

By integrating structured knowledge from highly resolved gene expression annotations, we sought to identify the relevant cells, tissues, and brain regions potentially implicated in phenotypes of ADRD risk factors. We performed several cell type-specific enrichment analyses in s-LDSC using annotations established in different previous studies (Fig. 5, left). In parallel, we capitalized on MAGMA to identify phenotype-relevant gene sets associated with the same cell-type group datasets as LDSC (Fig. 5, right). The figures for MAGMA show the P-values from the model coefficients to inform on the significance of the gene set for a given phenotype. For each annotation, the trait-specific results are grouped and averaged into phenotype groups representing a major risk category for the same annotations. For example, ‘Alcohol intake frequency’, ‘Alcohol intake versus 10 years previously’, and ‘Amount of alcohol drunk on a typical drinking day’ were combined together across the gene expression enrichment for each annotation to form the phenotype group ‘Alcohol Intake’.

The cell-type group analyses revealed distinct enrichment patterns for loneliness, lack of social support, and ADRD risk. Loneliness and lack of social support share mechanistic overlaps in their stratified heritability with several other major ADRD risk factors in LDSC especially. ADRD, on the other hand, is relatively more divergent from its risk factors, except for the physical health traits. In both LDSC and MAGMA, loneliness and especially lack of social support are enriched in the CNS. In other words, SNPs associated with both aspects of social isolation were also overexpressed in the central nervous system, highlighting the CNS as an important tissue involved in social richness. Several other ADRD risk factors including smoking, alcohol intake, education, electronic use, and sleep were also enriched in the CNS. Further, ADRD was highly enriched in the immune system. Moreover, based on the tissue-specific GTEx annotations, ADRD showed high enrichment for blood and spleen body systems, and no significant enrichment for any brain-related tissues in both LDSC and MAGMA. Cardiovascular health, diabetes, and vision also showed no significant enrichments for any brain-related tissues in both LDSC and MAGMA. Loneliness and lack of social support were enriched in brain-related annotations and showed similar enrichment patterns to major ADRD risk factors, except for risk traits related to physical health, such as diabetes and cardiovascular health.

The main takeaways from the cell-type- and tissue-specific enrichment analyses are the enrichment patterns for loneliness and lack of social support in neurons and brain-related tissues, and for ADRD in blood and immune-related cells and tissues, corroborated across the two distinct partitioned heritability frameworks (LDSC and MAGMA).

Clustering of the enrichment analyses

To identify deeper mechanistic overlap between phenotypes, we next evaluated correlations among traits based on their associations with 568 tissue- and cell-type-specific annotations. We concatenated the full set of screened 568 genetic annotations into a single vector of enrichment properties for each phenotype. We created a matrix of enrichment P-values for each given annotation across the 10 ADRD GWAS (including the APOE region) and the 80 ADRD risk factors (90x568). We repeated the process to create a 90x568 matrix with the 10 ADRD GWAS excluding the APOE region for validation purposes. We then computed a correlation matrix to find the correlation in the pattern of partitioned heritability between each phenotype (90x90). The trait-specific correlations from the enrichment results were further clustered to explore mechanistic similarities (Fig. 6, left). We also averaged the trait-specific correlations according to the risk categories and the major risk groups were hierarchically clustered based on enrichment patterns in stratified gene expression (Fig. 6, right). Phenotypes implicating similar cell types and tissues were identified by hierarchical clustering. The spectral clustering analysis on the UKBB revealed that the majority of classical ADRD risk factors were reflected in the first cluster containing both social richness determinants in LDSC and MAGMA. The first main cluster reflected traits from all risk pillars, including lifestyle and behavioural factors (sleep, use of electronics, smoking), personality traits (neuroticism), physical health (hearing difficulties), and socioeconomic status (household income, financial satisfaction). Corroborated across the two analysis frameworks, ADRD summary statistics were situated in the same group as cardiovascular health, diabetes, vision, and mood disorders, though with small correlation values. Consistent with genetic correlation patterns, the multidimensional clustering revealed that the social dimensions were highly correlated and closely clustered with several ADRD risk traits**,** after accommodating effects for age and sex

differences. Conversely, ADRD was comparatively less clustered with the other major risk traits. The complete cross-correlation results are shown in Supplementary Figure 6.

Discussion

The present study traces the multifaceted inter-relations between social isolation and major ADRD risk factors based on their genetic architectures. Our collective findings suggest that both perceived and objective facets of social isolation – loneliness and lack of social support – share genetic components with classical ADRD risk factors, but less so with ADRD itself. In fact, across a comprehensive portfolio of genetic correlation assays, the major ADRD risk factors showed a stronger genetic link with social isolation factors than with ADRD. We further explored which cell type-, tissue-, and pathway-specific genomic signatures were most salient to the biological processes regulating the two social traits and ADRD risk. To the best of our knowledge, this is the first study that explicitly targeted the possible biological overlaps between social isolation and ADRD by advanced population genetic analyses.

By systematically charting genetic correlations across 80 quantitative traits and 10 previously published ADRD summary statistics, we have demonstrated that the genetic factors contributing to social isolation are intertwined with ADRD risk factors at a fundamental biological level. In our previous work, we showed that loneliness and lack of social support were systematically associated with classical ADRD risk factors at the behavioural level [28]. The present genetic correlation analyses (LDSC) extended several observations from our own epidemiological findings, such that both loneliness and lack of social support shared important amounts of genetic variation with almost all major ADRD risk factors, including neurotic personality traits, sleep disturbance, smoking, and hearing problems. These results suggest that the genetic predispositions for social isolation and ADRD risk factors overlap, highlighting a shared biological basis. Moreover, loneliness (mean genetic correlation r_g: 0.34) and lack of social support

(mean genetic correlation r_g: 0.21) held high average genetic correlations across our catalogue of examined phenotypes related to classic ADRD risk factors. While the overlap of significant genes based on MAGMA-based gene analyses indicated smaller genetic overlap, the average proportion of overlapping genes across all the ADRD risk phenotypes was also high for loneliness (mean genetic overlap: 10.0) and lack of social support (mean genetic overlap: 6.36), especially compared with the ADRD summary statistics. These findings indicate that the classic risk factors of ADRD share a strong overlap in underlying genetic variants with each other. The major ADRD risk factors share a greater genetic intersection with both aspects of social isolation than with ADRD. Currently, the conceptual framework, supported by existing literature, suggests that social connectedness influences psychological factors, lifestyle engagement, and treatment adherence, which in turn affect gene expression and immunological responses. For instance, social connectedness has been linked to improved mental and physical health outcomes, such as reduced depression, anxiety, and coronary heart disease, which can influence overall health and cognitive function [5, 26, 48]. These behavioral and psychological factors have already been shown to drive changes in gene expression and immune function, contributing to the biological processes underlying aging and disease [49].

To corroborate our present genome-wide results, we compared the proportion of overlapping FUMA-mapped genes between our genome-wide association results and previously reported GWAS data. Not only did both social traits show notable overlap with their corresponding previously reported GWAS from the GWAS Catalog, but these traits also shared high proportions of overlap with ADRD, as well as neuroticism. Our FUMA results showed that the genes of interest associated with the social isolation measures are enriched in pre-defined gene sets that highly

overlap with genes of interest associated with Alzheimer's disease and neuroticism. This finding provides further evidence supporting the notion that there are possibly shared biological processes in the genetic foundations of social isolation and ADRD. As such, the mechanistic pathways among the investigated phenotypes clearly demonstrated a degree of agreement.

Notably, our results showed the genetic correlations between loneliness and the 10 ADRD GWAS to be consistently low. Indeed, the genetic correlation between perceived social isolation and ADRD has been repeatedly shown to be low [27, 50-52], yet the possible relationship between social isolation and ADRD has been garnering increasing attention in recent years [2, 53-55]. Present and previous research converge on the conclusion that these two traits share a fair amount of variance with each other at the phenotypical level, but the variance that is heritable in origin is not shared across these traits. In contrast, our strong and consistent genetic correlations between loneliness and classical ADRD risk factors further support the claim that the interlocking of loneliness and ADRD is relatively more rooted in a shared basis in lifestyle factors and aspects of the living environment.

Among the observed general functional categories not specific to any cell type, the significantly higher enrichment of the associated variants from loneliness for conserved regions, greater than coding regions, is intriguing and confirms some previous research on loneliness [27]. Such conserved regions are loci sequences that are found in highly evolutionarily conserved genetic regions in mammals [46, 56, 57]. According to Cacioppo et al. (2014), the evolutionary psychology account posits that self-awareness of loneliness may have evolved as an aversive alarm signal, akin to pain, thirst, and hunger. This signal motivates individuals to repair and maintain

social relationships to protect their well-being, reproductive fitness, and ultimately the propagation of their genes [58]. This hypothesis provides context for understanding how social isolation might be biologically embedded in broader adaptive systems. It also suggests that loneliness functions as an adaptive mechanism to promote social engagement and, by extension, enhance survival and reproductive success. Our research findings revealed a consistent pattern of genetic enrichment between social isolation and several major ADRD risk factors, such as smoking, financial status, sleep disturbances, and electronic device use. We speculate that these findings may align with the evolutionary psychology notion in that social isolation and its associated risk factors reflect underlying biological and adaptive mechanisms that impact both social behaviour and health outcomes. Specifically, the overlap between social isolation and ADRD risk factors could indicate that our genetic foundation may have evolved to address social needs and also influence health risks associated with neurodegenerative diseases.

Additionally, our partitioned heritability analyses showed that the genetic architecture of ADRD features enrichments in super-enhancers and H3K27ac marks (defined as an active enhancer mark [47]). Enhancers are regulatory regions that control the expression levels of surrounding genes [59]. Super-gene enhancers generally refer to sets of active enhancers in close genomic proximity [60]. Dysregulation of specific enhancers may disrupt the activity of key genes that lead to the onset and progression of ADRD [59, 61]. Our findings suggest that ADRD shares an important intersection in the enrichment pattern underlying cardiovascular health and diabetes but shows a weaker overlap with other classical risk factors.

ADRD is traditionally considered a central nervous system disorder. However, converging experimental, epidemiological, and clinical evidence suggest that the multifaceted pathogenesis of ADRD might involve various processes beyond the brain [62]. In line with our current tissue-specific findings leveraging the GTEx resource, one study found that non-brain tissues, especially whole blood, were implicated in late-onset Alzheimer's disease pathology [63]. Bolstering our findings on cell type enrichments, another genetic study on Alzheimer's disease found that 77 genes unrelated to *APOE* and differentially associated with two dominant dimensions of brain atrophy – widespread brain atrophy and focal medial temporal lobe atrophy – were overrepresented in differentially expressed gene sets in organs other than the brain, including the heart, pancreas/pituitary gland, liver, muscle, and kidney [64]. While ADRD is predominantly a CNS disorder, our findings contribute to a growing body of evidence suggesting that systemic factors and various non-CNS tissues may also play a role in the disease's multifaceted pathogenesis. Contrary to the conventional textbook wisdom that ADRD will be solely enriched in the central nervous system, as a brain disease, the ADRD summary statistics used in our analyses were most enriched in the general immune system-related tissues and cells, notably the spleen (which is a hub of immune cells) and whole blood across both LDSC and MAGMA.

In line with a recent paper on immune system crosstalk in ADRD, we advocate that Alzheimer's disease should be viewed as a systemic disease that involves dynamic processes in the peripheral and central immune compartments [65]. Consistent with the high enrichment of ADRD in whole blood, the progression of ADRD was found to be accompanied by reduced cerebral blood flow in specific spatial patterns [66]. The blood-brain barrier, a highly selective semipermeable structural and chemical barrier which prevents foreign objects from invading the brain tissue, has

also been repeatedly shown to be involved in the pathogenesis of Alzheimer's disease, after the emergence of cognitive deficits [67-69]. The involvement of ADRD in the spleen is also in line with recent studies on the potential role of this immune organ in the genesis of ADRD [70, 71].

We further sought to identify the relevant cell and tissue types implicated in the regulation of loneliness and lack of social support. We explored which cell and tissue types were most relevant to the underlying biological processes regulating the examined social dimensions and the classic ADRD risk factors. Among the tissue-specific annotations, both loneliness and lack of social support were highly enriched within brain-related tissues in LDSC and MAGMA.

Consistently, previous gene-based association studies have found significant enrichment results for loneliness in regions surrounding genes preferentially expressed in the basal ganglia, cerebellum, cerebellar hemisphere, cortex, anterior cingulate cortex, and substantia nigra [27]. SNP-based studies found the genetic loci significantly associated with loneliness to regulate gene expression in five brain tissue compartments: cortex, frontal cortex, cerebellum, cerebellar hemisphere, and anterior cingulate cortex [27]. Another study of lonely individuals reported diminished activation in brain reward regions such as the nucleus accumbens [27]. And, among their 10 examined target cell types, Day et al. found that the gene expression enrichment for loneliness was only significant in the central nervous system [6].

The most important finding in our study was the interlocking pattern of enrichment between the social traits and the classical risk factors of ADRD. Looking at the cross-correlations throughout 568 enrichment analyses in cell-type and tissue annotations for our 100 target

phenotypes in the UKBB, we found that loneliness and lack of social support were closely grouped with major health-related risk factors of ADRD in both LDSC and MAGMA. We further uncovered that ADRD was most closely related to cardiovascular health, diabetes, and vision problems in both LDSC and MAGMA. These findings suggest that our target social traits play a particularly significant role in the genetic underpinnings of ADRD risk factors and hold a far stronger link relative to ADRD itself.

To ensure rigour in our findings and conclusions, we used two different statistical methods (LDSC and MAGMA) to connect the studied phenotype's genetic architecture to a cell type or tissue. These two methods are based on different assumptions and algorithms. In brief, with LDSC we determined enrichment by looking at the phenotype's *SNP-heritability* (including non-protein-coding genetic regions) in the most cell type- or tissue-specific genes. By means of MAGMA, we tested whether the *gene-level association* (excluding non-protein-coding genetic regions) with the trait increased with cell type-specificity. Both techniques account in different ways for confounders like linkage disequilibrium and gene size [72]. In aiming to reduce population heterogeneity effects while maintaining a large sample size, another limitation of our analysis was the need to restrict our analyses to the European ancestry to produce the GWAS results. Moreover, Our findings are therefore not necessarily applicable to populations from other ancestries. Finally, the CLSA cohort we used as an independent replication study to replicate the associates with individual loci was not of comparable size to the UK Biobank. Even with imputed genetic data from more than 20,000 participants available after quality control, the CLSA was too small to get interpretable heritability results, as shown in Supplementary Figures 3, 4 and 5. Genetic correlation measures were rendered complicated since if at least one trait is shown as non-heritable in the

smaller cohort of the CLSA, then the traits will not be genetically correlated because there will be no genetic basis for one of them. This represents a challenge for genetic studies of complex traits with extremely large discovery datasets, such as the UK Biobank, particularly for traits that are uncommonly measured.

In conclusion, our findings support the accumulating evidence that multiple dysfunctional processes may contribute to ADRD pathogenesis, placing a premium on processes outside the brain, such as components of the immune system. Our population-scale assessment suggests that the examined social lifestyle determinants are genetically interlocked with ADRD-related neurodegeneration risk factors. Especially loneliness, but also lack of social support, show strong mechanistic confluence with the heritable ADRD risk traits. The heritability enrichment profiles of social isolation in the CNS spotlight them as promising targets for preventive clinical action against stress, which further compounds as a classical risk to the immune system. Despite efforts to strictly define ADRD as a condition of only the CNS, our results nominate the rarely considered view that ADRD is a systemic body-wide disease.

Conclusion

Overall, our findings support the view that multiple pathological processes might contribute to AD pathogenesis, especially processes outside the brain. Our population-scale assessment suggests that the examined social lifestyle determinants are genetically interlocked with ADRD-related neurodegeneration risk factors. Especially loneliness, but also lack of social support, show strong mechanistic confluence with the heritable determinants of ADRD risk. The heritability enrichment profiles of social isolation in the CNS, adrenal pancreas and glial cells spotlight them as promising targets for preventive clinical action against stress, which further compounds as a classical risk to ADRD through the immune system. The cell-type specific analyses for social isolation underline that both neuronal and glial cells deserve closer attention for ADRD prevention. Despite efforts to strictly define ADRD as a CNS problem, our results indicate that ADRD should be viewed as a systemic disease, triggered by breakdowns in the whole body.

Methods

Two population cohorts

The UK Biobank (UKBB) constitutes a large prospective epidemiological cohort that combines behavioural and demographic assessments with genetic and cognitive measures [67]. This vast dataset follows a population of 502,506 individuals (52.84% females) recruited from across the United Kingdom (UK), aged 40–69 years at enrollment (mean age 56.5, SD 8.1 years). All participants provided written, informed consent and the study was approved by the Research Ethics Committee (REC number 11/NW/0382). Details about the UK Biobank project are provided at http://www.ukbiobank.ac.uk. Data for the current analyses were obtained under UK Biobank application number 25163. The mandate of this resource is to be approximately representative of the UK general population. A rich variety of phenotypic and health-related information is available on each participant, including biological measurements, lifestyle indicators, and imaging of the body and brain. Genome-wide microarray profiling has been collected on all UKBB participants, providing many opportunities to discover new genetic associations and the genetic bases of complex traits.

The Canadian Longitudinal Study on Aging (CLSA) is the largest existing prospective epidemiological cohort in Canada. This resource offers a wide range of phenotypic, genetic and brain-imaging information in 30,097 individuals (50.9% females), aged 44-89 when recruited (mean age 63.0, SD 10.3 years), from 11 cities across Canada [69]. The demographic characteristics of CLSA participants have been reported elsewhere [69]. Ethics approval was obtained by the Research Ethics Board at McGill University (REB file #20-05-068). The focus of

the CLSA initiative is to examine the aging process from mid-life to old age and offer researchers the advantage of studying the cumulative effect of factors on the health and disturbance of the aging population spanning from mid-life. Of relevance to the present study, the CLSA initiative also places special emphasis on characterizing a variety of social functions, including the amount of social engagement and social support, with their correspondences in biological, physical and psychological functions.

Target phenotype definition

Social isolation traits analyzed in this study were derived from self-reported answers to questions administered via the assessment centre touchscreen. For the loneliness target phenotype, we used the yes/no answer from the UK Biobank question 'Do you often feel lonely?' (data field 2020). Analogously, in CLSA, our loneliness target measure was based on the question 'How often did you feel lonely?', with the yes answer encoded as 'all of the time (5-7 days)'. For the social support target phenotype, our UK Biobank analyses were based on the question 'How often are you able to confide in someone close to you?', as a measure of the frequency of social support (data field 2110). Our study modelled lack of social support as all instances less than 'daily or almost daily'. Analogously, in CLSA, lack of social support was determined as whether the participants have 'someone to confide in or talk to about yourself or your problems?', where the answers 'all of the time' and 'most of the time' were taken as the negative case.

Regarding risk factors for Alzheimer's disease, the full description of the other key aetiopathological traits (78 in the UKBB and 58 in the CLSA) included in our analyses can be found in Supplementary Tables 1 and 2. These ADRD risk phenotypes were chosen based on our

previous work which described well-established and potentially modifiable risk factors of ADRD [70]. In total, 80 key ADRD risk phenotypes were used for genome-wide association studies (GWAS) and post-GWAS analyses, representing personal habits and lifestyle factors, physical health, mental health, and societal and external factors. In the UKBB and the CLSA, several items among the ADRD risk factors are defined such that the directionality of the numerical encoding is different from the encoding that we used in our present study. That is, in all our models, we ensured that a higher value consistently indicated a higher expression of a given phenotype; and that a lower value meant less. The entirety of our pre-processing for each item is available in our code (http://github.com/dblabs-mcgill-mila/ADCORR).

To quantify the risk for neurodegenerative disease, we examined ten GWAS summary statistics on Alzheimer's disease from several largest-in-kind studies; for the sake of replicability. 1) The Lambert et al. (2013) stage 1 GWAS is a meta-analysis of 4 previously published GWAS data sets consisting of 17,008 AD cases and 37,154 controls [71]. Marioni et al. (2018) provided four summary statistics based solely on the self-report of parental history of Alzheimer's dementia: 2) 27,696 cases of maternal AD (260,980 controls), 3) 14,338 cases of paternal AD (245,941 controls) from the UK Biobank, 4) a meta-analysis of log-odds and standard errors from 2) and 3) to define parental AD with 42,034 cases, and 5) a meta-analysis of 2), 3), and the summary statistics from the Lambert et al. stage 2 GWAS with 8,572 AD cases and 11,312 controls [72]. 6) The Kunkle et al. (2019) clinically diagnosed GWAS includes genotyped and imputed data from 21,982 Alzheimer's disease cases and 41,944 cognitively normal controls [73]. 7) Jansen et al. (2019) meta-analyzed several AD datasets, including previously published GWAS datasets, non-public datasets (PGC-ALZ), and the UK Biobank to create a large GWAS of clinically diagnosed

AD and AD-by-proxy (71,880 cases, 383,378 controls) [74]. 8) The first GWAS from Schwartzentruber et al. (2021) used 53,042 proxy cases from the UK Biobank, such that the AD status was based on individuals who were either diagnosed with AD or who reported a parent or sibling having dementia, and 355,900 controls [75]. 9) The second GWAS from Schwartzentruber et al. was formed from the meta-analysis of the first GWAS results with the Kunkle et al. GWAS described above (that does not contain participants from the UK Biobank), for a total of 75,024 cases (including proxies), and 397,844 controls [75]. 10) Finally, the Wightman et al. (2021) GWAS is the largest in terms of sample size and the most recent AD GWAS. Like Jansen et al., it includes both proxy and non-proxy cases from multiple cohorts, with 90,338 (46,613 proxy) cases and 1,036,225 (318,246 proxy) controls [76]. We used multiple ADRD GWAS in our validation analyses to determine whether results are replicable across a complementary set of cohorts.

Genotyping, imputation, and quality control

The UKBB March 2020 release provided microarray genotyping data for 489,212 individuals and 93,095,601 genetic variants. Genotype imputation was performed using the Haplotype Reference Consortium (HRC), UK10K haplotype resource, and 1000 Genomes Phase 3 reference panels. Details of the genotyping quality control (QC) were described elsewhere [77]. In addition to the QC performed by the UK Biobank, we followed more stringent quality control metrics previously used by the Neale Lab (http://www.nealelab.is/uk-biobank/). We further excluded participants who i) did not have genetically inferred sex the same as self-reported sex, ii) had high genotype missingness or extreme heterozygosity, and iii) were excluded from the kinship inference process or had ten or more 3rd-degree related relatives identified in the cohort. To acknowledge genetic ancestry as a major source of population stratification, we only included

individuals of European descent (both self-reported and genetically inferred) in our analyses. To this end, we restricted our analysis to individuals who self-identified by questionnaire as being of 'White-British', 'Irish', or 'White' ancestry. It is those subject samples that were used to compute the genetic principal components (data field 22020). Participants for whom the provided principal component (PC) score was closest to the average score of the European 1000 Genomes sample were considered to be of European descent: specifically, participants who were not within 7 standard deviations for the first 6 PCs were excluded from further analysis. Using PLINK 2, we filtered out subjects who showed high missing genotype rate (> 1%) and genetic variants that had high missing rate (> 1%), low minor allele frequency (< 0.001), low imputation INFO score (> 0.8), and significant deviation from Hardy-Weinberg equilibrium (*P-value* < 1e-10). After individual- and variant-level quality control in UKBB data, we considered 361,129 participants of white-British ancestry and 12,979,072 single nucleotide polymorphisms (SNPs).

The CLSA genetic data, released in 2020, provides microarray genotyping for 26,622 individuals and 307,467,504 genetic variants (including the sex chromosomes) [78]. We closely followed the same quality control protocols for the CLSA as used for the UK Biobank cohort. We removed participants from further analysis who i) did not have genetically inferred sex the same as self-reported sex, ii) were identified as outliers in genotype missingness or heterozygosity, and iii) had one relative of 3rd-degree or closer among the set of genotyped individuals. As in our UKBB data, we only included individuals of European genetic ancestry based on principal components analysis of the genotypes and were within 7 standard deviations for the leading 6 PCs, analogous to UKBB (cf. previous paragraph). The same genotype quality control metrics were

used in PLINK. After these quality control procedures, we were left with 22,741 subjects and 12,439,110 SNPs remaining as the basis for downstream analysis steps.

GWAS of phenotypes in UKBB and CLSA

Following careful curation of the phenotypic and genotypic data, we conducted genome-wide association analysis (GWAS) based on the 80 target risk phenotypes in the UKBB data using the fastGWA tool implemented in the Genetic Complex Trait Analysis (GCTA) software [79]. The fastGWA is a widely used tool for genome-wide analyses of biobank-scale data that controls for population stratification and for relatedness [80]. To adjust for potential subtle population stratification effects, we included the first 20 UKBB-provided genetic principal components as covariates. Following the recommendation of the developers and a previously implemented framework that conducted rigorous GWAS analysis of 7,221 high-quality phenotypes in the UK Biobank (https://github.com/Nealelab/UK_Biobank_GWAS), we considered several additional covariates in these analyses: age, sex, age2, sex*age, sex*age2. The full downstream genomic analysis steps for the UKBB are outlined in Supplementary Figure 1.

SNP-based heritability and genetic correlations

Based on the summary statistics obtained from GWAS, we then used LD score regression as implemented in the LDSC toolkit [41] to estimate the proportion of phenotypic variance that can be explained by genetic differences in the population, a statistic known as SNP-based heritability, h^2_{SNP}, for our social isolation measures and ADRD risk factors. LDSC computes an LD score by summarizing the correlations of a given SNP with all its neighbouring SNPs within

100 kb flanks. Further, the GWAS $\chi 2$ statistic was regressed against the LD score, and the slope obtained from LD Score regression provides an estimate of heritability (h^2_{SNP}) explained by all SNPs included in the LD score. We used precomputed LD scores that were calculated from the 1000 Genomes European data.

Next, genetic correlations (r_g) were calculated using LDSC between each pair of the psychiatric, behavioural, and lifestyle-related traits (initially 80 in the UKBB and 60 in the CLSA, including the social isolation traits) for which summary-level data were available and the 10 ADRD GWAS summary statistics (Table 1). Generally, genetic correlations range between −1 and 1. However, the LD score regression implemented in LDSC is not a bounded estimator. Hence, the r_g estimated by LDSC can slightly exceed the range. Genetic correlations for which the *P-value* survived the correction for multiple testing (Bonferroni-corrected $P < 0.00056$ (=0.05/90) in the UKBB) were considered significant in our study. To see if our genetic correlation results for the ADRD summary statistics are not driven by *APOE*, which contains a number of variants in high linkage disequilibrium, we repeated our analyses excluding the *APOE* region (chr19: 44,400–46,500 kb).

Partitioned heritability analysis

To systematically explore the enrichment of GWAS-identified genetic variant effects for pathway-specific, cell type-specific, or tissue-specific functions, we performed stratified LD score regression (s-LDSC) based on the per-SNP heritability of the different target phenotypes. Using this methodology, we could calculate whether specific annotations of the genome contribute more than others to explaining h^2_{SNP}. Enrichment here is defined as the proportion of h^2_{SNP} in a given

category divided by the proportion of variants in that category. We first applied s-LDSC to the full baseline assay probing 24 functional annotations that are not specific to any cell type, including coding regions, promoter regions, enhancers, introns, and evolutionarily conserved regions in the genome [41].

In addition to the analyses using the full baseline assay, we performed analyses using cell-type and tissue-specific annotations to supplement the baseline assay. We performed several different cell-type–specific analyses using annotations from different studies: 24 functional annotations for the baseline model [41], 53 tissue-specific annotations from the Genotype-Tissue Expression (GTEx) v6 project [81], 220 individual cell-type–specific annotations from Finucane et al. [41], 10 cell-type groups created from the 220 Finucane et al. annotations [41], 54 cell-type–specific annotations from Domcke et al. [82], 172 cell-type–specific annotations from Cao et al. [83], 18 cell-type–specific annotations from Corces et al. [84], and 17 cell-type–specific annotations from Velmeshev et al. [85]. The two latter studies are brain-specific annotations. Except for the GTEx annotations, all s-LDSC analyses were done on provided BED files for each annotation. For the 53 GTEx tissue-specific annotations, we tested tissue gene expression based on the t-statistics corresponding to the specific expression of each gene in each tissue (provided by Finucane et al. [81]). Following the original analysis, we selected the top 10% of genes, added a 100kb window around the transcribed regions, and applied s-LDSC to the resulting genome meta-information.

Carrying out LDSC on a given target phenotypes created 568 separate models encompassing all studied annotations. To rank these cell-type and tissue-specific annotations, we

report the P-value for gene expression enrichment, as done in recent genetic studies [1, 66]. We report the enrichment P-values of phenotype heritability within each cell-type and tissue-specific functional category, as enrichment is easily understood and interpretable regarding the relationship between phenotype heritability and cell-type and tissue-specific annotations. Based on the proportion of per-SNP-heritability associated with each annotation, s-LDSC calculates an enrichment score and an associated enrichment P-value. All figures showing the heritability partitioning results display the enrichment P-values associated with a tissue or cell type. The cell types or tissues were determined as significantly associated with the target phenotype if the enrichment P-value survived a Bonferroni correction for multiple testing ($P < 0.0005$ (=0.05/100), in the UKBB, for 80 ADRD risk factors, 10 ADRD summary statistics, and 10 ADRD summary statistics excluding the *APOE* region).

Linking SNP loci to genes

We also used Multi-marker Analysis of GenoMic Annotation (MAGMA) to find the genome-wide significant genes associated with our social measures and ADRD risk factors. MAGMA proceeds in two steps. First, MAGMA's gene-based analysis uses multiple linear principal components regression to link SNPs from the summary statistics to genes. This allows assessing the joint effect of all variants within all 19,427 protein-coding genes included in the NCBI 37.3 database. For each phenotype, gene-level association statistics were obtained using MAGMA (window size 10 kb upstream and downstream of each gene) using the SNP-wise mean model. This approach allows to combine P-values in the specified windows surrounding each gene into a gene-level P-value while accounting for linkage disequilibrium (LD) between variants (computed using the European panel of 1000 Genomes Project Phase 3) [86].

Second, to compare our results with the LDSC genetic correlation findings at the SNP level, we used genome-wide significant genes to explore the links between the target phenotypes on a gene level. By analyzing the genes assigned to each significant SNP (SNP-wise mean model), we computed a matrix that quantifies the extent of overlapping genes. In this matrix, the cell at the i^{th} column and j^{th} row signifies the proportion of overlapping significant genes (with a P-value < 2.5e−06) between two GWAS studies. This proportion is calculated by dividing the number of genes that are significant in both GWAS i and GWAS j by the total number of significant genes in GWAS i (https://atlas.ctglab.nl/multiGWAS). It is important to note that this division to obtain the overlap proportion renders the final matrix asymmetric, as the order of comparison between the two GWAS studies can affect the results.

Gene-set analysis

Building upon our gene analysis in MAGMA, we delved into gene-set analysis in MAGMA to explore how the genes associated with our traits of interest are expressed in relevant tissue and cell types, in a parallel framework to partition the heritability of our target phenotypes in LDSC. Our two different statistical methods (LDSC and MAGMA), based on different assumptions and algorithms, rigorously explore phenotype-relevant tissues and cell types. MAGMA evaluated whether the gene-level genetic association of the phenotype of interest linearly increased with tissue and cell-type expression specificity [66]. We used the same gene expression profiles as for the LDSC analyses and applied the bedtools intersect tool to link all SNPs from the LDSC annotation files to genes using the NCBI 37.3 database as a reference. Just as done for the LDSC analyses, the major histocompatibility complex (MHC) region

(chr6:26,000–34,000 kb) was excluded because this region has a complex LD structure [87]. This was performed allowing for a window of 10 kb upstream and downstream of each gene to capture the genetic contribution of SNPs located in close proximity [66]. The resulting competitive gene sets were used to uncover significant tissues and cell types which were then compared against the LDSC results.

FUMA validation of gene enrichment profiles

Finally, we aimed to determine whether these genes are overrepresented in gene sets associated with particular biological functions. To this end, FUMA annotates input summary statistics by mapping lead SNPs to genes. FUMA enables the prioritization of genes that are highly likely involved in the target trait under investigation. We used FUMA (v1.3.6a) to assess our summary statistics for loneliness and lack of social support against previously reported GWAS used in FUMA. FUMA first took GWAS summary statistics as input and provided extensive functional annotation for all SNPs in genomic areas identified by lead SNPs. Then this analysis framework identified a list of gene IDs from the lead SNPs and annotated genes in the biological context [40]. FUMA uses sets of differentially expressed genes (sets of genes which are more (or less) expressed in a specific tissue compared to other tissue types), including the 53 tissue types from the GTEx v6 RNA-seq data to test for overrepresentation of biological functions. As FUMA builds on Multi-marker Analysis of GenoMic Annotation (MAGMA, cf. above), FUMA was not included in our main analyses but as a confirmational gene-level analysis.

Figures

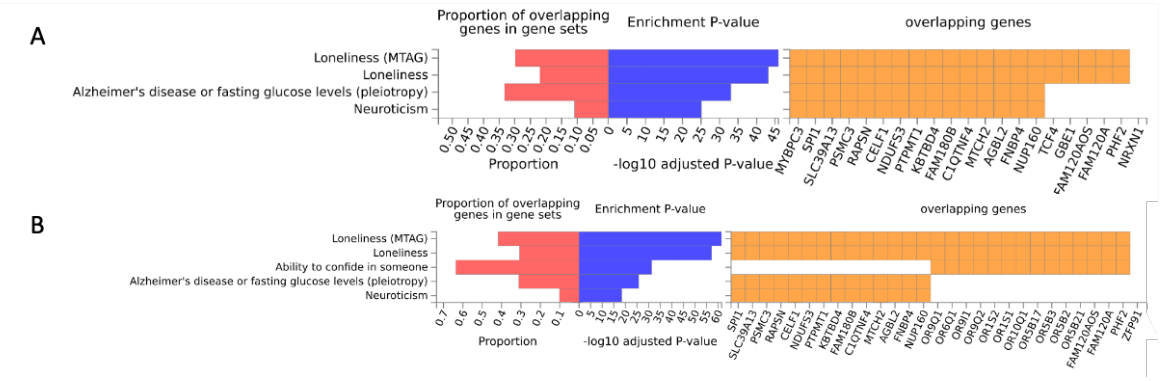

Figure 1. Previously established genetic loci in social isolation and Alzheimer's disease converge on a shared genetic basis. (A) FUMA analysis of loneliness and (B) FUMA analysis of lack of social support. The proportions of overlapping genes in the tested tissue-specific gene sets (53 tissue types from the GTEx RNA-seq data) and the enrichment P-value reveal the shared biological functions of prioritized genes for the target phenotypes. Strong overlap with the previously reported social isolation phenotypes validates our GWAS summary data, and further points to strong genetic links with Alzheimer's disease. In short, for both loneliness and lack of social support, the proportion of overlapping genes is also highest with Alzheimer's disease phenotypes, thus highlighting important shared biological functions. The abbreviation MTAG in Figure 1 refers to Multi-Trait Analysis of GWAS, which integrates data from multiple variables pertaining to loneliness to identify shared genetic influences for loneliness.

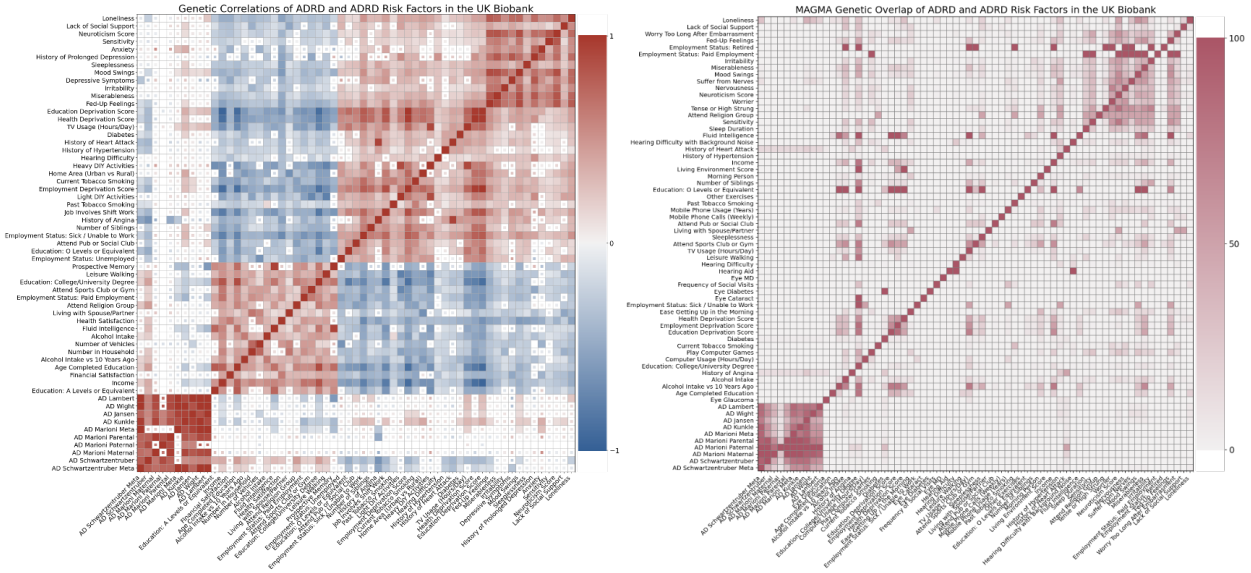

Figure 2. Social isolation shows strong genetic overlap with classical ADRD risk factors. (Left) LDSC examines the genetic correlations across 80 classical ADRD risk factors and 10 ADRD GWAS (with the *APOE* region). Correlations were clustered based on their mutual matrix. Larger squares correspond to significant P-values. Genetic correlations that are significantly different from zero after Bonferroni correction for the 90 tests in this analysis are marked with full-sized squares, while non-significant correlations are indicated with smaller squares. The genetic correlations of loneliness and lack of social support across all phenotypes were closest to neuroticism and several other personality traits (e.g. stress as captured by fed-up feelings and miserableness), depression, anxiety, and insomnia. (Right) MAGMA examines genetic overlap across the 80 ADRD risk factors and 10 ADRD GWAS. Each cell within the resulting heatmap represents the proportion of overlapping significant genes (P-value <2.5e−06) between two given GWAS summary statistics. This proportion is calculated by considering the number of genes shared between the phenotypes represented by the respective row and column, relative to the total number of significant genes in each of those studies. The division to obtain the overlap proportion renders the final matrix asymmetric (cf. Methods). Only phenotypes containing at least one genome-wide significant gene are included in the heatmap, the proportion of overlapping significant genes for loneliness and lack of social support were closest to the personality traits and employment status. Full genetic correlation results are shown in Supplementary Figure 2.

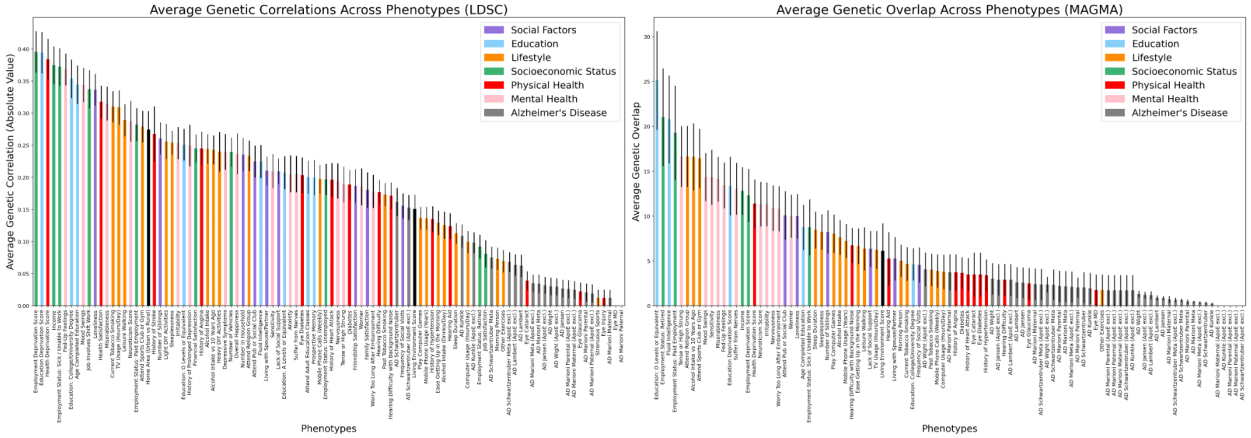

Figure 3. Loneliness shows genetic overlap with a diversity of ADRD risk factors. To gain a synoptic overview, the average of the genetic correlation results in LDSC (left) and the MAGMA genetic overlap results (right) were taken across all phenotypes for each ADRD risk factor. 80 ADRD risk factors and 20 ADRD GWAS (with and without the *APOE* region) were used in the LDSC genetic correlation analyses and in the MAGMA genetic overlap analyses. The genetic correlations were converted to absolute values. Among all classical ADRD risk traits, loneliness maintained a high average genetic overlap with ADRD risk factors, even comparatively greater than those of ADRD itself.

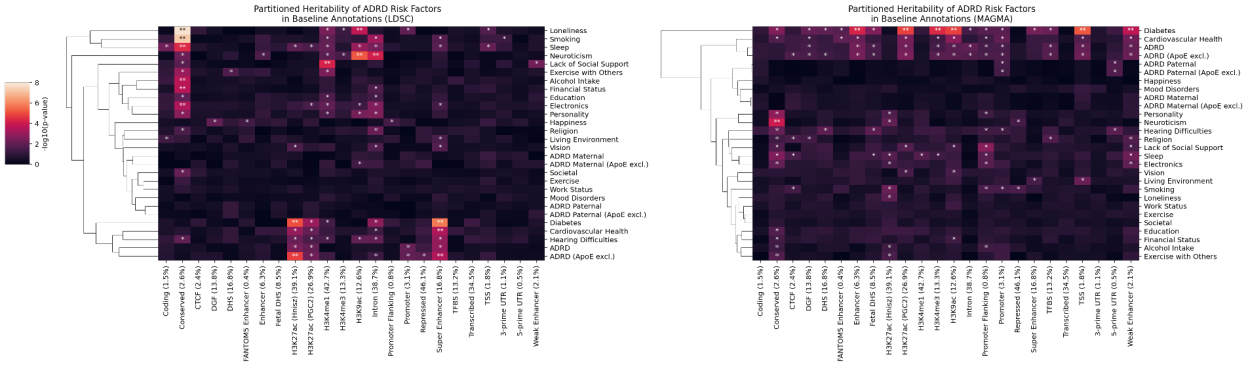

Figure 4. Enrichment estimates are strongest for social dimensions and ADRD risk traits in conserved regions and for ADRD in enhancer regions. Stratified LD score regression results with the full baseline model (24 genomic annotations that are not cell type-specific) show that loneliness and lack of social support have large and statistically significant enrichments for conserved regions among pathway-specific annotations, shared with several major ADRD risk factors. The partitioned heritability of ADRD shows strong enrichment in super-enhancers and histone H3K27ac markers, closely clustered with cardiovascular health and diabetes in LDSC. TFBS, transcription factor binding site. DGF, digital genomic footprint.

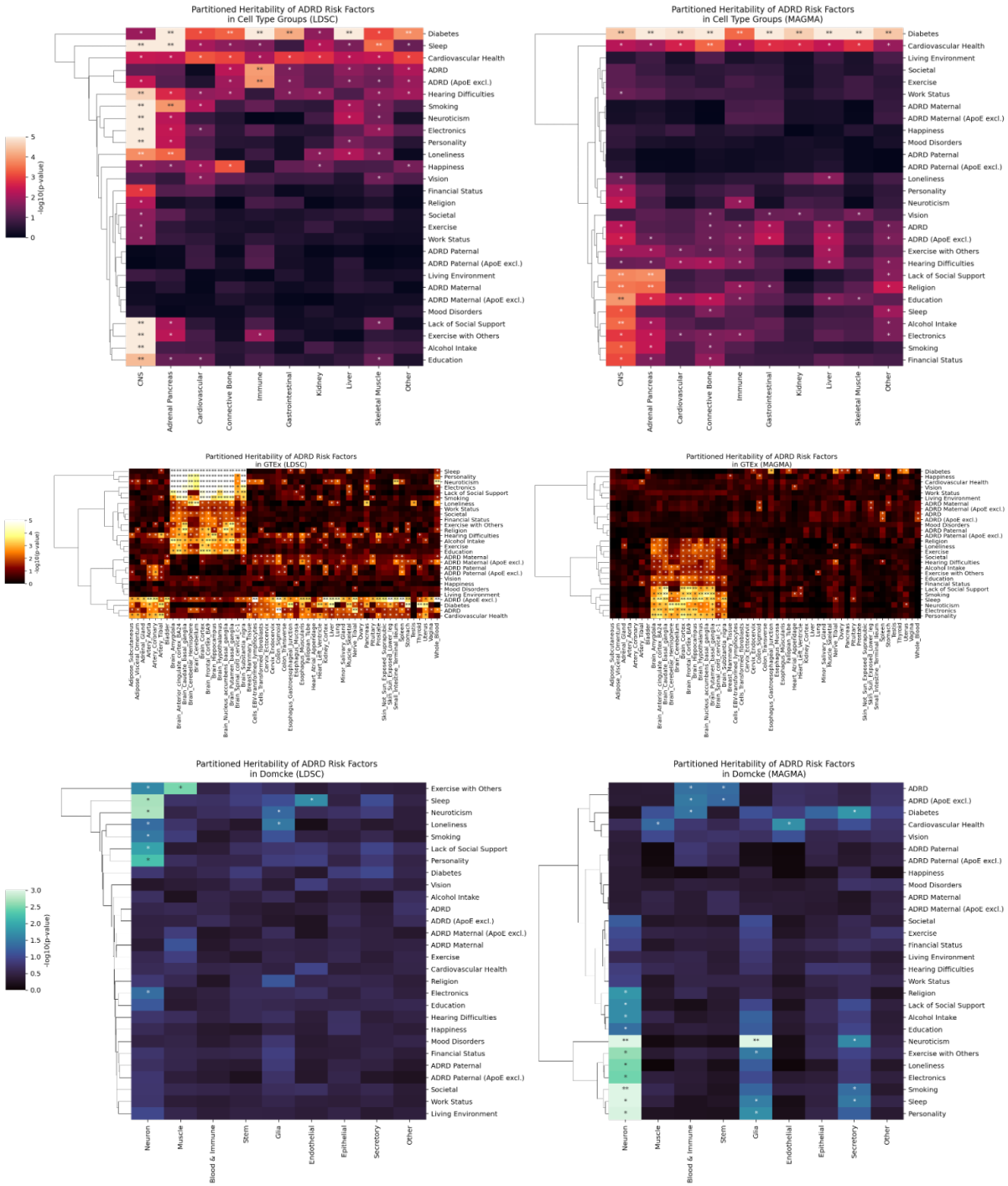

Figure 5. Well-established ADRD risk factors hold important gene expression enrichments in the whole body. Partitioned heritability in the UKB for major ADRD risk factors across cell-type group annotations from Finucane et al. (top row), brain-related tissue annotations from GTEx (middle row), and cell-type-specific annotations from Domcke et al. (bottom row) in LDSC (right) and MAGMA (left). Genome-wide association results for classical risk phenotypes were grouped into high-level risk factors of ADRD. In LDSC, loneliness and lack of social support are both greatly enriched in the CNS, and ADRD is highly enriched in the immune system. Both aspects of social isolation and classical ADRD risk factors share several mechanistic overlaps in their partitioned heritability. Loneliness and lack of social support are both enriched in brain-related tissues and in neurons, in similar enrichment patterns with the major ADRD risk factors. ADRD is instead enriched in whole blood and spleen, and in blood- and immune-related cells.

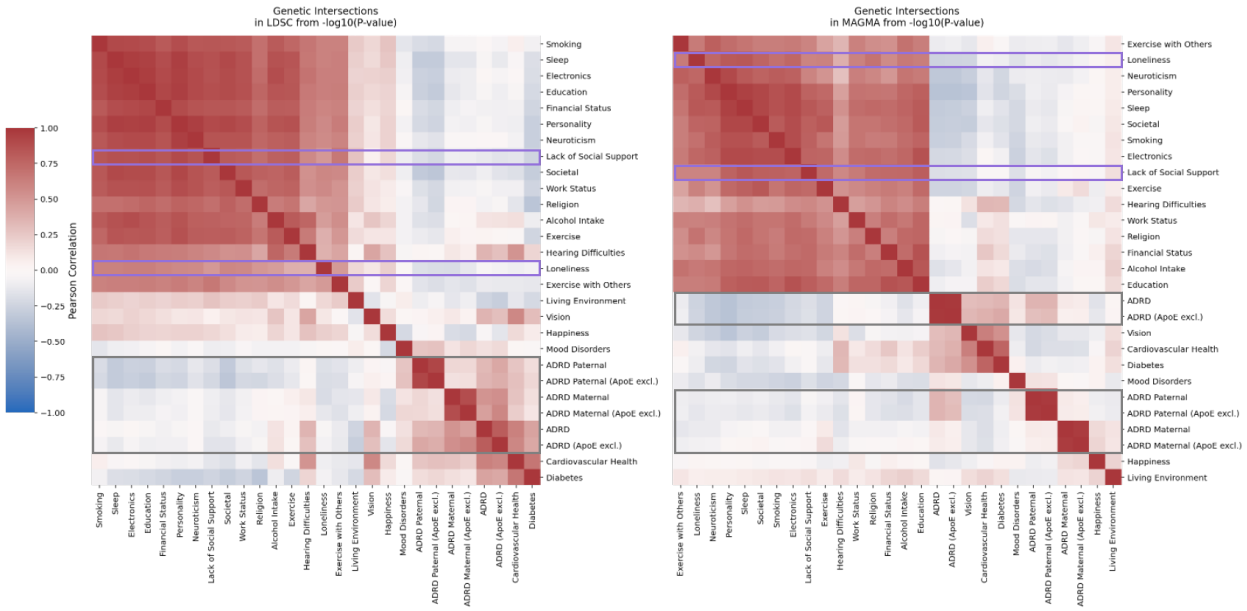

Figure 6. The enrichment of each phenotype across all annotations shows strong mechanistic similarities. Cross-correlation of the partitioned heritability in LDSC (left) and MAGMA (right) of each phenotype across all 568 tissue-specific, cell-type-specific, and brain region-specific annotations. Both social richness determinants in LDSC and MAGMA were closely clustered with several major ADRD risk factors, comparatively stronger intersections with these traits than ADRD GWAS that fall outside the large cluster.

Tables

Paper	*Summary Statistic*	*Date (Year)*	*Cases / Controls*	*Note*	*Used Proxies*
Lambert et al.	AD Lambert	2013	17,008 cases / 37,154 controls	Meta-analysis of 4 previously published GWAS datasets	No
Marioni et al.	AD Marioni Maternal	2019	27,696 cases of maternal AD / 260,980 controls	Self-report of parental history of Alzheimer's dementia (Maternal AD)	Yes
	AD Marioni Paternal	2019	14,338 cases of paternal AD / 245,941 controls	Self-report of parental history of Alzheimer's dementia (Paternal AD)	Yes
	AD Marioni Parental	2019	27,696 cases of maternal AD / 260,980 controls	Self-report of parental history of Alzheimer's dementia (Maternal AD)	Yes
	AD Marioni Paternal	2019	14,338 cases of paternal AD / 245,941 controls	Self-report of parental history of Alzheimer's dementia (Paternal AD)	Yes
Kunkle et al.	AD Kunkle	2019	21,982 cases / 41,944 controls	Clinically diagnosed GWAS	No
Jansen et al.	AD Jansen	2019	71,880 cases / 383,378 controls	Meta-analysis of several AD datasets with both proxy and non-proxy cases	Yes
Schwartzentruber et al.	AD Schwartzentruber	2021	53,042 proxy cases / 355,900 controls	Proxy cases from the UK Biobank	Yes
	AD Schwartzentruber Meta	2021	75,024 cases / 397,844 controls	Meta-analysis of AD Schwartzentruber and AD Kunkle	Yes
Wightman et al.	AD Wightman	2021	90,338 (46,613 proxy) cases / 1,036,225 (318,246 proxy) controls	Meta-analysis of several AD datasets with both proxy and non-proxy cases	Yes

Table 1. Description of the ADRD summary statistics.

Supplementary Material

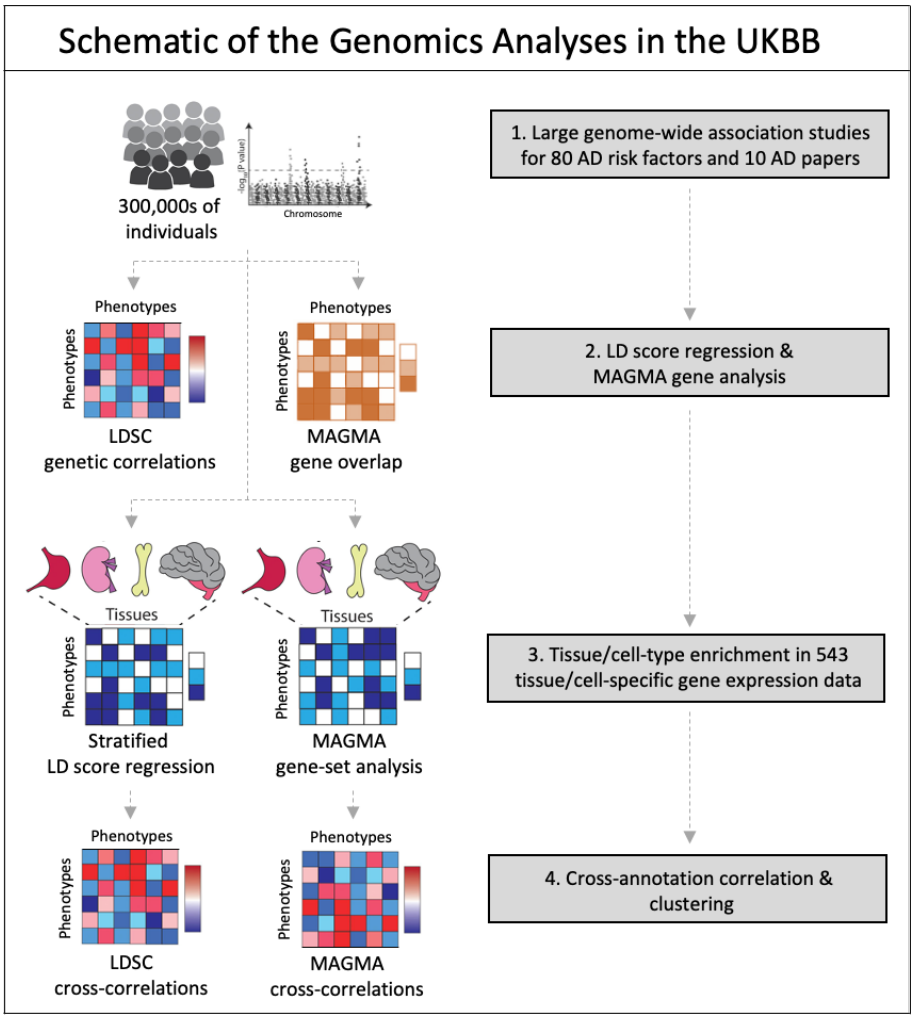

Fig. S1. Schematic of the genomic analysis steps for the UK Biobank.

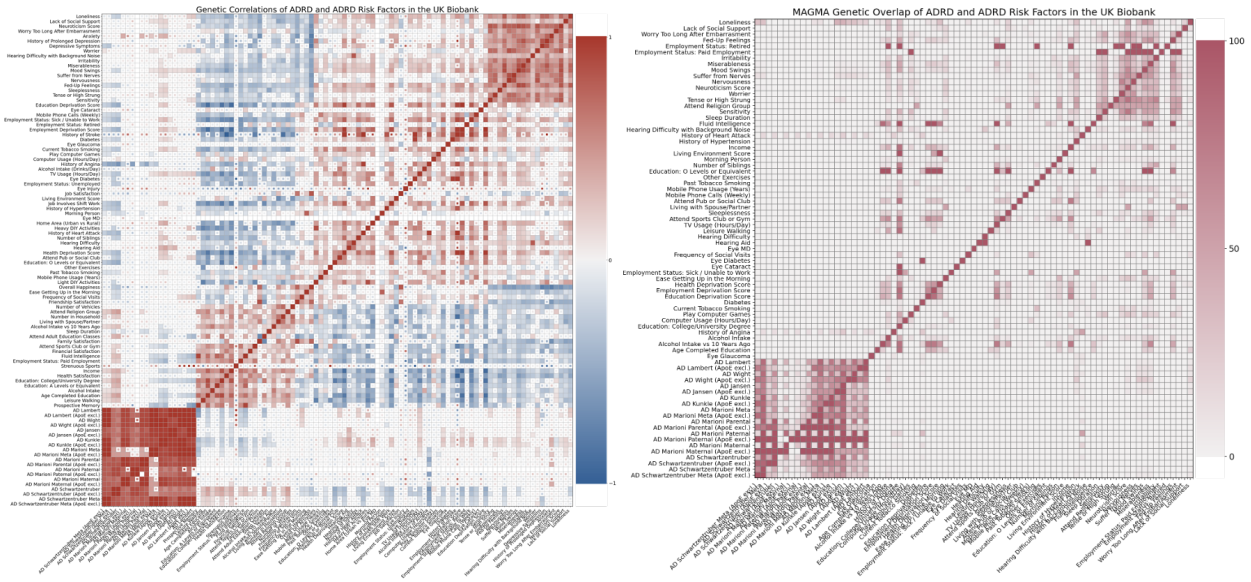

Fig. S2. Genetic correlations in UKBB with all ADRD risk factors and ADRD summary statistics remain unchanged when including and excluding the *APOE* region from ADRD. (Left) LDSC examines the genetic correlations across 80 classical ADRD risk factors and 20 ADRD GWAS (including and excluding the *APOE* region). Correlations were clustered based on their mutual matrix. Larger squares correspond to significant P-values. Genetic correlations that are significantly different from zero after Bonferroni correction for the 90 tests in this analysis are marked with an asterisk. The ADRD summary statistics share strong genetic correlations with themselves, but not with the classical risk factors, including and excluding the APOE region. (Right) MAGMA examines genetic overlap across the 80 ADRD risk factors and 20 ADRD GWAS. Each cell within the resulting heatmap represents the proportion of overlapping significant genes (P-value <2.5E−06) between two given GWAS summary statistics. This proportion is calculated by considering the number of genes shared between the phenotypes represented by the respective row and column, relative to the total number of significant genes in each of those studies. The division to obtain the overlap proportion renders the final matrix asymmetric (cf. Methods). Only phenotypes containing at least one genome-wide significant gene are included in the heatmap. Similar to the LDSC genetic correlations, The ADRD summary statistics share strong genetic correlations with themselves, but not with the classical risk factors, including and excluding the APOE region.

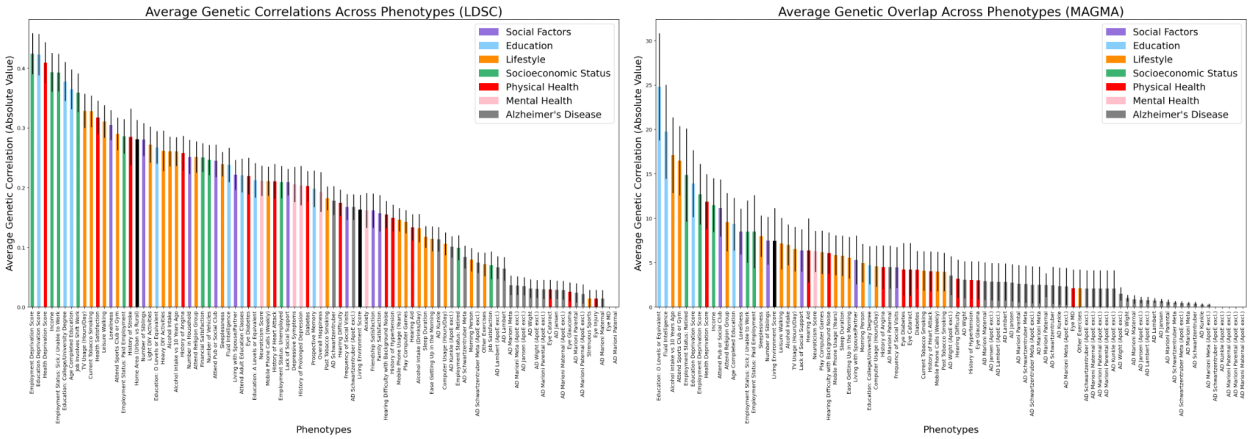

Fig. S3. Loneliness still holds a high average genetic correlation across all phenotypes in the UKBB, even after excluding personality traits. The average of the genetic correlation results in LDSC (left) and the MAGMA genetic overlap results (right) were taken across all phenotypes for each ADRD risk factor. 80 ADRD risk factors and 20 ADRD GWAS (with and without the *APOE* region) were used in the LDSC genetic correlation analyses and in the MAGMA genetic overlap analyses. The genetic correlations were converted to absolute values. Among all classical ADRD risk traits, loneliness still maintained a high average genetic overlap with ADRD risk factors, comparatively greater than those of ADRD itself, even after excluding the personality traits which hold the highest genetic overlap with loneliness and lack of social support.

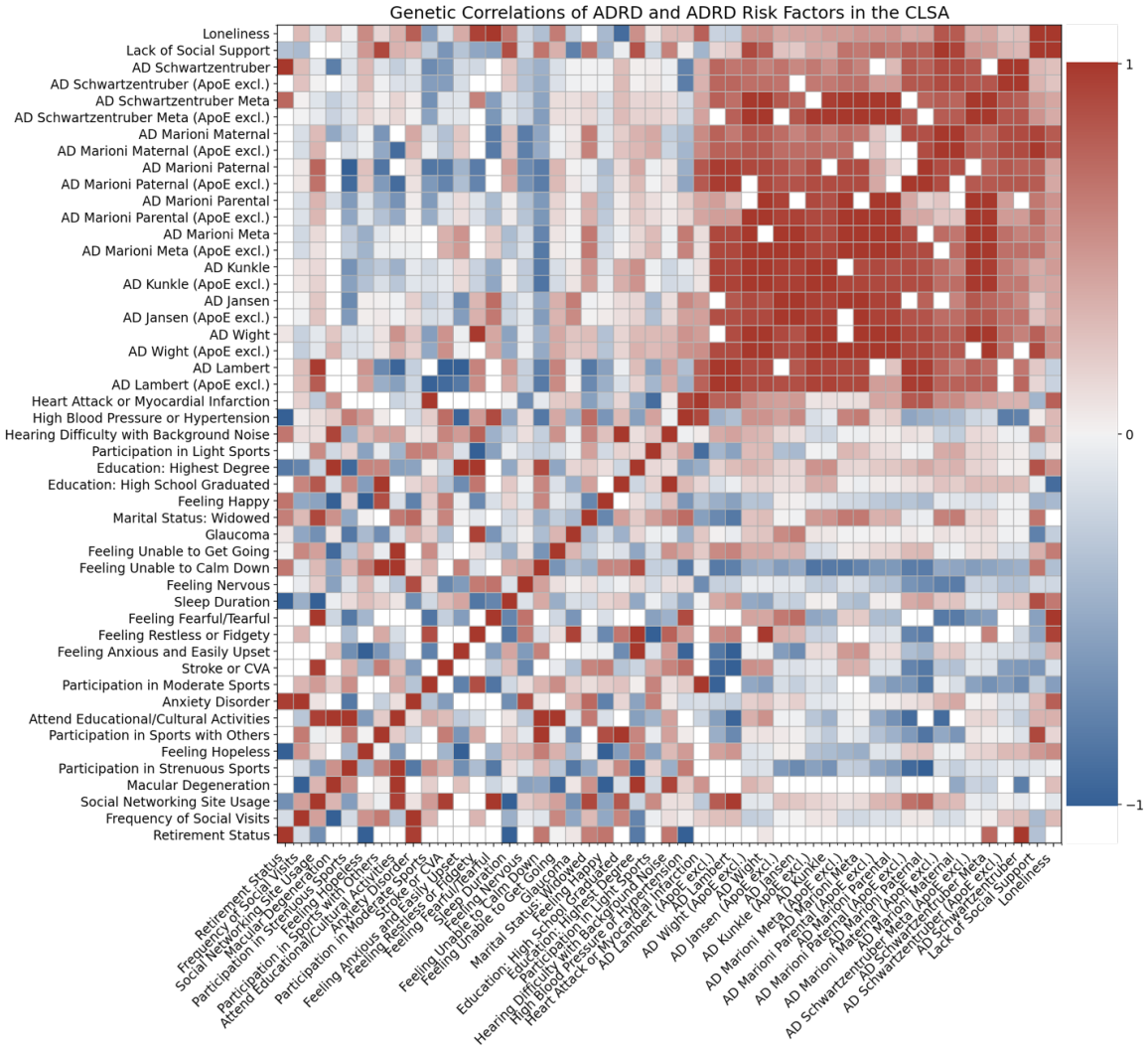

Fig. S4. The genetic correlations of both social isolation dimensions in the CLSA show interesting spectral clustering. Genetic correlations among 60 classical ADRD risk factors from CLSA and 20 ADRD GWAS (with and without the *APOE* region) were analyzed by LDSC. Correlations were clustered based on the similarity matrix. P-values are not reported, because almost all CLSA phenotypes had very small SNP-heritability and non-significant genetic correlation results. The MAGMA genetic overlap is not reported because not enough CLSA phenotypes had any significant genes.

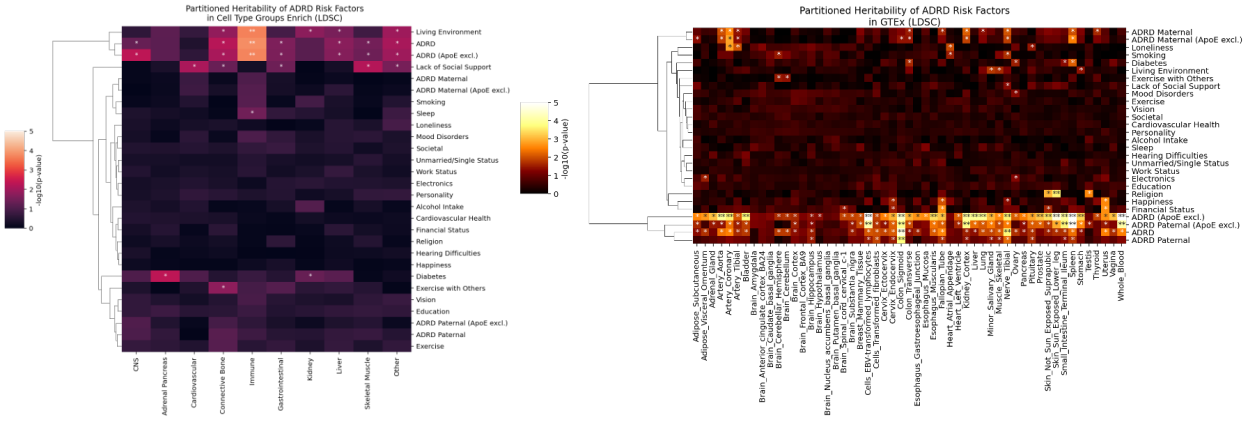

Fig. S5. The CLSA phenotypes have non-significant partitioned heritability results in LDSC. Given the small or non-interpretable SNP-heritability, the CLSA phenotypes have non-significant partitioned heritability results for cell-type (left) or tissue-specific (right) annotations in LDSC and MAGMA (not shown).

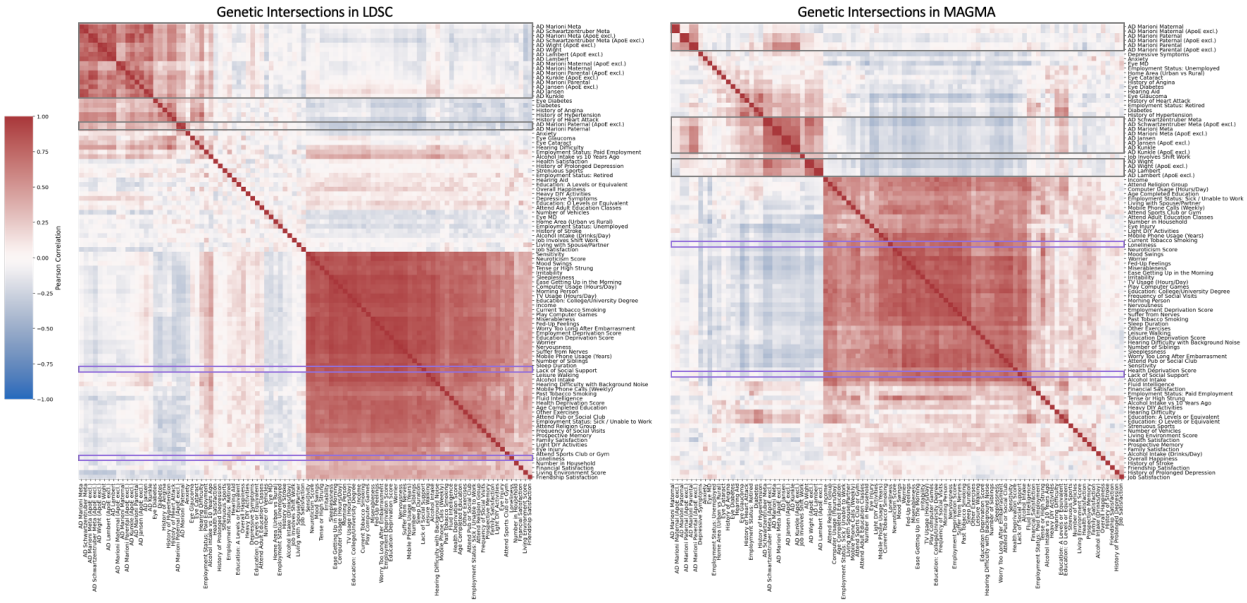

Fig. S6. The complete enrichment of each ADRD risk factor and ADRD summary statistics across all annotations showed strong mechanistic similarities. Cross-correlation of the partitioned heritability in LDSC (Left) and MAGMA (Right) of each phenotype across all 568 tissue-specific, cell-type specific, and brain region-specific annotations. Both social richness determinants in LDSC and loneliness in MAGMA were closely clustered with several major ADRD risk factors, comparatively stronger intersections with these traits than ADRD GWAS that fall outside the large cluster.

Phenotype	Description	Binary	h2 (%)	h2 SE	Intercept	Intercept SE
Loneliness	Do you often feel lonely?	✓	7.85	0.0046	1.0127	0.0073
Lack of Social Support	How often are you able to confide in someone close to you? (Reversed encoding)		4.13	0.0023	1.0110	0.0087
Age Completed Education	At what age did you complete your continuous full-time education?		2.55	0.0018	1.0162	0.0068
Alcohol Intake vs 10 Years Ago	Compared to 10 years ago, how much do you drink?		3.02	0.0020	1.0160	0.0076
Alcohol Intake	About how often do you drink alcohol?		8.26	0.0039	1.0370	0.0107
Alcohol Intake (Drinks/Day)	How many drinks (units of alcohol) containing alcohol do you have on a typical day when you are drinking?		0.47	0.0013	0.9944	0.0063
Education: A Levels or Equivalent	A levels / AS levels or equivalent (includes the Higher School Certificate)	✓	1.77	0.0026	1.0057	0.0074
History of Angina	Has a doctor ever told you that you have had angina?	✓	6.61	0.0093	1.0154	0.0068
Anxiety Symptoms	Over the last 2 weeks, how often have you been bothered by any anxiety symptoms: feeling nervous, anxious or on edge?		0.54	0.0014	0.9932	0.0065
Education: College/University Degree	College or University degree	✓	29.17	0.0087	1.0842	0.0132
Computer Usage (Hours/Day)	In a typical day, how many hours do you spend using the computer?		4.34	0.0022	1.0129	0.0079
Play Computer Games	Do you play computer games?		7.37	0.0030	1.0232	0.0087
Current Tobacco Smoking	Do you smoke tobacco now?		5.36	0.0026	1.0065	0.0086
History of Prolonged Depression	Have you ever had a time in your life when you felt sad, blue, or depressed for two weeks or more in a row?	✓	0.50	0.0021	1.0079	0.0060
Depressive Symptoms	Over the last 2 weeks, how often have you been bothered by any depressive symptoms: feeling down, depressed, or hopeless?		0.44	0.0013	0.9962	0.0063
Diabetes	Has a doctor ever told you that you have diabetes?"	✓	20.49	0.0123	1.0357	0.0100

Attend Adult Education Classes	Do you attend adult educations classes once a week or more often?	✓	2.70	0.0050	0.9889	0.0061
Education Deprivation Score	This domain measures the extent of deprivation in terms of education, skills and training in an area. It reflects the educational disadvantages within an area.		6.11	0.0026	1.0796	0.0089
Employment Deprivation Score	This domain measures the employment deprivation in an area conceptualised as involuntary exclusion of the working age population from the labour market.		6.20	0.0027	1.0757	0.0090
Employment Status: Paid Employment	Currently in paid employment or self-employed.	✓	2.18	0.0025	1.0158	0.0069
Employment Status: Retired	Currently retired.	✓	1.53	0.0024	1.0049	0.0059
Employment Status: Sick / Unable to Work	Currently unable to work because of sickness or disability.	✓	12.49	0.0095	1.0064	0.0071
Employment Status: Unemployed	Currently unemployed	✓	5.06	0.0130	0.9980	0.0065
Eye Problems: Cataract	Has a doctor told you that you have cataract?	✓	1.84	0.0038	1.0096	0.0069
Eye Problems: Diabetes	Has a doctor told you that you have diabetes-related eye disease?	✓	5.24	0.0110	1.0097	0.0060
Eye Problems: Glaucoma	Has a doctor told you that you have glaucoma?	✓	6.44	0.0086	1.0140	0.0074
Eye Problems: Injury	Has a doctor told you that you have an injury or trauma resulting in loss of vision?	✓	0.80	0.0122	1.0110	0.0063
Eye Problems: MD	Has a doctor told you that you have macular degeneration?	✓	N/A	N/A	N/A	N/A
Family Satisfaction	In general, how satisfied are you with your family relationships?		0.53	0.0013	1.0047	0.0061
Fed-Up Feelings	Do you often feel 'fed-up'?	✓	10.81	0.0048	1.0219	0.0094
Financial Satisfaction	In general, how satisfied are you with your financial situation?		0.90	0.0013	0.9875	0.0069
Fluid Intelligence Score	This is a simple unweighted sum of the number of correct answers given to the 13 fluid intelligence questions.		2.52	0.0017	0.9961	0.0072
Friendship Satisfaction	In general, how satisfied are you with your friendships?		0.60	0.0013	0.9967	0.0061
Frequency of Social Visits	How often do you visit friends or family or have them visit you?		3.89	0.0023	1.0191	0.0079

Ease Getting Up in the Morning	On an average day, how easy do you find getting up in the morning?		7.04	0.0032	1.0397	0.0100
Overall Happiness	In general, how happy are you?		0.55	0.0012	1.0067	0.0059
Health Satisfaction	In general, how satisfied are you with your health?		0.89	0.0015	0.9935	0.0073
Health Deprivation Score	This domain measures premature death and the impairment of quality of life by poor health. It considers both physical and mental health.		4.27	0.0027	1.1355	0.0084
Hearing Aid	Do you use a hearing aid most of the time?	✓	3.06	0.0062	0.9952	0.0063
Hearing Difficulty with Background Noise	Do you find it difficult to follow a conversation if there is background noise (such as TV, radio, children playing)?	✓	8.92	0.0042	1.0203	0.0080
Hearing Difficulty	Do you have any difficulty with your hearing?	✓	3.85	0.0022	1.0130	0.0088
History of Heart Attack	Has a doctor ever told you that you have had a heart attack?	✓	14.67	0.0132	1.0099	0.0075
Heavy DIY Activities	In the last 4 weeks, did you spend any time doing heavy DIY (eg: weeding, lawn mowing, carpentry, digging)?	✓	0.96	0.0021	1.0041	0.0060
Home Area (Urban vs Rural)	Is the participant's home postcode in a more 'urban' area vs a 'rural' area? The classification is derived by combining each participant's home postcode with data generated from the 2001 census.		0.44	0.0012	1.0186	0.0061
History of Hypertension	Has a doctor ever told you that you have had high blood pressure?	✓	17.41	0.0082	1.0479	0.0147
Average Household Income	What is the average total income before tax received by your household?		6.81	0.0029	1.0430	0.0100
Irritability	Are you an irritable person?	✓	10.90	0.0067	0.9956	0.0107
Job Satisfaction	In general, how satisfied are you with the work that you do?		0.29	0.0012	1.0005	0.0063
Light DIY Activities	In the last 4 weeks, did you spend any time doing light DIY (eg: pruning, watering the lawn)?	✓	1.81	0.0022	1.0125	0.0068
Living Environment Score	This domain measures the quality of individuals' immediate surroundings both within and outside the home.		1.30	0.0017	1.0768	0.0077
Miserableness	Do you ever feel 'just miserable' for no reason?	✓	9.60	0.0054	1.0119	0.0104
Mood Swings	Does your mood often go up and down?	✓	10.60	0.0048	1.0153	0.0093
Morning Person	Do you consider yourself to be more a 'morning' person vs an 'evening' person?		9.34	0.0035	1.0334	0.0107

Number in Household	Including yourself, how many people are living together in your household?		0.99	0.0013	1.0119	0.0064
Number of Siblings	How many brothers and sisters do you have?		3.12	0.0020	1.0317	0.0081
Number of Vehicles	How many cars or vans are owned, or available for use, by you or members of your household?		2.98	0.0019	1.0223	0.0067
Suffer from Nerves	Do you suffer from 'nerves'?	✓	8.34	0.0056	0.9908	0.0089
Nervousness	Would you call yourself a nervous person?	✓	11.67	0.0070	1.0103	0.0114
Neuroticism Score	This is an externally derived summary score of neuroticism, based on 12 neurotic behaviour domains.		7.80	0.0041	1.0034	0.0108
Education: O Levels or Equivalent	O levels / GCSEs or equivalent (includes the School Certificate)	✓	1.71	0.0025	1.0131	0.0074
Moderate Exercises	In the last 4 weeks, did you spend any time doing other exercises (eg: swimming, cycling, keep fit, bowling)?	✓	2.13	0.0023	0.9968	0.0063
Past Tobacco Smoking	In the past, how often have you smoked tobacco?		7.72	0.0033	1.0132	0.0095
Mobile Phone Usage (Years)	For approximately how many years have you been using a mobile phone at least once per week to make or receive calls?		5.24	0.0026	1.0187	0.0085
Mobile Phone Calls (Weekly)	Over the last 3 months, on average how much time per week did you spend making or receiving calls on a mobile phone?		2.94	0.0019	1.0028	0.0073
Prospective Memory	This field condenses the results of the prospective memory test.		0.46	0.0014	1.0047	0.0070
Attend Pub or Social Club	Do you attend a pub or social club once a week or more often?	✓	4.58	0.0033	1.0202	0.0077
Living with Spouse/Partner	Are the other people who live with you your husband, wife or partner?	✓	4.64	0.0032	1.0066	0.0070
Attend Religion Group	Do you attend a religious group once a week or more often?	✓	7.01	0.0043	1.0129	0.0074
Sensitivity	Are your feelings easily hurt?	✓	9.39	0.0046	1.0113	0.0086
Job Involves Shift Work	Does your work involve shift work?		0.82	0.0013	1.0047	0.0064
Sleep Duration	About how many hours sleep do you get in every 24 hours? (please include naps)		6.66	0.0031	1.0161	0.0091
Sleeplessness	Do you have trouble falling asleep at night or do you wake up in the middle of the night?		6.48	0.0027	1.0086	0.0088

Attend Sports Club or Gym	Do you attend a sports club or gym once a week or more often?	✓	6.29	0.0035	1.0122	0.0076
Strenuous Sports	In the last 4 weeks, did you spend any time doing strenuous sports?	✓	0.27	0.0036	1.0065	0.0066
History of Stroke	Has a doctor ever told you that you have had a stroke?	✓	1.43	0.0122	1.0074	0.0061
Tense or High Strung	Would you call yourself tense or 'highly strung'?	✓	7.74	0.0055	0.9898	0.0087
TV Usage (Hours/Day)	In a typical day, how many hours do you spend watching TV?		13.77	0.0044	1.0460	0.0116
Leisure Walking	In the last 4 weeks, did you spend any time walking for pleasure (not as a means of transport)?	✓	6.77	0.0036	1.0273	0.0072
Worrier	Are you a worrier?	✓	11.97	0.0074	0.9928	0.0121
Worry Too Long After Embarrassment	Do you worry too long after an embarrassing experience?	✓	9.33	0.0047	1.0142	0.0096

Table S1. Description and SNP-Heritability of the examined risk factors and social indicators in the UK Biobank. SNP-heritability for binary outcomes is reported on the liability scale, assuming that the population prevalence matches the prevalence in the UK Biobank analysis set.

Phenotype	Description	Binary	h2 (%)	h2 se (%)	Intercept	Intercept se
Alcohol Intake	About how often during the past 12 months did you drink alcohol?	✓	-1.40	0.0432	1.0233	0.0183
Angina	Has a doctor ever told you that you have angina (or chest pain due to heart disease)?		-3.85	0.0431	1.0087	0.0176
Anxiety Disorder	Do you have an anxiety disorder?	✓	6.82	0.0523	0.9805	0.0178
Feeling Anxious and Easily Upset	Has a doctor ever told you that you have an anxiety disorder such as a phobia, obsessive-compulsive disorder or a panic disorder?		4.91	0.0513	1.0263	0.0207
Feeling Easily Bothered	How often were you bothered by things that usually don't bother you?		-0.28	0.0451	0.9960	0.0190
Feeling Unable to Calm Down	In the past 30 days, how often did you feel you could not calm down?		4.17	0.0410	1.0003	0.0186
Attend Club/Fraternal Activities	In the past 12 months, how often did you participate in Service club or fraternal organization activities?	✓	-6.99	0.0413	1.0462	0.0176
Participate in Computer Activities	Have you participated in computer activities?	✓	-5.99	0.0410	1.0204	0.0173
Lack of Social Support	Someone to confide in or talk to about yourself or your problems? (Reversed binarized encoding)	✓	3.38	0.0441	1.0049	0.0192
Currently Working	Are you currently working?	✓	-4.03	0.0374	1.0240	0.0164
Clinical Depression	Do you have clinical depression?	✓	-3.75	0.0409	1.0326	0.0217
Positive Depression Screen	Positive screen for depression.	✓	N/A	N/A	N/A	N/A
Diabetes or High Blood Sugar	Has a doctor ever told you that you have diabetes, borderline diabetes or that your blood sugar is high?"	✓	-4.67	0.0454	1.0413	0.0206
Attend Educational/Cultural Activities	In the past 12 months, how often did you participate in Educational and cultural activities involving other people such as attending courses, concerts, plays, or visiting museums?		2.38	0.0474	1.0049	0.0186
Cataracts	Has a doctor ever told you that you have cataracts?	✓	N/A	N/A	N/A	N/A

Glaucoma	Has a doctor ever told you that you have glaucoma?	✓	9.26	0.0405	0.9692	0.0166
Macular Degeneration	Has a doctor ever told you that you have macular degeneration?	✓	1.94	0.0448	0.9970	0.0186
Feeling Fearful/Tearful	How often did you feel fearful or tearful?		1.30	0.0425	1.0051	0.0201
Frequency of Social Visits	In the past 12 months, how often did you participate in family- or friendship-based activities outside the household?		8.45	0.0487	0.9927	0.0191
Feeling Unable to Get Going	How often did you feel that you could not “get going”?		6.55	0.0397	1.0156	0.0178
Feeling Happy	How often were you happy?		10.12	0.0446	0.9936	0.0170
Hearing Aids	Do you use any aids, specialized equipment, or services for persons who are deaf or hard of hearing, for example, a volume control telephone or TV decoder?	✓	N/A	N/A	N/A	N/A
Hearing Difficulty with Background Noise	Do you find it difficult to follow a conversation if there is background noise, such as TV, radio or children playing, even if using a hearing aid as usual?	✓	13.55	0.0575	0.9660	0.0179
Heart Attack or Myocardial Infarction	Has a doctor ever told you that you have had a heart attack or myocardial infarction?	✓	2.41	0.0429	1.0010	0.0167
Education: Highest Degree	What is the highest degree, certificate, or diploma you have obtained?		8.50	0.0452	0.9983	0.0174
Education: High School Graduated	Did you graduate from high school (secondary school)?	✓	5.37	0.0399	0.9763	0.0173
Feeling Hopeless	In the past 30 days, how often did you feel hopeless?		5.16	0.0440	1.0089	0.0152
High Blood Pressure or Hypertension	Has a doctor ever told you that you have high blood pressure or hypertension?	✓	4.28	0.0458	1.0338	0.0201
Total Household Income	What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past 12 months?		N/A	N/A	N/A	N/A
Loneliness	How often did you feel lonely? (Binarized encoding)	✓	7.83	0.0447	0.9704	0.0167

Number of Close Friends	Not counting family members, how many people do you consider close friends – that is, people you can confide in and talk over personal matters with?		-3.07	0.0439	1.0429	0.0185
Number in Household	How many people, not including yourself, currently live in your household?		-2.93	0.0431	1.0379	0.0175
Number of Siblings	How many, if any, living siblings (sisters, brothers) do you have?		-1.15	0.0504	1.1907	0.0216
Feeling Nervous	In the past 30 days, how often did you feel nervous?		11.01	0.0634	1.0788	0.0222
Prospective Memory	Accuracy of response to the prospective memory test.		-3.52	0.0409	1.0091	0.0197
Marital Status: Divorced	Marital / partner status: Divorced.	✓	-2.46	0.0374	1.0155	0.0162
Marital Status: Married/Living with Partner	Marital / partner status: Married / Living with a partner in a common-law relationship.	✓	-2.64	0.0410	1.0367	0.0172
Marital Status: Single	Marital / partner status: Single, never married or never lived with a partner.	✓	-3.90	0.0415	1.0306	0.0178
Marital Status: Widowed	Marital / partner status: Widowed.	✓	6.54	0.0473	0.9877	0.0198
Attend Religious Activities	In the past 12 months, how often did you participate in church or religious activities such as services, committees or choirs?		-0.85	0.0459	1.0439	0.0211
Feeling Restless or Fidgety	In the past 30 days, how often did you feel restless or fidgety?		1.02	0.0364	1.0090	0.0169
Retirement Status	What is your retirement status?	✓	1.11	0.0407	1.0024	0.0174
Feeling Unable to Sit Still	In the past 30 days, how often did you feel unable to sit still?		-0.49	0.0442	1.0317	0.0199
Sleep Duration	Number of sleep hours during past month.		10.78	0.0508	0.9873	0.0201
Current Cigarette Smoking	At the present time, do you smoke cigarettes daily, occasionally or not at all?”		-1.46	0.0450	1.0051	0.0220
Social Networking Site Usage	Do you use social networking sites?	✓	4.24	0.0410	0.9969	0.0163
Participation in Light Sports	Over the past 7 days, how often did you engage in light sports or recreational activities such as bowling, golf with a cart,		8.68	0.0408	0.9781	0.0170

	shuffleboard, badminton, fishing or other similar activities?					
Participation in Moderate Sports	Over the past 7 days, how often did you engage in moderate sports or recreational activities such as ballroom dancing, hunting, skating, golf without a cart, softball or other similar activities?		3.92	0.0456	0.9828	0.0183
Participation in Sports with Others	In the past 12 months, how often did you participate in Sports or physical activities that you do with other people?		3.18	0.0341	0.9913	0.0162
Participation in Strenuous Sports	Over the past 7 days, how often did you engage in strenuous sports or recreational activities such as jogging, swimming, snowshoeing, cycling, aerobics, skiing, or other similar activities?		5.25	0.0439	1.0056	0.0172
Stroke or CVA	Has a doctor ever told you that you have experienced a Stroke or CVA (cerebrovascular accident)?	✓	5.23	0.0479	0.9813	0.0200
Feeling Tired Out	In the past 30 days, how often did you feel tired out?	✓	N/A	N/A	N/A	N/A
Watch TV	Have you participated in watching TV?		-9.41	0.0413	1.0359	0.0183
Home Area (Urban vs Rural)	Does the participant live in a more 'urban' area vs a 'rural' area?		N/A	N/A	N/A	N/A
Vision Aids	Besides glasses or contact lenses, do you use any aids or specialized equipment for persons who are blind or visually impaired, for example, magnifiers or Braille reading materials?	✓	0.90	0.0406	1.0026	0.0191
Work Involves Commute	Do your typical weekly trips include work commute?	✓	N/A	N/A	N/A	N/A
Worked (Paid or Volunteer) in Past Week	In the past 7 days, have you worked for pay or as a volunteer?	✓	-1.43	0.0424	1.0215	0.0202
Hours Worked (Paid or Volunteer)	In the past 7 days, how many hours have you worked for pay or as a volunteer?		-4.08	0.0457	1.0236	0.0180
Current Working Status (Hours)	What is your current working status?		N/A	N/A	N/A	N/A

Feeling Worthless	In the past 30 days, how often did you feel worthless?		-4.11	0.0463	1.0318	0.0190

Table S2. Description and SNP-Heritability of the examined risk factors and social indicators in the CLSA. SNP-heritability for binary outcomes is reported on the liability scale, assuming that the population prevalence matches the prevalence in the CLSA analysis set.

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Discussion

This study provides a comprehensive examination of the multifaceted interplay between social isolation and ADRD risk, emphasizing the intricate connections between both perceived and objective facets of social deprivation and classical ADRD risk factors. Our analyses, leveraging data from two nationally representative population cohorts of older adults from the UK Biobank and the Canadian Longitudinal Study on Aging, highlight the consistent associations between social isolation and ADRD risk factors even after adjusting for age and sex differences. To the best of our knowledge, this is the first study to explicitly target behavioural, genetic, and biological links between social isolation and a wide array of most-studied ADRD risk factors, providing a detailed population-level overview.

Among all the examined risk measures of ADRD, we found personality traits to feature the largest behavioural associations and genetic correlations with social isolation. Specifically, the neuroticism score, which reflects a person's level of emotional volatility and vulnerability to stress, showed one the strongest effect size for loneliness and lack of social support, in the context of all the considered ADRD risk factors. Such findings are consistent with the understanding that personality traits, particularly those reflecting emotional sensitivity like neuroticism, are closely linked to experiences of loneliness and social support. Previous research has also shown a relation between personality traits and social isolation in genome-wide assessments in the UK Biobank [48]. Consistent with this observation, a population-based study of approximately 7,000 male and female adult twins investigating the relationship between the personality trait of neuroticism, the occurrence of stressful life events, and the quality of interpersonal relationships, showed that levels

of neuroticism are closely related to poor interpersonal relationships [49]. Specific personality traits like neuroticism, early-life experiences, and learned predispositions have previously been shown to affect an individual's susceptibility to the effects of stressors [50]. Stress responses have evolved as adaptive reactions to any intrinsic or extrinsic stimulus that threatens homeostasis [51]. Stress pile-up and emotional coping have been argued previously to contribute to the underlying reasons why lonely people are more often smokers [52], binge drinkers [53], and binge-watchers [54, 55]. Our findings showed similar trends of associations between our social isolation dimensions and smoking, alcohol consumption, and television viewing. Moreover, they show strong associations between sleep disturbance and loneliness, a finding that aligns with previous research suggesting that social isolation increases hypervigilance to social threats [56], thereby reducing sleep quality.

The interconnectedness of social isolation, stress, and the classical lifestyle determinants in ADRD risk highlights the role of social connections as critical buffers against stressors. Given that stress responses can vary significantly based on individual factors, the presence or absence of social support plays a crucial role in modulating these physiological reactions. Social support can dampen physiological stress responses through a phenomenon termed the social buffering of stress [57]. For instance, individuals with greater social support coped better with post-traumatic stress disorder (PTSD) after a natural disaster [58] or with depression after myocardial infarction [59]. Many reports have shown that feelings of loneliness and reduced social support occur especially in individuals who report higher stress levels [60-62]. The theory of interpersonal social buffering posits that social connections and support systems provide emotional and practical resources that help individuals cope with stress [52, 63]. These psychosocial resources can reduce physiological

responses to stress, such as cortisol levels, which are often elevated in individuals experiencing chronic stress or loneliness [64]. Understanding the link between social isolation, stress, and the major ADRD risk factors can inform more effective interventions to improve cognitive health and prevent or delay the onset of ADRD. For example, studies have shown that lower cortisol levels can improve sleep quality and reduce the risk of developing stress-related behaviours that contribute to cognitive decline [65], such as physical inactivity, substance abuse, and social withdrawal. These behavioural changes highlight the importance of exploring how social connections and stress management influence lifestyle factors associated with ADRD risk.

The underlying neurobiological mechanisms of this social buffering could be related to the activity of the hypothalamic–pituitary–adrenocortical (HPA) axis, one of the major neuroendocrine systems [66]. As the main producer of glucocorticoids, including cortisol, the HPA axis plays an important role in regulating the stress response [67]. In human studies and animal models, the HPA axis stress response to threats was dampened with the presence or support of a conspecific [68]. Loneliness, while being a state of mind driven by existential survival, has also strongly been associated with the activation of the HPA axis [68]. Social isolation poses a significant survival threat to social species, like humans, prompting physiological adaptations to manage this challenge. The body's stress response involves elevated levels of glucocorticoids, such as cortisol, which increase energy availability by mobilizing stored nutrients. However, when social needs remain unmet, persistent isolation – perceived or objective – can disrupt HPA axis regulation, leading to glucocorticoid resistance, weakened immune responses, and related health issues [68].

When we sought to find which cell and tissue types were most relevant to the underlying biological processes regulating the examined social determinants and the classic ADRD risk factors by integrating gene expression data, we found that among the cell type groups and the tissue-specific annotations, both loneliness and lack of social support were highly enriched within the central nervous system (CNS) and the brain-related tissues in LDSC and MAGMA. However, another significant enrichment for the social isolation dimensions was found in the adrenal pancreas. Loneliness is enriched in the adrenal pancreas in LDSC, and lack of social support is enriched in the adrenal pancreas in MAGMA. This finding may be related to the association between extended psychological stress due to social isolation and the disruption of the HPA axis, which is considered the primary stress adaptation pathway in the body. As a key component of the HPA axis, the adrenal cortex—the outer part of the adrenal glands—releases glucocorticoids, primarily cortisol, in response to a cascade of hormonal signals triggered by the perception of a stressor. Furthermore, our findings indicate that traits related to sleep are also enriched in the adrenal pancreas in LDSC. This is consistent with existing research showing that sleep deprivation is associated with elevated cortisol levels and impaired HPA axis regulation [69]. Given that glucocorticoid release follows the circadian rhythm [70], sleep disruptions can be related to glucocorticoid overload and have significant negative health effects. This physiological cascade links behavioural findings to genetic results, highlighting again the interconnectedness of social isolation, stress, and major ADRD risk factors [71].

Physical health factors, such as cardiovascular conditions, diabetes, and physical exercise, also exhibit some links to social isolation. Consistent with existing research, the results of our behavioural analyses demonstrate that objective social isolation detrimentally affects

cardiovascular health, increasing risks of hypertension [72] and coronary heart disease [73], which are associated with subsequent dementia risk. However, across all the examined ADRD risk factors, the physical health factors exhibited the smallest effect associations with social isolation. Comparatively, in our genetic cross-correlations throughout 568 enrichment analyses in cell-type and tissue annotations, we found that physical health factors were closely related to ADRD in both LDSC and MAGMA, but not social isolation. Our findings suggest that ADRD shares an important intersection in the enrichment pattern underlying cardiovascular health and diabetes but shows a weaker overlap with other classical risk factors.

Contrary to the conventional textbook wisdom that ADRD is solely enriched in the CNS, our analyses reveal a significant enrichment of ADRD summary statistics in general immune system-related tissues and cells. Notably, our findings highlight the spleen—a central hub of immune cells—and whole blood as being particularly enriched across both LDSC and MAGMA analyses. This observation challenges the traditional view and suggests that ADRD may involve systemic components beyond just the brain. Converging experimental, epidemiological, and clinical evidence also suggests that the multifaceted pathogenesis of ADRD might involve various processes beyond the brain [74]. When we repeated our genetic analyses excluding the APOE region, which contains a number of variants in high linkage disequilibrium, we found similar patterns of enrichment for ADRD, indicating that the results were not solely driven by APOE. APOE is the most significant genetic risk factor for ADRD and has been shown to interact with stress in complex ways. The APOE ε4 allele is linked with increased vulnerability to stress and cognitive decline, potentially due to its impact on amyloid-beta metabolism and neuroinflammation [75, 76]. Research shows that stress-induced cortisol dysregulation, associated

with HPA axis activity, can influence APOE-related mechanisms, thereby linking stress with increased ADRD risk [77, 78]. The enrichment of ADRD risk in whole blood and immune cells aligns with this interaction, as immune system dysregulation and chronic inflammation, exacerbated by stress and influenced by APOE genotype, are implicated in ADRD. The APOE ε4 allele's association with altered immune responses and increased inflammation contributes to ADRD's systemic pathology beyond the central nervous system [76]. This systemic involvement underscores the importance of considering the immune system and whole blood factors in understanding and addressing ADRD risk.

Overall, our study underscores the significant behavioural and genetic intersections between social isolation and ADRD risk, revealing that loneliness and lack of social support are intricately interlocked with classical ADRD risk factors. The complex interplay between social isolation and the major risk traits of ADRD may be largely related to stress. The COVID-19 pandemic exacerbated social isolation and stress, further illuminating their detrimental effects on cognitive health. Prolonged isolation and heightened stress during the pandemic have been associated with increased cognitive decline, underscoring the urgent need for interventions that address these intertwined issues to mitigate ADRD risk. Stressors such as confinement contributed to increased perceived stress, negative emotions, and poor sleep quality, which in turn were linked to subjective cognitive decline [79]. Yaya Li et al. (2022) demonstrated that older adults experienced greater cognitive decline during the pandemic due to poor social relationships [80]. However, their study also noted that the use of information and communications technology (ICT) could mitigate these negative effects by reducing feelings of loneliness and social isolation, suggesting ICT as a potential intervention to support cognitive health. The most important findings

in our study were the widespread behavioural cross-associations and the interlocking pattern of enrichment between the social traits and the classical (non-health-related) risk factors of ADRD. Notably, the enrichment of ADRD in immune-related tissues and whole blood challenges the traditional CNS-centric view of the disease, suggesting a more systemic involvement. Our findings support the accumulating evidence that multiple dysfunctional processes may contribute to ADRD pathogenesis, placing a premium on processes outside the brain, such as components of the immune system. Our population-scale assessment emphasizes the necessity of considering different facets of social isolation/connection in developing holistic strategies to mitigate ADRD risk, thereby paving the way for more effective and comprehensive preventive interventions.

Limitations and Future Directions

Our study observed SNP-based heritability estimates of 7.85% (SE 0.0046) for loneliness and 4.13% (SE 0.0023) for lack of social support. These estimates are comparable to those reported by the Neale Lab's analysis of over 4,000 traits and disorders in the UK Biobank, which found SNP-based heritability of 8.15% (SE 0.00595) for loneliness and 4.07% (SE 0.00266) for the ability to confide (equivalent to our lack of social support phenotype) (https://nealelab.github.io/UKBB_ldsc/). Abdellaoui et al. (2019) also reported an SNP-based heritability of 8.1% (SE 0.07) for their categorical loneliness measure in the UK Biobank. While our heritability estimates are lower compared to these studies, they remain within a comparable range [86]. Variations in phenotype definitions, measurement approaches, and population characteristics may contribute to these discrepancies.

While our research focused on the link between social isolation and ADRD risk, these risk factors are also known to influence a range of other conditions. Investigating whether the genetic associations and enrichment patterns observed in our study hold for diseases beyond ADRD could provide deeper insights into the systemic impacts of social isolation. This expanded approach could help delineate the common and unique genetic pathways that underlie various health risks associated with social isolation, thereby broadening the scope and applicability of our findings. Additionally, future research should expand on our study to include a more diverse range of populations across different age groups, ethnicities, and socioeconomic backgrounds. By incorporating a wider demographic, we can identify any unique patterns or risk profiles that may be present in different subgroups.

Conclusion

By analyzing data from two large, nationally representative cohorts, we have elucidated the consistent behavioural, genetic, and enrichment intersections between social isolation and various ADRD risk factors. Notably, our findings underscored the interconnectedness of social isolation, stress, and the classical lifestyle determinants and personality traits in ADRD risk, highlighting the role of social connections as potential buffers against stress. Additionally, our research challenged the conventional focus on the central nervous system by revealing substantial enrichment of ADRD risk in immune-related tissues and whole blood, suggesting a more systemic involvement in the disease's pathogenesis. The implications of our study are particularly relevant in light of the COVID-19 pandemic, which has exacerbated social isolation and stress, further illuminating their detrimental effects on cognitive health. Our findings advocate for a holistic approach to ADRD prevention, emphasizing the importance of addressing both subjective and objective social dimensions. Future research should build on these insights by exploring the broader systemic impacts of social isolation and expanding the demographic scope to refine and validate our findings. By integrating these diverse perspectives, we can develop more effective strategies to mitigate ADRD risk and enhance overall cognitive health.

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