The shared genetic architecture of modifiable risk for Alzheimer's disease: a genomic structural equation modelling study

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Abstract

Targeting modifiable risk factors may help to prevent Alzheimer's disease (AD), but the pathways by which these risk factors influence AD risk remain incompletely understood. We identified genome-wide association studies for AD and its major modifiable risk factors. We calculated the genetic correlation among these traits and modelled this using genomic structural equation modelling. We identified complex networks of genetic overlap among AD risk factors, but AD itself was largely genetically distinct. The data were best explained by a bi-factor model, incorporating a Common Factor for AD risk, and three orthogonal sub-clusters of risk factors. Taken together, our findings suggest that there is extensive shared genetic architecture between AD modifiable risk factors, but this is largely independent of AD genetic pathways. Extensive genetic pleiotropy between risk factors may influence AD indirectly by decreasing cognitive reserve or increasing risk of multimorbidity, leading to poorer brain health. Further work to understand the biology reflected by this communality may provide novel mechanistic insights that could help to prioritise targets for dementia prevention.

Keywords

Alzheimer's disease; dementia; shared genetics; risk factors; dementia prevention

1 Introduction

The rising prevalence of Alzheimer's disease (AD) is a growing public health concern. However, estimates in several high-income countries show a decrease in age-specific incidence of dementia in recent birth cohorts (Ahmadi-Abhari et al., 2017; James et al., 2018; Wu et al., 2017). This change has been attributed to improved access to education, reduction in the prevalence of cardiovascular disease and the uptake of healthy lifestyle behaviours, such as increased physical activity (Ahmadi-Abhari et al., 2017; Langa et al., 2017; Wu et al., 2017). There is increasing interest in targeting dementia risk factors with a view to preventing or delaying the onset of dementia.

The recent Lancet Commission report on Dementia Prevention, Intervention and Care highlighted 12 potentially modifiable risk factors for dementia and estimated that elimination of these factors at key stages of life could prevent up to 40% of all-cause dementia cases (Livingston et al., 2020). However, the mechanisms by which these factors influence dementia risk, and whether they are truly causal, remain incompletely understood. Some factors such as sleep disturbance, social isolation, depression and hearing difficulty could, at least partly, serve as prodromal risk markers rather than causal risk factors (Brommelhoff et al., 2009; Hardy et al., 2016; Holwerda et al., 2014; Leng et al., 2021). Furthermore, the proposed modifiable risk factors often co-occur and are strongly correlated (Peters et al., 2019). Despite this, current research predominantly focuses on bivariate relationships or select subsets of risk factors, so potential networks of shared aetiological pathways that could additively influence dementia risk remain largely unmeasured. An improved understanding of causal pathways to clinical dementia development is urgently needed to support prevention efforts through the prioritisation of targets for intervention studies.

Advances in large, well-powered genome-wide association studies (GWASs) have shed light on the shared genetic architecture of complex traits and global pleiotropy. Significant bivariate genetic correlations measured by linkage disequilibrium (LD) score regression have

been demonstrated between many behavioural and disease traits (Brainstorm Consortium et al., 2018; Bulik-Sullivan et al., 2015a; Hagenaars et al., 2020; Hill et al., 2016; Tylee et al., 2018), indicating that extensive overlap in genetic pathways is present between seemingly distinct phenotypes. In the field of psychiatric genetics, genomic structural equation modelling (SEM) studies have identified patterns of shared genetic architecture between multiple psychiatric disorders, suggesting that these disorders have shared pathophysiological mechanisms driven by common pleiotropic risk variants in addition to disease-specific mechanisms (Grotzinger et al., 2019; Lee et al., 2019).

In this study, we aimed to apply these approaches to AD and its major risk factors. We hypothesised there would be complex patterns of shared genetic architecture between AD and its risk factors, and that a factor analysis approach would suggest distinct aetiological pathways between different groups of traits. This novel application could help to uncover shared or moderating risk factor pathways and will inform future work to better understand potential causal biological mechanisms that link modifiable risk factors to AD.

2 Material and methods

2.1 Trait selection and quality control

In addition to AD itself, we selected AD risk factors that were identified by the Lancet Commission on Dementia Prevention, Intervention and Care (Livingston et al., 2020). The report identified 12 major modifiable risk factors, 10 of which were included in this analysis (less education, hearing loss, hypertension, high alcohol intake, obesity, smoking, depression, social isolation, physical inactivity and type 2 diabetes). Air pollution exposure was excluded as heritability estimates are low (all air pollution exposures had heritability estimates <0.015 in UK Biobank (https://nealelab.github.io/UKBB_ldsc/index.html)). We also excluded traumatic brain injury as there was not an appropriate GWAS available for this phenotype or a relevant proxy. We additionally included traits for sleep disturbance and

socioeconomic deprivation (Jitlal et al., 2021; Xu et al., 2020). These were highlighted by the Lancet Commission as having strong associations with dementia risk, but with insufficient evidence for causality for them to be included in the final list of major modifiable risk factors (Livingston et al., 2020). We included two traits to measure social isolation (feelings of loneliness and less social activity) because existing literature indicates that these components of social isolation may have differential effects on dementia risk (Holwerda et al., 2014; Wilson et al., 2007).

Publicly available GWAS summary statistics for each of the 14 included traits were identified (**Table 1**) (Jansen, P.R. et al., 2019; Kunkle et al., 2019; Scott et al., 2017; Wray et al., 2018) and underwent quality control according to the pre-established protocols for LD score regression and genomic SEM (Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b; Grotzinger et al., 2019; Zheng et al., 2016). Criteria for inclusion were GWAS studies that had a sample size >5,000 and only included unrelated European ancestry samples (Zheng et al., 2016). Because this analysis sought to measure shared genetic architecture between traits, we also ensured that summary statistics had not been adjusted for potentially modifiable heritable covariates (such as hypertension or BMI) as this procedure can bias genetic effect estimates by controlling for the shared pathways that you wish to measure (Aschard et al., 2015). In contrast, we only included summary statistics that had been adjusted for relevant potentially non-modifiable covariates including age, sex and population principal components (PCs) to ensure that any measured genetic effects were not being biased by participant age, between-sex differences or population stratification. Furthermore, we did not include GWAS summary statistics that had been analysed using linear mixed modelling methods for their association testing due to their potential to produce differential LD estimates compared to traditional regression methods (Loh et al., 2018; Yang et al., 2014). Detailed phenotypic and sample descriptions are outlined in the **Supplementary Methods**. We chose to use the Kunkle et al. (2019) AD GWAS data because more recent AD GWASs also include proxy-AD cases (i.e. individuals with parental family history of AD)

(Bellenguez et al., 2020; Jansen, I.E. et al., 2019; Schwartzentruber et al., 2021; Wightman et al., 2021). Whilst this approach has proven useful for increasing power in GWAS discovery, we felt that inclusion of proxies would add unnecessary noise into our model by creating a more heterogenous AD phenotype.

SNPs with a minor allele frequency (MAF) over 1% and an imputation (INFO) score above 0.9 were retained. As not all GWAS summary statistics supply this information, we filtered SNPs to Hapmap 3 SNPs to ensure that the SNPs we included met our MAF and INFO criteria.

2.2 Heritability and genetic correlation estimation

We initially checked the univariate SNP-based heritability of each trait to ensure that they all had heritability Z scores >4 (Bulik-Sullivan et al., 2015a). Heritability estimates were expressed on the liability scale for binary traits and the observed scale for continuous traits. Population prevalence for binary traits was defined based on recent estimates in European ancestry cohorts (**Table 1** and **Supplementary Methods**).

We then measured the genetic correlations between all pairs of traits to ensure that there was enough intercorrelation for genomic SEM to be appropriate, but that there were no correlations above 90% (Yoo et al., 2014). This was to ensure that we did not include highly multicollinear traits within our model, which may have induced bias towards a certain model specification due to near-complete genetic overlap between two traits (Tarka, 2018). We used a Bonferroni corrected significance threshold for 105 pairwise tests ($p < 4.76E\text{-}4$).

Both these steps were performed using *LDSC* software following pre-established protocols (Bulik-Sullivan et al., 2015a; Zheng et al., 2016) and calculated using publicly available LD scores and weights computed from 1000 Genomes European data restricted to Hapmap 3 SNPs with the major histocompatibility complex (MHC) region removed. The MHC region is located on chromosome 6 and encodes the human leukocyte antigen (HLA) complex, which is associated with key pathways related to the immune system. However, the region

comprises a dense network of genes that often contain SNPs that exert disproportionately large effect sizes, and the area displays extreme LD, so it is routinely removed from LD score regression and genomic factor analysis due to its tendency to bias heritability and genetic correlation results (Grotzinger et al., 2019; Zheng et al., 2016). Therefore, we omitted the MHC region from all our analyses in the current study (including the subsequent genomic SEM analyses).

2.3 Genomic factor analysis

Genomic factor analysis was performed in R version 3.6.3. Because the underlying latent structure of genetic covariance between the included traits was unknown, we initially undertook a genomic exploratory factor analysis (EFA) to identify how many factors best explained the common genetic variance. We then used this to guide the specification of the parameters of a follow-up genomic confirmatory factor analysis (CFA).

Owing to the unavailability of suitable replication GWAS datasets for all of our traits, we ran the EFA in the odd autosomes and the CFA in the even autosomes as a cross-validation to minimise model overfitting. This approach has been utilised in a recent genomic SEM study (Grotzinger et al., 2020).

We undertook multivariable LD score regression (using the same pre-computed LD scores and weights as we had in the bivariate analysis) to calculate the underlying genetic covariance matrix and its associated sampling covariance matrix in odd autosomal data to use as the input for EFA (Grotzinger et al., 2019). Using EFA we tested different numbers of factors to identify which model performed best using pre-defined criteria (**Supplementary Methods**). We used oblique (promax) rotation, which assumed correlation between factors, because the results of pairwise LD score regression indicated that there were high levels of genetic correlation between most traits, so it was unlikely that the latent constructs would be uncorrelated.

To test model fit we performed CFA using the output from an additional multivariable LD score regression in the even autosomes. We specified the parameters of the CFA using the results of the best performing model from EFA (i.e. the 3-factor model). We examined multiple models within these parameters by comparing how inclusion of cross-loadings, negative loadings and higher loading cut-off levels influenced model fit. We assessed model fit by comparing recommended test results and cut-off points (Grotzinger et al., 2019) (**Supplementary Methods**). From these results, we took the best performing model and using data from all autosomes we measured its overall genome-wide model fit.

We additionally tested the genome-wide performance of a common factor model, a hierarchal model and a bi-factor model (**Supplementary Methods**). We ran all of the models using diagonally weighted least squares estimation as this method accounts for differences in GWAS sample size and is more accurate for modelling binary traits (Beauducel and Herzberg, 2006; Grotzinger et al., 2019).

As AD susceptibility is highly influenced by the *APOE* gene located on chromosome 19, we also tested our model with this gene region removed to assess whether the covariance that AD displayed in the models was mainly driven by *APOE*. We removed SNPs from the *APOE* region +/- 100kB (chr19: 45,309,039–45,512,650) based on the same human genome assembly as the included GWAS summary statistics (GRCh37/hg19) and re-ran our models. SNPs either side of the *APOE* region were also removed because this region has several additional AD-associated SNPs that are in high LD with the two key *APOE* SNPs associated with differential AD risk (rs7412 and rs429358) (Kulminski et al., 2018; Kulminski et al., 2020). Although this was an arbitrary cut-off, we felt that this specification sufficiently removed the region that was most likely to be influencing our LD score regression estimates since it removed the *APOE* SNPs that have a disproportionately high effect size compared to the rest of the genome, as well as the SNPs that are in high LD with them, whilst minimizing the risk of being over-conservative and removing shared genetic effects on chromosome 19 that are not being driven by genes in the *APOE* region.

All our model parameters are reported as standardized values (i.e. they represent genetic correlation coefficients rather than covariances), since they are easier to interpret when making comparisons between different models. Standardized estimates are automatically produced by the genomic SEM software by re-calculating the models using a correlation matrix and its associated sampling correlation matrix as the input, which is converted from the original covariance-based matrices (Grotzinger et al., 2019).

As our pipeline was relatively complex, Figure 1 provides an overview of the key methodological steps that we performed in our study and acts as a stepwise guide for other researchers who may wish to perform a similar type of analysis applied to their own research question.

2.4 Sensitivity analyses

Loadings for AD varied substantially between the EFA in odd autosomes, the CFA in even autosomes and the genome-wide CFA, whereas the risk factor parameters stayed largely comparable. We hypothesised that this may be because AD is more oligogenic than the other traits and so may show differential genetic correlations between chromosomes compared to highly polygenic traits since risk variants may be less evenly spread across the autosomes (Zhang et al., 2020). We therefore performed post-hoc sensitivity analyses to compare genetic correlation estimates measured in different chromosomal groupings and model fit when CFA was based on EFA parameters estimated from the even autosomes and all autosomes (**Supplementary Methods**).

3 Results

3.1 Heritability and genetic correlation estimation

All 14 traits displayed heritability Z scores >4, indicating that the traits were sufficiently heritable to be modelled using genomic SEM (**Table 1**).

We then measured SNP-based genetic correlations between all pairs of traits using LD score regression. All of the risk factor traits displayed Bonferroni significant positive correlations with multiple other risk factors, indicating a complex network of genetic correlation suitable for factor analysis (**Figure 2a** and **Supplementary Table 1**). Of the risk factors, hearing difficulty and systolic blood pressure were the most genetically distinct (see **Figure 2b**). AD did not display any Bonferroni significant genetic correlations with any of the risk factors, though it did share a nominally significant genetic correlation with less education (p = 0.0014) (see **Figure 2** and **Supplementary Table 1**).

3.2 Factor analysis

EFA indicated that a 3-factor model fitted the data best (**Figure 3**, **Supplementary Tables 2-4** and **Supplementary Results**). Using the parameters of the 3-factor EFA, we ran CFA in the even chromosomes to establish model fit. As systolic blood pressure did not display any positive loadings above our pre-defined cut-off it was omitted from our subsequent models. The best fitting CFA included positive loadings ≥0.25 (except for insomnia, which only had loadings ranging between 0.20-0.24, so we included its highest loading) and cross-loadings but excluded negative loadings (**Table 2**). Model fit and loadings were comparable when tested in all autosomes (**Table 2** and **Figure 4a**).

Comparison of the 3-factor, common factor, hierarchal factor and bi-factor models revealed that the bi-factor model provided the best model fit across all autosomes (**Table 2** and **Figure 4**). In the bi-factor model, the Common Factor was influenced by all of the included traits and the factors from the CFA formed orthogonal sub-clusters of variance between specific sets of AD risk factors that were independent of AD (**Figure 4d**). The model fit and loadings remained similar after excluding *APOE* (**Table 2** and **Supplementary Figure 3**).

3.3 Sensitivity analyses

Our sensitivity analyses found that in comparison to the risk factor traits, AD displayed substantial differences in pairwise genetic correlation estimates and EFA loading estimates between the odd and the even chromosomes (**Supplementary Table 5** and **Supplementary Results**). However, follow-up genomic factor analysis that calculated CFA models based on EFA parameters estimated in even autosomes and all autosomes instead of the odd autosomes, produced poorer model fit statistics than our original model, indicating that our model is preferable (**Table 2** and **Supplementary Results**).

4 Discussion

In this study, we modelled the shared genetic architecture between AD and its potentially modifiable risk factors. LD score regression highlighted pervasive genetic overlap between risk factor traits, but AD was largely genetically unique. We built on this by using factor analysis and genomic SEM to model this shared genetic architecture. The best fitting bi-factor model demonstrated the presence of a small common genetic liability between AD and its risk factors, likely mediated by less education, while the remaining genetic covariance was explained by three orthogonal clusters of risk factors, independent of AD genetics. These findings demonstrate a richly interconnected network of genetic communality between AD risk factors which may, in part, explain established epidemiological associations and suggest new avenues for both understanding the mechanisms by which modifiable risk factors influence AD synergistically, and aid the discovery of the components of missing heritability through multivariate GWAS.

Pairwise LD score regression revealed many significant genetic correlations, indicating a substantial genetic overlap between AD risk factors. However, AD had no significant genetic correlations with its risk factors, suggesting that it is genetically distinct from them. Our findings support previous work that found AD to have a greater amount of unique genetic variance compared to psychiatric, behavioural or cardiometabolic traits (Brainstorm

Consortium et al., 2018; Bulik-Sullivan et al., 2015a). The strongest correlation for AD was with less education, which is consistent with previous Mendelian randomisation results that suggest a causal effect of less education on AD risk (Anderson et al., 2020; Andrews et al., 2021; Larsson et al., 2017).

Factor analysis identified an optimal 3-factor model, in which each factor contained a distinct cluster of traits, allowing us to generate some hypotheses about the mechanisms that might be reflected in these factors. Factor 1 had positive loadings for risk factors that are strongly associated with reduced life expectancy (smoking, deprivation, less education and physical inactivity) (Holford et al., 2014; Lewer et al., 2020; Warburton et al., 2010) together with a negative loading for AD. This factor might reflect only an apparent protective effect of these factors on AD due to premature mortality and survival bias (Hernán et al., 2008; Kukull, 2001; Weuve et al., 2015), or could simply reflect a clustering of these traits independent of AD. Factor 2 had highly stable positive loadings for a majority of the risk factors and a positive loading for AD, suggesting that it might represent a common genetic pathway to AD across metabolic, psychiatric and lifestyle traits. Factor 3 included positive loadings for a subset of risk factors that have complex relationships with AD in that they have all been hypothesised to be disease prodromes as well as causal risk factors (Brommelhoff et al., 2009; Hardy et al., 2016; Holwerda et al., 2014; Johnson et al., 2020; Leng et al., 2021). Moreover, systolic blood pressure negatively loaded onto this factor, and whereas risk of dementia is associated with higher blood pressure in mid-life, blood pressure declines during the period prior to cognitive symptoms and dementia diagnosis (Lane et al., 2019; Ma et al., 2019; Perera et al., 2020; Sproviero et al., 2020). It is therefore possible that Factor 3 reflects AD prodromes, and hence reverse causality between AD and these traits.

A bi-factor model provided the best model fit in genomic SEM. This model highlighted a Common Factor of shared genetic liability between all of the included traits, in addition to the three distinct orthogonal clusters of covariance identified by factor analysis. The only trait that did not pass inclusion into this model was systolic blood pressure due to its lack of

communality with the other traits. This may partly be due to the complex relationship with blood pressure at the different stages of AD (Lane et al., 2019; Ma et al., 2019; Perera et al., 2020; Sproviero et al., 2020).

AD loaded positively onto the Common Factor but lost its positive loading for Factor 2. The Common Factor had particularly high associations with being less educated, less physically active and more socially isolated, indicating that these risk factors have the highest influence within this construct. Since less education was the only trait in LD score regression to share a substantial genetic correlation with AD, as well as significant correlations with all of the other risk factors (except for hearing difficulty), it therefore seems likely that the small loading of AD may be due to its shared genetic architecture with being less educated, rather than a universal shared component with all of the risk factors. Previous studies measuring bivariate associations have highlighted a causal genetic link between less education and AD (Anderson et al., 2020; Andrews et al., 2021; Larsson et al., 2017) and its early life occurrence makes it a stronger candidate for being on the causal pathway to AD than other proposed risk factors that seem to exert risk later in life so are more likely to be linked by reverse causation (Livingston et al., 2020). This is an important finding because it supports the idea that education is a key protective factor for AD and indicates that education may be an influential moderator in the associations seen between AD and other modifiable risk factors in epidemiological studies via extensive genetic pleiotropy. In contrast, our sensitivity analyses indicated that AD covariance with its risk factors is likely confined to a few specific genomic regions rather than being caused by genome-wide pleiotropy, which is in line with previous findings that AD is more oligogenic than its risk factors (Zhang et al., 2020). Only 2% of AD's genetic variance was explained by the model, indicating that AD is almost entirely genetically distinct from its risk factors, so the shared component may be entirely explained by its genetic correlation with less education. Interestingly, this mediating genetic pathway is unlikely to be driven by the *APOE* region since the loadings for AD and model fit stayed comparable when the *APOE* region was omitted from the analysis.

In contrast, AD risk factors display high levels of genetic overlap. The three orthogonal clusters identified in the factor analysis were largely unchanged in the bi-factor model, except that Factor 2 only retained high loadings with traits associated with sedentary lifestyle behaviours (type 2 diabetes, obesity, higher alcohol intake and physical inactivity). Despite their lack of direct shared genetic liability with AD, the likely relevance of these 3 sub-clusters is two-fold. Firstly, multimorbidity has been shown to increase an individual's risk of developing AD, although the mechanisms for this remain unknown (Peters et al., 2019). The high levels of shared genetic architecture between sets of known AD risk factors may represent mutual genetic liabilities between groups of traits that increase an individual's likelihood of developing multiple conditions, or they might be associated with more generic 'unhealthy' behaviour and social circumstance. Secondly, although these clusters display no direct shared genetic pathway with AD, these shared pathways may exert synergistic pathophysiological effects that create a microenvironment within the brain that leads to an increased propensity to develop AD indirectly, such as reducing cognitive reserve or via gene-environment interactions.

There are several important limitations to this work. AD had the lowest heritability Z score of any of the traits that we measured, which may have been due to its markedly smaller sample size, meaning that our analysis for AD was underpowered in comparison to its risk factors. Heritability may also be adversely influenced by the heterogeneous nature of AD outcomes in the original GWAS (Ryan et al., 2018). The use of endophenotypes has been shown to produce more homogenous genetic phenotypes. However, the current GWAS data for molecular biomarkers of AD pathology have poor heritability estimates and sample sizes too small to be used reliably for genomic SEM (Deming et al., 2017; Lord et al., 2021). More recent AD GWASs have increased power by including proxy-cases (Bellenguez et al., 2020; Jansen, I.E. et al., 2019; Schwartzentruber et al., 2021; Wightman et al., 2021), but we felt that for our current study this would have diluted our phenotype too much for subsequent modelling in genomic SEM.

Another important limitation is that we have only used samples from European ancestry owing to the confounding effects of ancestral variation in LD score regression. Although sampling efforts in more diverse ancestral groups have started to increase, there is still a significant lack of data for many phenotypes for non-European groups and we were thus unable to perform an analysis that would include all our traits of interest (Martin et al., 2019). Therefore, it is possible that these findings cannot be generalised to other populations. There is increasing evidence that AD risk factors exert differential effects on AD onset across diverse ethnicities (Babulal et al., 2019; Bothongo et al., 2022; Mukadam et al., 2019) and so, as sufficient data become available, it will be crucial to perform similar analyses in a range of ethnic groups to support targeted prevention strategies globally.

Lastly, our current model only measures shared common genetic architecture, but does not identify shared rare genetic variance, environmental pathways or gene-environment interactions. There is evidence to suggest that an individual's genetic profile can influence the magnitude of the effect that modifiable risk factors have on AD risk via gene-environment interactions (Dunn et al., 2019; Eid et al., 2019). Furthermore, increasing age remains the largest risk factor for AD and various epigenetic changes have been associated with both AD and ageing (Li et al., 2019; Nativio et al., 2018; Reynolds et al., 2020), so gene-environment interactions may be especially important to explore. However, such studies require a good understanding of the underlying genetic architecture, so our current study provides a useful and novel foundation for future work in this area.

This work provides the basis for further study to identify the SNPs and downstream pathways that are shared within the latent constructs identified here and how they relate to dementia-related outcomes. Understanding the biological pathways that link AD risk factors could help to prioritise interventions that might prevent AD indirectly through maintaining cognitive reserve or reducing levels of multimorbidity. More broadly, future work in AD genetics should focus on phenotype optimisation and larger sample sizes of clinical AD cases that may lead to improved GWAS discovery and more links to risk factors may be

unearthed. Larger GWASs of AD biomarkers, such as CSF amyloid-β and tau, will enable exploration of how AD risk factors share genetics with these specific pathologies, providing a deeper understanding of whether risk factors influence AD genetically via shared architecture with pathological processes or by reducing cognitive reserve.

5 Conclusions

Taken together, these results demonstrate a complex pattern of shared genetic architecture between AD risk factors, including a Common Factor for AD risk that may link pathophysiological mechanisms across metabolic, psychiatric and lifestyle traits. However, AD itself is largely genetically distinct from its risk factors, and it seems likely that the small level of genetic overlap seen between AD and its risk factors is moderated by education, rather than via directly shared genetic pathways with all risk factors. However, the high level of shared genetics between risk factors may influence AD onset indirectly through increasing cognitive burden and multimorbidity leading to poor brain health. Understanding the biology underpinning this extensive communality could yield novel preventive strategies to mitigate the growing global challenge of dementia.

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Declarations of Interest

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Author Contributions

IFF: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – Original draft. BMJ: Methodology; Writing – review & editing. GM: Methodology; Writing – review & editing. CJW: Methodology; Writing – review & editing. PLKB: Methodology; Writing – review & editing. SW: Methodology; Writing – review & editing. RD: Conceptualization;

Methodology. AJN: Conceptualization; Methodology; Writing – review & editing. KSB: Conceptualization, Methodology; Supervision; Writing – review & editing. AK: Conceptualization, Methodology; Supervision; Writing – review & editing. CRM: Conceptualization, Methodology; Supervision; Writing – Original draft.

Data Availability

The data used in this study are all publicly available for download at the following URLs:

AD - https://www.niagads.org/datasets/ng00075

Depression - https://www.med.unc.edu/pgc/download-results/?wpv-category=major-depressive-disorder

Insomnia - https://ctg.cncr.nl/software/summary_statistics

Type 2 diabetes - http://diagram-consortium.org/downloads.html

Neale lab (UK Biobank traits) - http://www.nealelab.is/uk-biobank

LD scores and weights - https://alkesgroup.broadinstitute.org/LDSCORE/

Reference genome file (Hapmap 3 SNPs) - https://utexas.app.box.com/s/vkd36n197m8klbaio3yzoxsee6sxo11v

A walkthrough of the code that we used in this study will be made available on GitHub upon publication.

Table 1: GWAS sample sizes and results of the univariate LD heritability estimation for the 14 traits. The sample sizes may differ from the numbers reported in the original GWAS because we only used publicly available and European data. Population prevalence figures are current estimates for age-specific European ancestry populations (see **Supplementary Methods** for further details). SE = standard error; GC = genomic control.

Trait	Total sample size (*cases vs controls*)	Population prevalence	Observed or liability scale	Total SNP-based heritability (SE)	Heritability Z score	Mean χ^2	λ GC	Intercept (SE)	Original GWAS
Alzheimer's disease	63,926 (*21,982 vs. 41,944*)	0.05	Liability	0.0674 (0.0108)	6.2407	1.118	1.0926	1.0302 (0.0084)	Kunkle et al.(Kunkle et al., 2019)
Major depressive disorder	173,005 (*59,851 vs. 113,154*)	0.13	Liability	0.0977 (0.006)	16.2833	1.266	1.2365	0.9943 (0.009)	Wray et al.(Wray et al., 2018)
Insomnia	386,533 (*109,402 vs. 277,131*)	0.32	Liability	0.084 (0.0038)	22.1053	1.3659	1.3101	1.0152 (0.0089)	Jansen et al.(Jansen, P.R. et al., 2019)
Loneliness	355,583 (*63,508 vs. 292,075*)	0.08	Liability	0.0616 (0.0035)	17.6	1.2766	1.2365	1.0162 (0.0074)	http://www.nealelab.is/uk-biobank/
Less social activity	360,063 (*108,704 vs. 251,359*)	0.30	Liability	0.0618 (0.0037)	16.7027	1.2705	1.2365	1.0174 (0.0075)	http://www.nealelab.is/uk-biobank/
Hearing difficulty	353,983 (*134,141 vs. 219,842*)	0.39	Liability	0.0826 (0.0039)	21.1795	1.3755	1.3068	1.024 (0.0085)	http://www.nealelab.is/uk-biobank/
Less education	357,549 (*61,093 vs. 296,456*)	0.27	Liability	0.2573 (0.0087)	29.5747	1.7806	1.5995	1.0635 (0.0111)	http://www.nealelab.is/uk-biobank/
Physical inactivity	359,263 (*21,255 vs. 338,008*)	0.18	Liability	0.1292 (0.0095)	13.6	1.1773	1.1619	1.0171 (0.007)	http://www.nealelab.is/uk-biobank/
Smoking	359,706 (*37,088 vs. 322,618*)	0.27	Liability	0.1969 (0.0102)	19.3039	1.3734	1.3034	1.0142 (0.0084)	http://www.nealelab.is/uk-biobank/
Alcohol intake frequency	360,726 (*N/A*)	N/A	Observed	0.0797 (0.0036)	22.1389	1.6203	1.4926	1.0521 (0.0105)	http://www.nealelab.is/uk-biobank/
Body mass index	354,831 (*N/A*)	N/A	Observed	0.2316 (0.0073)	31.726	2.8005	2.1764	1.132 (0.0164)	http://www.nealelab.is/uk-biobank/
Deprivation status	360,763 (*N/A*)	N/A	Observed	0.0332 (0.0019)	17.4737	1.2532	1.2299	1.0194 (0.0071)	http://www.nealelab.is/uk-biobank/
Systolic blood pressure	340,159 (*N/A*)	N/A	Observed	0.1403 (0.0052)	26.9808	2.0666	1.6985	1.0909 (0.0134)	http://www.nealelab.is/uk-biobank/
Type 2 diabetes mellitus	159,208 (*26,676 vs. 132,532*)	0.06	Liability	0.121 (0.0084)	14.4048	1.2311	1.1459	0.9979 (0.0087)	Scott et al.(Scott et al., 2017)

Table 2: Model fit statistics for each of the genomic SEM models performed in even autosomes, all autosomes, all autosomes with the *APOE* region removed and the post-hoc sensitivity analyses. CFA = confirmatory factor analysis; EFA = exploratory factor analysis.

Autosomes used	Autosomes EFA parameters based on	Model type	EFA loading cut-off	Factor correlations (Y/N)	Cross loadings (Y/N)	Negative loadings (Y/N)	Degrees of freedom	X^2 statistic	Akaike Information Criterion (AIC)	Comparative Fit Index (CFI)	Standardised Root Mean Square Residual (SRMR)
Even	Odd	CFA	0.2	Y	Y	N	Model did not converge				
Even	Odd	CFA	0.2	Y	Y	Y	Model did not converge				
Even	Odd	CFA	0.2	Y	N	Y	74	1029.605	1091.605	0.7938	0.0825
Even	Odd	CFA	0.2	Y	N	N	62	607.4996	665.4996	0.8670	0.0718
Even	Odd	CFA	0.25	Y	Y	N	59	505.4162	569.4162	0.8912	0.0642
Even	Odd	CFA	0.25	Y	Y	Y	71	947.9721	1015.972	0.8108	0.0770
All	Odd	CFA	0.25	Y	Y	N	59	1140.305	1204.305	0.8490	0.0638
All	NA	Common factor	NA	NA	NA	NA	65	1681.427	1733.427	0.7743	0.0967
All	Odd	Hierarchal	0.25	NA	Y	N	59	1140.306	1204.306	0.8490	0.0638
All	Odd	Bi-factor	0.25	NA	Y	N	49	449.961	533.961	0.9440	0.0538
Excl. *APOE*	Odd	CFA	0.25	Y	Y	N	59	1115.992	1179.992	0.8590	0.0636
Excl. *APOE*	NA	Common factor	NA	NA	NA	NA	65	1700.368	1752.368	0.7818	0.0966
Excl. *APOE*	Odd	Hierarchal	0.25	NA	Y	N	59	1115.991	1179.991	0.8590	0.0636
Excl. *APOE*	Odd	Bi-factor	0.25	NA	Y	N	49	452.3386	536.3386	0.9462	0.0536
Odd	Even	CFA	0.2	Y	Y	N	Model did not converge				
Odd	Even	CFA	0.2	Y	N	N	62	896.9278	954.9278	0.8073	0.0740
Odd	Even	CFA	0.25	Y	Y	N	Model produced unstable estimates due to negative residual variances				
All	Even	CFA	0.2	Y	Y	N	Model did not converge				
All	Even	CFA	0.2	Y	N	N	62	1621.472	1679.472	0.8096	0.0721
All	Even	CFA	0.25	Y	Y	N	61	1605.599	1665.599	0.8114	0.0720
All	All	CFA	0.2	Y	Y	N	59	1676.953	1740.953	0.8024	0.0649
All	All	CFA	0.2	Y	N	N	62	1621.472	1679.472	0.8096	0.0721
All	All	CFA	0.25	Y	Y	N	60	1621.83	1683.83	0.8093	0.0677

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Figures

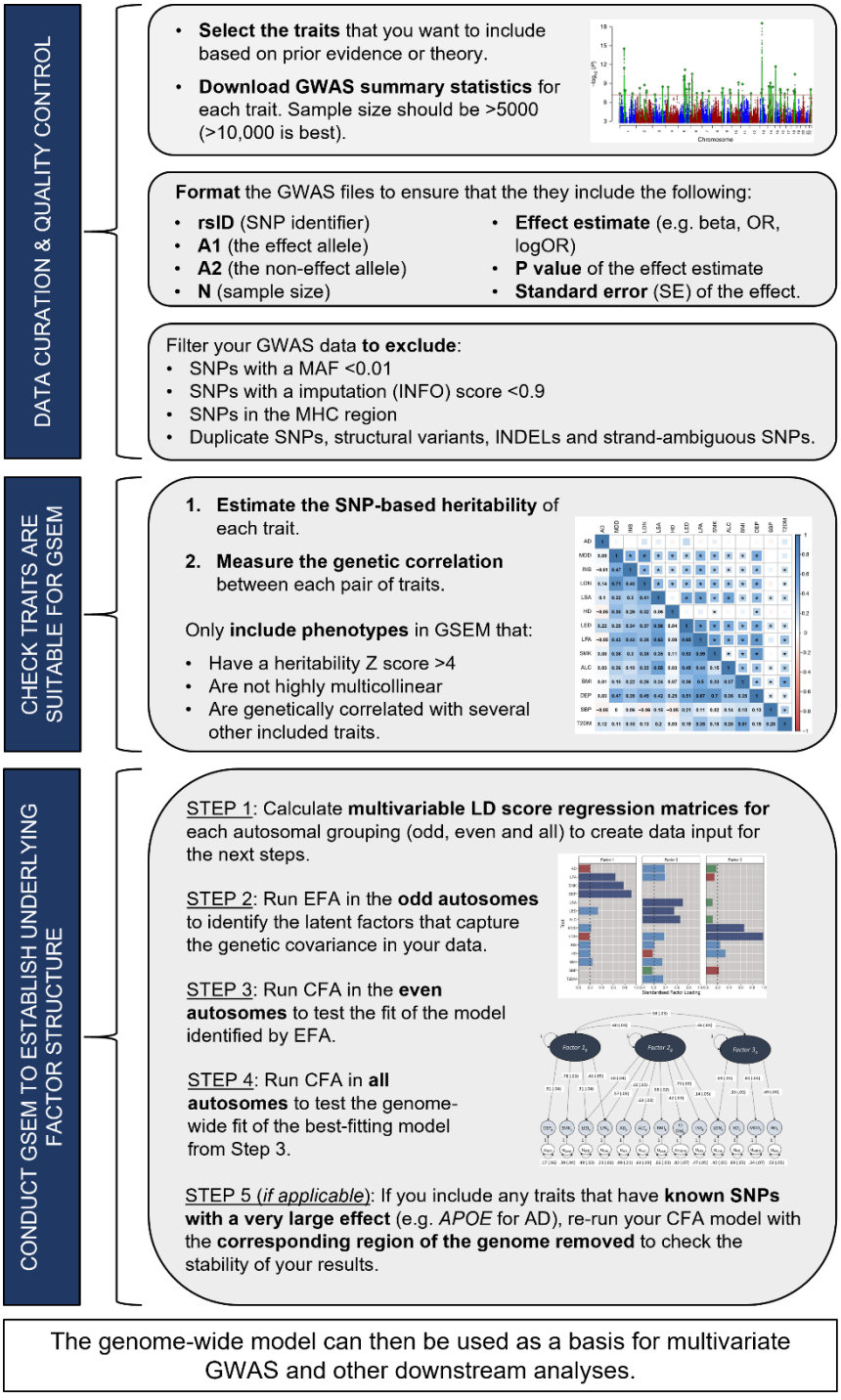

Figure 1 A flowchart providing an overview of the pipeline that we used in this study to identify the underlying latent profile of genetic covariance between our included traits. We based our pipeline on those developed by Bulik-Sullivan et al. (2015a; 2015b) for LD score regression and Grotzinger et al. (2019) for genomic SEM. The Manhattan plot example is taken from Wray et al. (2018).

GWAS Genome-wide association study; SNP single nucleotide polymorphism; OR odds ratio; MAF minor allele frequency; MHC major histocompatibility complex; INDELs insertions and deletions; GSEM genomic structural equation modelling; LD linkage disequilibrium; EFA exploratory factor analysis; CFA confirmatory factor analysis; APOE apolipoprotein; AD Alzheimer's disease.

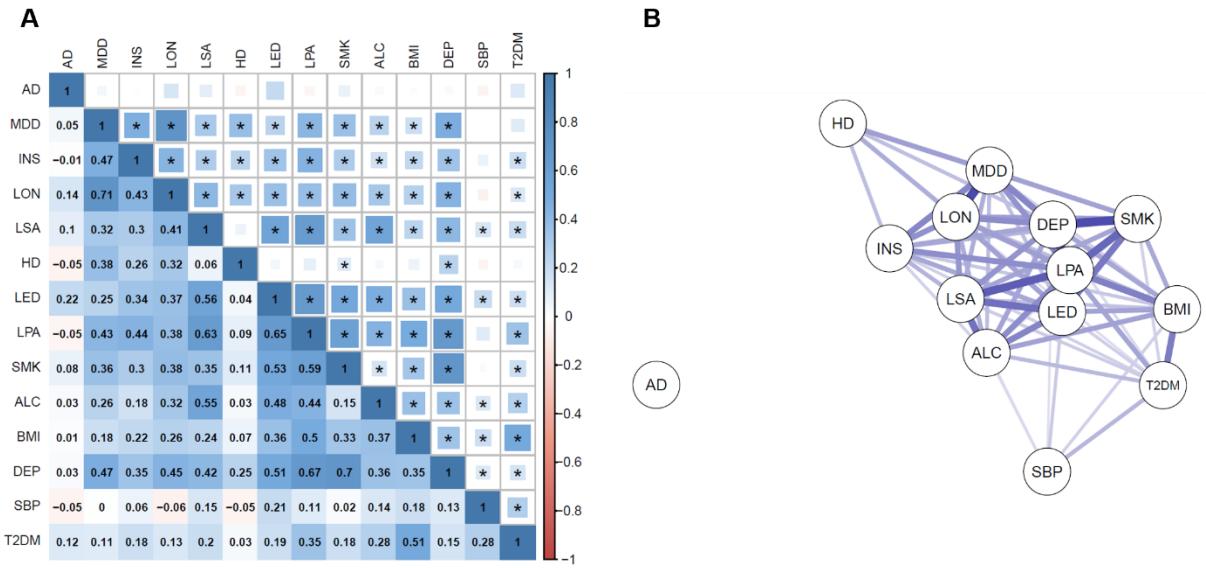

Figure 2 (A) A heatmap of pairwise genome-wide genetic correlations between all 14 traits based on LD score regression, and (B) a weighted undirected graph showing the structure of the significant genetic correlations that are present between the 14 traits in our analysis. In **Figure A** the upper triangle of the matrix displays the strength of correlation (size of each square) and significant associations passing Bonferroni correction ($p < 4.76E\text{-}4$) are marked with an asterisk. The lower triangle shows the correlation coefficient values. In both triangles, the shade of each square denotes a positive (blue) or negative (red) correlation, varying in shade by magnitude of correlation. In **Figure B,** each trait forms an individual node (depicted by a circle) and the lines joining them are edges which represent pairwise correlation coefficients between traits. Only Bonferroni significant relationships are included. The stronger the correlation, the shorter and wider the edge and the darker the colour. As all the significant correlations were positive, all edges are blue.

AD Alzheimer's disease; MDD major depressive disorder; INS insomnia; LON loneliness; LSA less social activity; HD hearing difficulty; LED less education; LPA physical inactivity; SMK smoking; ALC alcohol intake frequency; BMI body mass index; DEP deprivation status; SBP systolic blood pressure; T2DM type 2 diabetes mellitus.

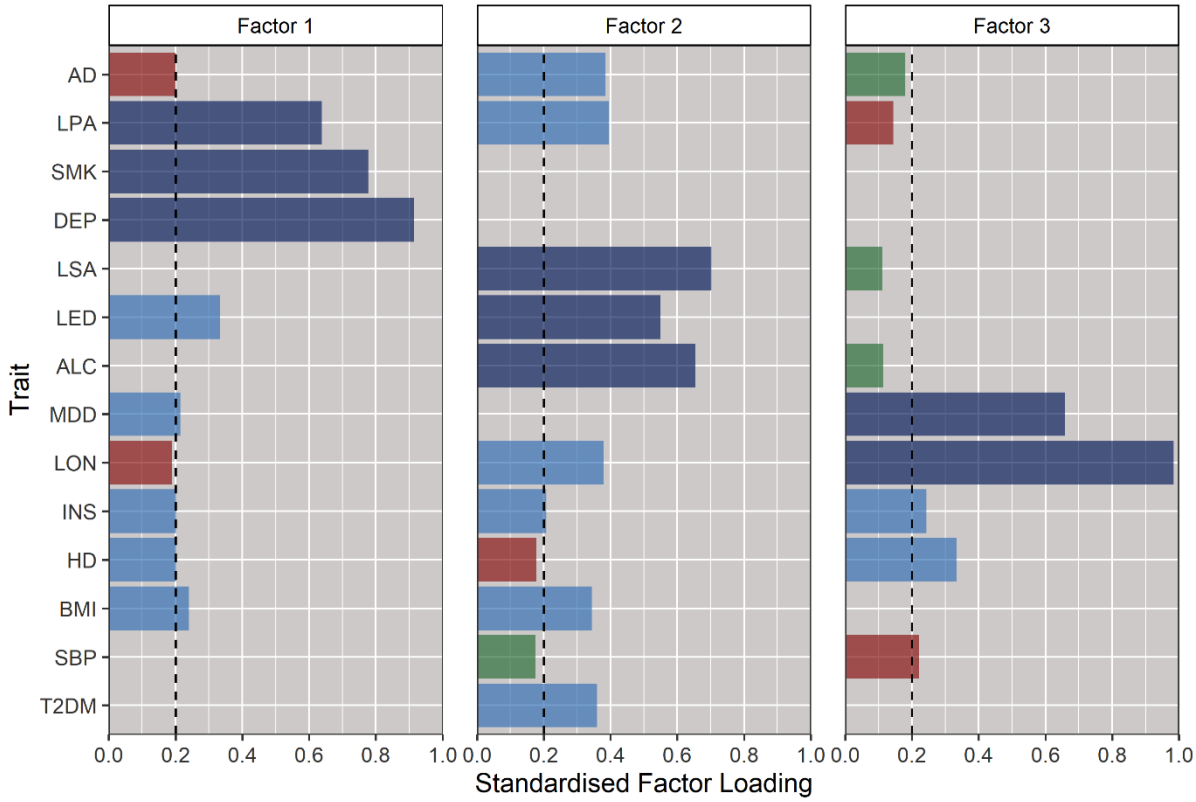

Figure 3 Standardised factor loadings for the 3-factor genomic exploratory factor analysis model based on data from the odd autosomes. Each bar on the plot denotes the factor loading of each trait on each of the 3 factors. Each vertical rectangle represents a factor. These factors are ordered by the amount of total variance they explain (left to right). The vertical dashed line represents the chosen cut-off threshold (0.20). The colour of the bar represents the factor loading strength. Dark blue denotes highly stable positive loadings (>0.40), light blue represents positive loadings between 0.20 to 0.40, green denotes positive loadings not meeting our cut-off threshold (between 0 and 0.20) and red represents negative loadings.

AD Alzheimer's disease; MDD major depressive disorder; INS insomnia; LON loneliness; LSA less social activity; HD hearing difficulty; LED less education; LPA physical inactivity;

SMK smoking; ALC alcohol intake frequency; BMI body mass index; DEP deprivation status; SBP systolic blood pressure; T2DM type 2 diabetes mellitus.

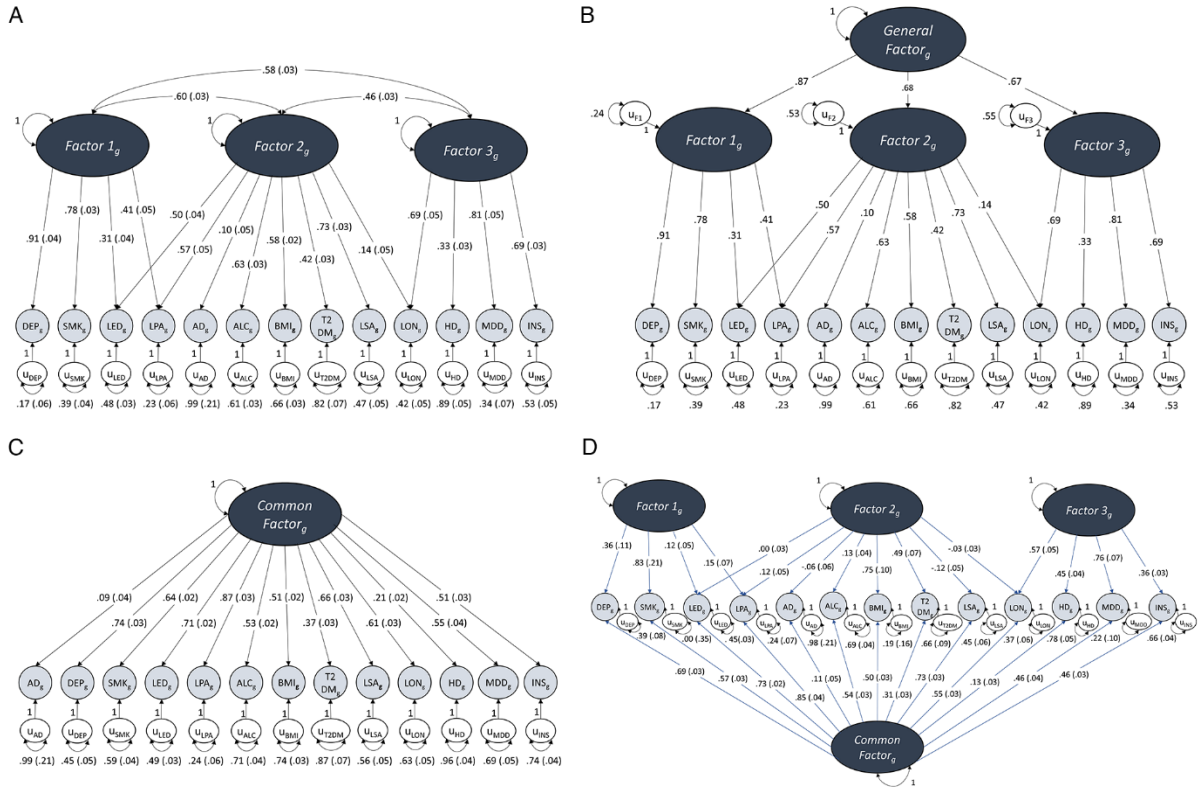

Figure 4 Path diagrams of the standardised solutions for the (A) 3-factor CFA, (B) hierarchal model, (C) common factor and (D) bi-factor model conducted across all autosomes. The dark grey ovals represent latent unobserved constructs (factors), the pale grey circles are the observed traits made up of the measured genetic variance of each included trait, the white circles represent the unique variance of each trait not explained by loadings into factors. Unidirectional arrows depict regression coefficients from the independent variable to the dependent variable, curved two-headed arrows between factors represent correlations between the factors and two-headed arrows connecting a variable to itself highlights the variance of a variable with itself. Numbers in brackets represent the standard error of each measured value. Due to its lack of positive loading onto any factor during EFA, systolic blood pressure was excluded from these models. **Figure A** displays the path diagram for the 3-factor CFA which shows the factor loadings for traits that displayed a

loading ≥ .25 at EFA. These three latent factors show moderate levels of inter-factor correlation. **Figure B** displays the path diagram of the hierarchal model where there is a second-order factor consisting of the shared genetic variance between the 3 latent constructs identified in the CFA. **Figure C** displays the path diagram for the common factor model where there is only one factor that depicts the overarching common variance between all included traits. **Figure D** displays the path diagram for the bi-factor model where there is a Common Factor of shared variance between all of the traits as well as 3 uncorrelated latent factors of sub-clusters of covariance that were specified by EFA in the same way as our CFA.

AD Alzheimer's disease; MDD major depressive disorder; INS insomnia; LON loneliness; LSA less social activity; HD hearing difficulty; LED less education; LPA physical inactivity; SMK smoking; ALC alcohol intake frequency; BMI body mass index; DEP deprivation status; T2DM type 2 diabetes mellitus.