Data supplement for Choi et al., An Exposure-Wide and Mendelian Randomization Approach to Identifying Modifiable Factors for the Prevention of Depression. Am J Psychiatry (doi: 10.1176/appi.ajp.2020.19111158)

SUPPLEMENTARY METHODS

Distinctions From Previous UK Biobank Studies of Depression

A number of recent studies have examined depression in the UK Biobank, including a GWAS of various depression phenotypes (Howard et al., 2018), genome-wide gene-environment analyses of depression in the context of trauma exposure (Coleman et al., 2020), and a phenome-wide association study examining relationships between depression PRS and a wide range of mental health/behavioral/imaging traits in the database, with accompanying Mendelian randomization analyses (Shen et al., 2020). This study is distinct from previous work in notable ways, including its: (1) specific focus on identifying and testing *modifiable* factors associated with depression, rather than comorbidities and related traits/outcomes; (2) *prospective* examination of observational associations between modifiable factors and clinically significant depression among individuals who did not appear actively depressed at baseline; and (3) testing the effects of modifiable factors on depression *even among individuals at high polygenic risk*, rather than examining polygenic or genome-wide relationships of depression with other traits of interest. No study to our knowledge—in the UK Biobank or beyond—has reported these phenotypic and/or MR results to answer our set of prevention-oriented empirical questions.

Genomic Quality Control

We performed quality control on the genomic data based on metrics provided by the UK Biobank[1]. Specifically, we removed participants who were outliers for heterozygosity or data

missingness, had putative sex chromosome aneuploidy, or were excluded from kinship inference. We also randomly removed one of each pair of subjects who were identified as third-degree relatives or closer. We retained participants with white British ancestry whose genomic data were used in autosome phasing and whose self-reported sex matched their genetically inferred sex. This resulted in an initial sample of 123,794 individuals of white British ancestry with high-quality genomic data in BGEN format.

Further Description of Variables

A. Depression

Baseline depression symptoms were measured via two Likert-scale items adapted from the PHQ-2 on depressed mood and anhedonia (response options ranging from "not at all" to "nearly every day"). Participants who positively endorsed at least one of these items at the level of "more than half the days" or higher were considered to have elevated depressive symptoms at baseline.

B. Reported traumatic life events

Exposure to childhood trauma was measured using items from a short form of the Childhood Trauma Questionnaire[2], of which three items pertaining to childhood physical, sexual, and emotional abuse were available. Each item was rated on a five-point Likert scale ranging from "never true" to "very often true." Correspondingly, three items measuring exposure to partner-based physical, sexual, and emotional abuse, respectively, had been developed for the UK Biobank study on a similar severity scale as childhood trauma. Finally, four items assessed other lifetime traumatic events (i.e., exposure to sexual assault, physically violent crime,

serious/life-threatening accident, and witnessing sudden violent death), and were coded as binary based on endorsed exposure at any point prior to follow-up.

C. Covariates

We extracted baseline variables on participant characteristics (i.e., participant sex, age, assessment center), sociodemographic factors (i.e., socioeconomic deprivation, employment status, household income, completion of higher education, urbanicity, household size), and health factors (i.e., BMI, and physical illness/disability). Specifically, socioeconomic deprivation was indexed using the Townsend deprivation index, calculated based on the national census output area in which participants' zip codes (at recruitment) are located. Household income was assessed average pre-tax total household income, with five options ranging from <18K to >100K. Individuals reported their educational qualifications and we derived a binary variable indicating completion of higher education (i.e., college or university-level degree) as in previous research (Davies et al., 2016). Urbanicity was classified based on whether participant was coded as living in an urban area of England/Wales or Scotland versus not, based on the home postal code matched to the 2001 census from the Office of National Statistics. Similarly, we derived a binary variable indicating current employment status, i.e., whether individuals positively endorsed paid employment or self-employment, and a binary variable indicating physical illness/disability, i.e., if individuals positively endorsed having any longstanding illness, disability, or infirmity. These variables were selected for inclusion as covariates as they could potentially bias the observed relationship between modifiable factors and depression (e.g., socioeconomic deprivation, urbanicity, or higher educational attainment may shape physical activity, diet, or media use patterns while also influencing depression risk), and were thus used to assess whether observed relationships between modifiable factors and depression would be

robust to potential confounding in these domains. Here, we sought to include covariates previously linked to mental health that may not be readily modifiable.

Data Cleaning and Processing

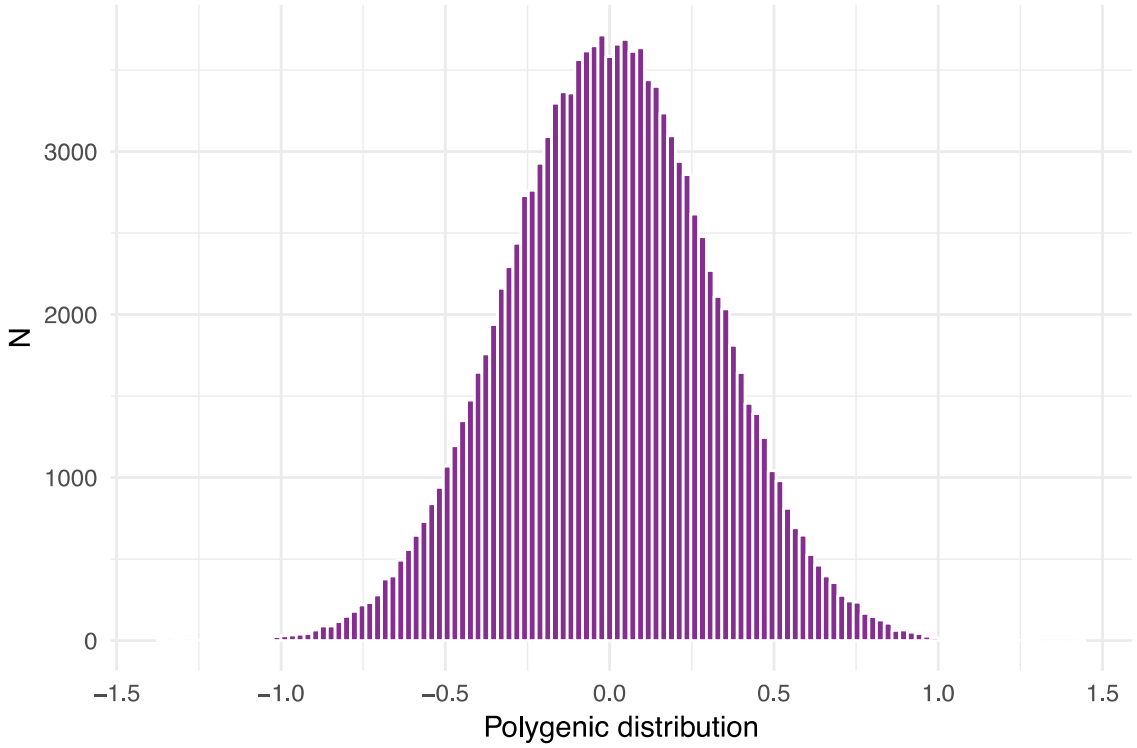
As summarized in **Table S1a**, we performed initial data processing of all exposure variables where relevant, excluding those that were missing for >20% of the sample. The dataset included multiple-choice categorical variables that were provided in array format based on the number of available choices (e.g., different types of activity) that were dummy coded into separate binary variables (i.e., yes/no for a given type of activity, assigning NA to those missing on the top-level array variable). For continuous variables where a coding option of -10 indicated a value of less than 1 (e.g., less than one hour per day), we recoded this response to 0.5 to approximate less than 1 but greater than 0; substantive results were largely unchanged when recoding more conservatively to 0 (not shown). Some factor variables were recoded to reflect rational categories and/or a logical ordinal progression, where responses of increasing quantity were organized in ascending order. After these initial processing steps, negative values (e.g., -1 for "do not know", -3 for "prefer not to answer") indicated items that participants did not answer and were thus set as missing for all remaining variables, except the Townsend deprivation index which was scaled across negative and positive values. Continuous variables were standardized with mean=0 and SD=1 for analysis.

Polygenic Scoring

Because PRS-CS (available as a Python package via https://github.com/getian107/PRScs) allows multivariate modeling of local LD patterns and can accommodate a range of underlying

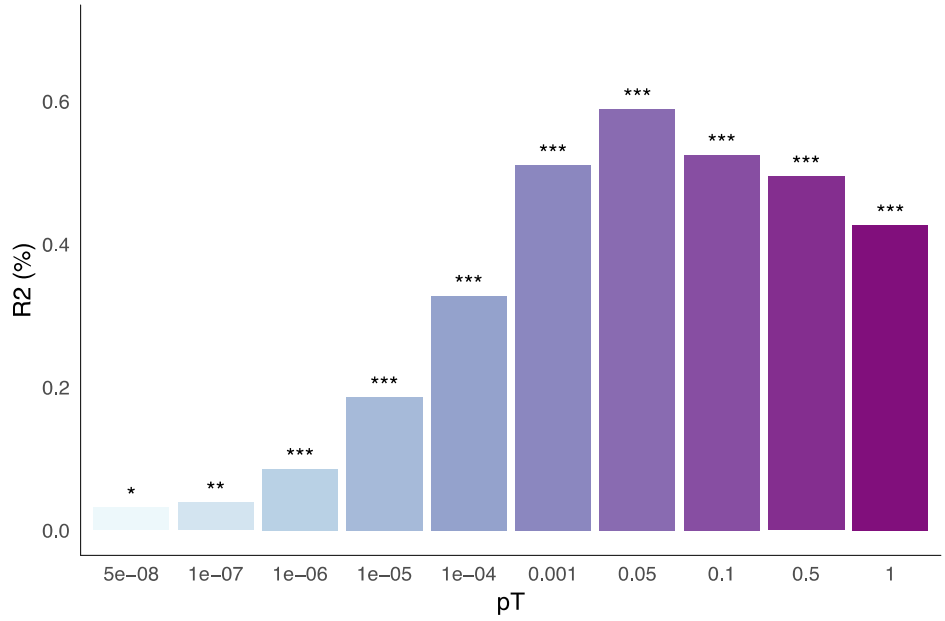
genetic architectures while preserving all SNPs for scoring, it generally demonstrates increased explanatory power compared to conventional and other Bayesian methods, particularly when using a large discovery GWAS[3].

Distribution of PRS-CS polygenic scores in the full analytic sample

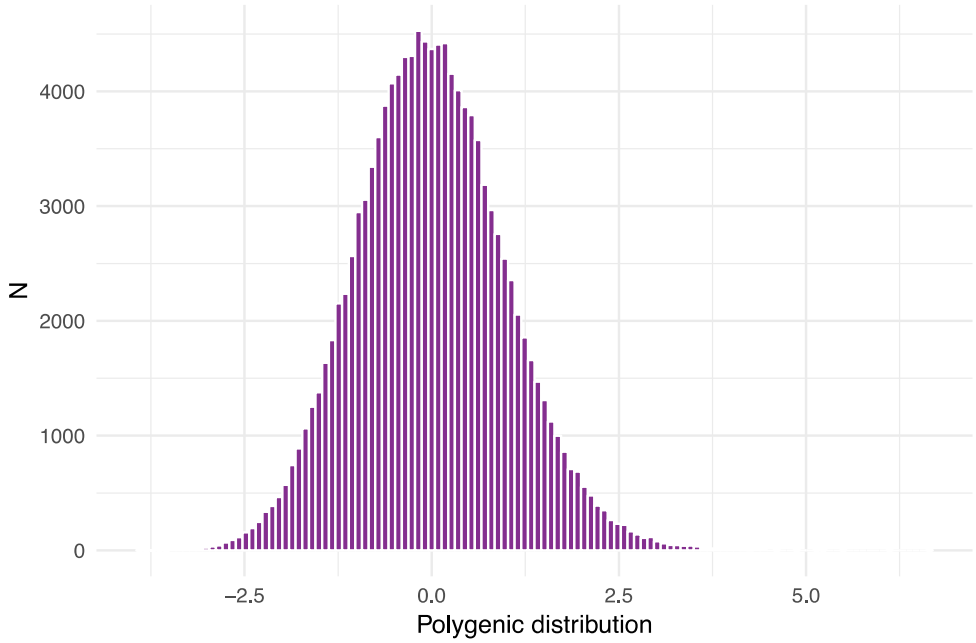


For comparison with the PRS-CS method (see standardized distribution above and Methods in main manuscript), conventional clumping and thresholding procedures for polygenic risk scoring were performed using PRSice2 software. The below figures show PRSice2 estimates of explanatory R^2 of PRS across varying p-value thresholds in relation to follow-up depression, and well as distribution of the standardized PRS at the p-value threshold selected with highest explanatory R^2. Despite selecting the p-value threshold with highest explanatory R^2, the odds ratio associated with the standardized conventional PRS (1.22) was slightly lower than for the standardized PRS-CS score (1.33) for follow-up depression.

Explanatory variance of conventional PRS across p-value thresholds in relation to follow-up depression



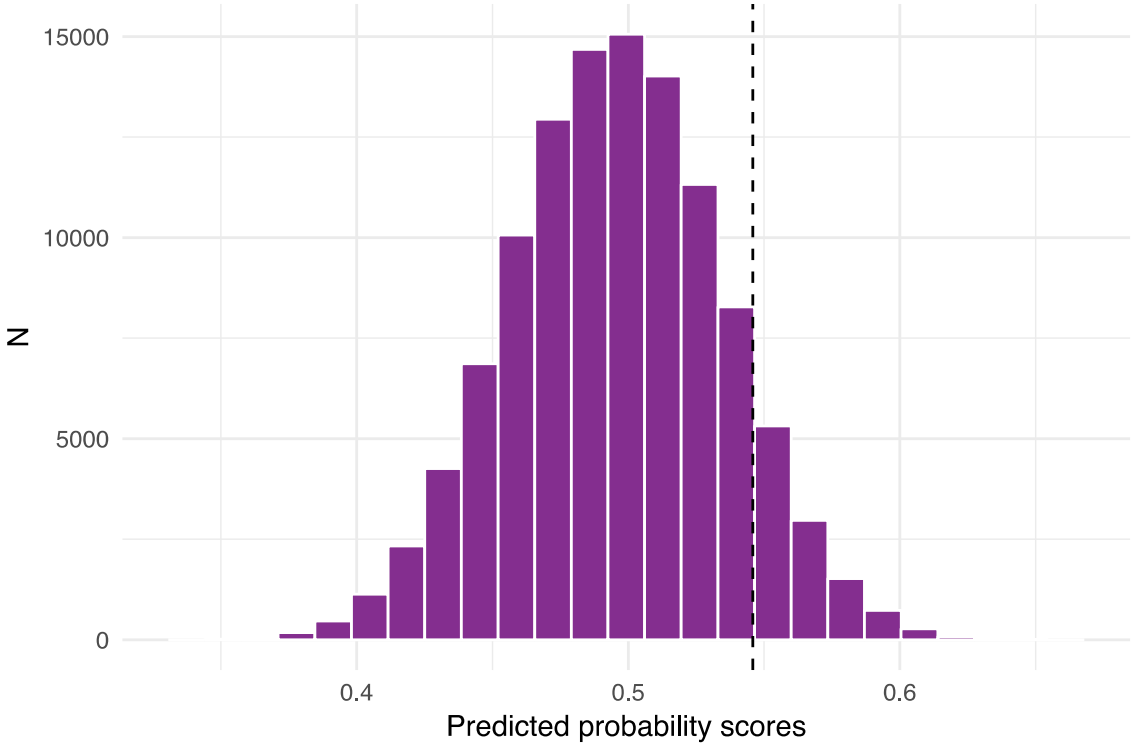
Distribution of scores for the top conventional PRS (pT=0.05)



Stratifying Participants Based on Polygenic Risk and Reported Traumatic Life Events

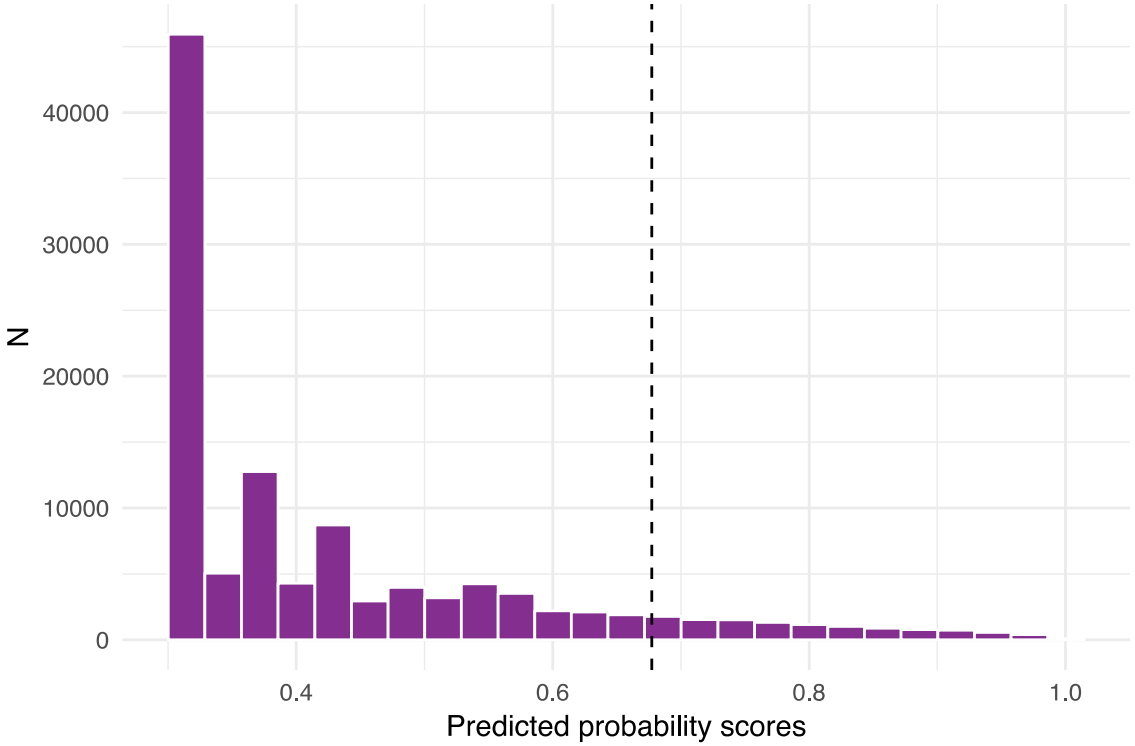
As described in the main Methods, we randomly sampled a holdout training sample of 1,000 participants with an even (50:50) split of cases and controls for follow-up depression. The rationale for a holdout sample of this size and case distribution was to derive predicted probabilities using the available risk factors in a smaller group of individuals drawn from the same study population for comparability, with standard enrichment of potential depression cases to improve statistical power for estimating the effects of each risk factor, while preserving relatively large sample sizes for the resulting analytic samples. We tested separate logistic regression models using clinically significant follow-up depression as the (binary) outcome, and (a) polygenic risk or (b) the set of reported traumatic life events, as independent variables. This strategy of estimating relative influences of different reported traumatic life events on follow-up depression based on a hold-out sample represented an alternative to the conventional strategy of assuming all events contribute equally to depression risk, which also has limitations. We used the resulting raw model coefficients derived from this training sample as variable weights to estimate predicted probability scores for follow-up depression among participants in the remaining testing sample (n=112,589) based on (a) polygenic risk (PRS) or (b) the set of reported traumatic life events (TLE). The weights used for variables in each risk set are reported below, along with the distribution and the cut-off point for establishing the high PRS or high TLE groups. As expected, the prevalence of follow-up depression was elevated within the high PRS group (6.1%) and the high TLE group (12.1%).

Predicted probability scores for polygenic risk and stratification point



Predicted probability scores derived from training variable weights: Polygenic risk score (0.50521). Dashed line indicates cut-off point for establishing at-risk group (> 90th percentile).

Predicted probability scores for traumatic life events and stratification point



Predicted probability scores derived from training variable weights: Childhood physical abuse (0.10297), childhood emotional abuse (0.44026), childhood sexual abuse (0.10870), physical partner violence (0.07899), partner emotional abuse (0.48035), partner sexual interference (0.07791), lifetime exposure to sexual assault (0.32085), lifetime exposure to sudden violent crime (0.26452), life-threatening accident (0.49588), and witnessing sudden violent death (0.29127). Dashed line indicates cut-point for establishing at-risk group (> 90th percentile).

Exposure-Wide Association (EWAS) Analyses

In the full sample, participants were 54% female and had a mean baseline age of 56.1 (standard deviation, SD = 7.7). 46% reported college or university qualifications, 65% reported current paid or self-employment, and 64% reported average pre-tax household income of 31,000 pounds or higher. Participants had a mean BMI of 26.7 (SD = 4.4) and 26% endorsed some physical illness/disability. Overall, 3.9% met the cut-off for clinically significant symptoms at follow-up. For further details, see **Table S1c**.

Univariate associations between each baseline factor and follow-up depression status, adjusting for an increasingly stringent set of covariates as summarized in the main Methods, were tested using the *PheWAS* R package. Association tests between specific factors (as predictor) and depression (as outcome) were performed using all available data, using a logistic regression framework due to the binary nature of the depression phenotype. Dichotomous exposure variables and covariates were entered as categorical predictors in each model, while non-dichotomous (continuous or ordinal) exposure variables and covariates were entered as predictors with linear assumptions. The analytic sample sizes for each tested association are summarized with all results in **Tables S2**.

Two-Sample Mendelian Randomization Analyses

A. Genetic instruments

In a two-sample MR design, instruments can be extracted from summary statistics of large-scale, non-overlapping genome-wide association studies (GWAS). We accessed the GWAS Atlas online database[4] (https://atlas.ctglab.nl) to obtain publicly available summary statistics for each UK Biobank-based factor that was identified in the fully adjusted univariate

association model for the full sample. GWAS Atlas summary statistics that were missing for five UK Biobank derived variables (i.e., meeting recommendations for moderate/vigorous/walking activity) were not tested in the MR framework; however, related traits (e.g., walking frequency) were examined as possible. GWAS Atlas summary statistics for binary variables were generated with odds ratio estimates (logistic), while summary statistics for other variables (continuous, ordinal) were generated with beta (linear) estimates. For depression, we retained the same set of summary statistics[5] for major depression used in previous steps for polygenic scoring in this sample. We clumped SNPs correlated at $r^2 > .0001$ in a 1000 kb window for independence based on European ancestry reference data from the 1000 Genomes Project. For genetic instruments, we selected highly associated SNPs (discovery GWAS p-value < 5x10E-7) for the exposure of interest. Prior MR studies have used relaxed p-value thresholds for selecting the most strongly associated instruments when genome-wide significant SNPs are limited[6,7]. Some of the planned sensitivity analyses require at least three instrument SNPs, which would not be possible for some traits and would not allow us to assess whether results were robust. We therefore sought to consistently apply a threshold relaxed by one decimal point from genome-wide significance to provide a reasonable number of SNPs for most traits under consideration without being so inclusive to introduce excessive horizontal pleiotropy.

B. Additional details for MR analyses

Using the *TwoSampleMR* package in R, we conducted MR analyses to estimate the effect of each modifiable factor on depression, and vice versa. The *TwoSampleMR* package harmonizes exposure and outcome datasets containing information on SNPs, alleles, effect sizes (odds ratios converted to betas via log transformation), standard errors, and p-values. In some cases, a modest

number of non-overlapping SNPs between exposure and outcome summary statistics could not be automatically queried for proxies and were not included in the analysis. In this study, ambiguous SNPs could not be inferred due to missing effect allele frequency information in GWAS Atlas summary statistics, and were therefore removed for analysis. Prior work has suggested that inclusion/exclusion of ambiguous SNPs does not substantively change MR results[8]. For significant MR results after statistical outlier removal, we further assessed horizontal pleiotropy using leave-one-SNP-out analyses (assessing the extent to which MR estimates are affected by the inclusion/exclusion of each instrument SNP); the modified Cochran's Q statistic (evaluating overall effect heterogeneity between instrument SNPs); and the MR Egger intercept test[9] (where a significant intercept deviation from the null suggests directional pleiotropy of SNP effects that could bias the IVW estimate).

For significant MR results, we also searched each instrument SNP in the PhenoScanner v2 database (http://www.phenoscanner.medschl.cam.ac.uk; last accessed February 2020) to identify cross-associations with any other phenotypes including depression-related traits at $p<1x10E-5$ with each instrument SNP or any SNPs in linkage disequilibrium at $r^2>0.80$, and assessed whether removing these SNPs substantively changed the pattern of results, as reported in **Tables S5a-d**. This is a relatively conservative approach as some of these phenotypes may lie on the same causal pathway (i.e., represent vertical pleiotropy, which is non-problematic for MR assumptions) but in order not to make arbitrary discriminations, we retained SNPs with no currently known cross-associations.

Additionally, as an index of instrument strength, mean F statistics were calculated for the set of genetic instruments for each modifiable factor (**Table S4e**), where F = beta^2 / se^2 for each exposure-related SNP. A mean F statistic of >10 has been posited as a rule of thumb for

adequate instrument strength[10]. Finally, for descriptive purposes, LD score regression-based genetic correlations were extracted from the GWAS Atlas database between modifiable factors that were at least nominally significant in the MR (**Table S4f**).

C. Horizontal pleiotropy sensitivity analysis results for significant factors

For confiding in others, no significant effect heterogeneity (Q statistic=5.5, p=0.78) was observed after removal of outliers, and the MR-PRESSO global test (p=0.82) and MR Egger intercept test (p=0.78) also did not provide evidence of horizontal pleiotropy. Given the lower number of SNPs tested, the IVW effect remained notably significant when relaxing the instrument SNP p-value threshold to 5x10E-6 (OR=0.89 [0.84-0.95], p=7.63E-4; 50 SNPs), and when retaining only SNPs with no known associations in the PhenoScanner v2 database (**Table S4a**).

For TV use, no significant effect heterogeneity (Q statistic=130.8, p=0.78) was observed after removal of outliers, and the MR-PRESSO global test (p=0.79) and MR Egger intercept test (p=0.44) also did not provide evidence of horizontal pleiotropy. The IVW estimate remained significant when retaining only SNPs with no known associations in the PhenoScanner v2 database (**Table S4b**).

For daytime napping, no significant effect heterogeneity (Q statistic=85.1, p=0.63) was observed after removal of outliers, and the MR-PRESSO global test (p=0.64) and MR Egger intercept test (p=0.39) also did not provide evidence of horizontal pleiotropy. The IVW estimate remained significant when retaining only SNPs with no known associations in the PhenoScanner v2 database (**Table S4c**).

For multivitamin use, no significant effect heterogeneity (Q statistic=5.70, p=0.34) was observed after removal of outliers, and the MR-PRESSO global test (p=0.39) and MR Egger

intercept test (p=0.60) also did not provide evidence of horizontal pleiotropy. However, the IVW estimate was not significant when retaining only SNPs with no known associations in the PhenoScanner v2 database (using the 5x10E-6 threshold as the 5x10E-7 did not have sufficient non-associated SNPs after removing any cross-associated SNPs) (**Table S4d**).

D. Summary of nominal MR results

Other MR findings were nominally significant at the traditional p<0.05 threshold (with consistent WM estimates unless otherwise noted; **Tables S3**)—which suggested potential beneficial effects of tea intake (IVW OR=0.95, 95% CI [0.91-0.99], p=1.63E-2); more frequent social visits (IVW OR=0.79, 95% CI [0.65-0.96], p=1.80E-2) and engaging in exercises like swimming and cycling (IVW OR=0.90, 95% CI [0.82-0.99], p=3.27E-2; non-significant WM estimate though directionally consistent), as well as deleterious effects of salt intake (IVW OR=1.10, 95% CI [1.01,1.19], p=3.45E-2) on the risk of depression.

We also observed nominal evidence in the reverse direction, suggesting depression may be associated with reduced gym/sports club use (IVW OR=0.93, 95% CI [0.88-0.98], p=7.10E-3), attendance at pubs/social clubs (IVW OR=0.92, 95% CI [0.87-0.98], p=8.03E-3), as well as increased computer use (IVW beta=0.05, 95% CI [0.01-0.09], p=7.97E-3) and playing computer games (IVW beta=0.01, 95% CI [0.001-0.03], p=3.27E-2; non-significant WM estimate), and supplementation not only with multivitamins (as noted earlier) but also vitamin B (IVW OR=1.14, 95% CI [1.02-1.27], p=1.89E-2; non-significant WM estimate though directionally consistent). Although walking was phenotypically associated with reduced odds for depression, MR results suggested that depression may be nominally associated with increased tendency for walking, whether for pleasure or as a form of transportation (IVW OR=1.05, 95% CI [1.004-

1.11], p=3.61E-2, non-significant WM estimate though directionally consistent; IVW OR=1.06, 95% CI [1.009-1.11], p=1.87E-2, respectively).

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