Appendix S1

Supplementary methods

Covariates

Sociodemographic factors included age, sex, ethnicity (white or others), Townsend deprivation index (TDI), employment status (employed or retired/Others), educational level (below or above college degree); participants reporting “None of the above” or “Prefer not to answer” were deleted. Lifestyle factors included smoking status and alcohol drinker status (never, previous, and current). Trained nurses measured height and weight, from which body mass index (BMI) was calculated. We divided obesity grades into two groups based on BMI for Europeans: lean (BMI < 25.0 kg/m^2) and non-lean (BMI ≥ 25.0 kg/m^2) group [1]. Result of triglycerides and Vitamin D were performed on blood sample, obtained from UK Biobank assessment Center visit. Additional details regarding the protocols can be found on the UK Biobank (UKB) website (https://www.ukbiobank.ac.uk). The annual average concentrations of particulate matter with aerodynamic diameter ≤ 2.5 micrometers ($PM_{2.5}$) was estimated using a Land Use Regression model developed by the European Study of Cohorts for Air Pollution Effects project.

Polygenic risk score (PRS) for AD

To evaluate the role of genetic susceptibility to AD in the association between psychiatric disorders and long-term risk of AD, we derived PRS for AD using summary statistics from genome-wide association studies (GWAS) as the base data. GWAS summary statistics for AD were obtained from the FinnGen consortium (https://www.finngen.fi/en/access_results; L12_ATOPIC). The FinnGen GWAS for AD was conducted in 31,245 cases and 432,874 controls, with all participants of European ancestry and no sample overlap with UKB. Genotype data from UKB were used as the target data. We generated PRS for AD using PRSice-2 [2]. For PRS analyses, we restricted participants to European genetic ancestry and excluded samples with sex discordance, excess heterozygosity or missingness, close relatedness, missing genotype data, or withdrawal from UK Biobank. Variants were harmonized between base and target datasets; ambiguous variants were removed, and SNPs were filtered by imputation quality and minor allele frequency before clumping. PRSice-2 was used to generate clumping-and-thresholding PRSs with LD clumping in the target

data (clumping distance 250 kb, r2 = 0.001). The default PRSice-2 scoring model was used, in which observed effect alleles are weighted by the corresponding GWAS effect size and summed across variants. The best-fit PRS was selected according to model R2 across the tested P-value thresholds and was used as the genetic susceptibility measure in interaction analyses.

Propensity score matching

Propensity score matching (PSM) was performed in the present study. A one to four greedy matching using nearest-neighbor matching with a caliper distance of 0.4 without replacement was performed based on the following strata including: sex, age, ethnicity, Townsend deprivation index, body mass index, employment status, education level, smoking status, alcohol drinker status, triglycerides, Vitamin D, $PM_{2.5}$, history of asthma and allergic rhinitis, and seven psychiatric disorders at baseline.

Mediating effects of plasma metabolome

Strategy 1 analyzed each plasma metabolomic marker separately. To comprehensively screen all possible metabolomic markers as potential mediators between psychiatric disorder and AD, we employed the regression-based causal mediation model proposed to estimate the mediation effect of each candidate metabolomic marker [3]. For each candidate metabolomic marker, 168 one-at-a-time pairwise mediation models were generated. The mediation effect and mediated proportion were computed for each candidate metabolomic marker. Strategy 2 clustered plasma metabolomic markers into different metabolic patterns before analysis. We first conducted a principal component analysis (PCA) on the whole plasma metabolomic markers using the "prcomp" package. The extracted principal components (PCs) were the metabolic patterns representing specific metabolic features. We analyzed the associations of psychiatric disorder with metabolic patterns and metabolic patterns with AD, respectively. These extracted metabolic patterns were also used to investigate their mediating role in the relationship between psychiatric disorder and AD. All mediation models were adjusted for potential confounding variables and performed by the "mediation" package. We established a standard three-variable path model, where linear regression was used for psychiatric disorder-metabolomic markers associations and survival regression was used for psychiatric disorder-AD and metabolomic markers-AD associations [4]. The significance of mediating effects was determined based on 5000 bootstrap iterations. All analyses

were conducted in R 4.4.3 and were corrected for multiple comparisons using Benjamini-Hochberg false discovery rate (FDR).

References

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