

An Exposure-Wide and Mendelian Randomization Approach to Identifying Modifiable Factors for the Prevention of Depression

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Objective: Efforts to prevent depression, the leading cause of disability worldwide, have focused on a limited number of candidate factors. Using phenotypic and genomic data from over 100,000 UK Biobank participants, the authors sought to systematically screen and validate a wide range of potential modifiable factors for depression.

Methods: Baseline data were extracted for 106 modifiable factors, including lifestyle (e.g., exercise, sleep, media, diet), social (e.g., support, engagement), and environmental (e.g., green space, pollution) variables. Incident depression was defined as minimal depressive symptoms at baseline and clinically significant depression at follow-up. At-risk individuals for incident depression were identified by polygenic risk scores or by reported traumatic life events. An exposure-wide association scan was conducted to identify factors associated with incident depression in the full sample and among at-risk individuals. Two-sample Mendelian randomization was then used to validate potentially causal relationships between identified factors and depression.

Results: Numerous factors across social, sleep, media, dietary, and exercise-related domains were prospectively associated with depression, even among at-risk individuals. However, only a subset of factors was supported by Mendelian randomization evidence, including confiding in others (odds ratio=0.76, 95% CI=0.67, 0.86), television watching time (odds ratio=1.09, 95% CI=1.05, 1.13), and daytime napping (odds ratio=1.34, 95% CI=1.17, 1.53).

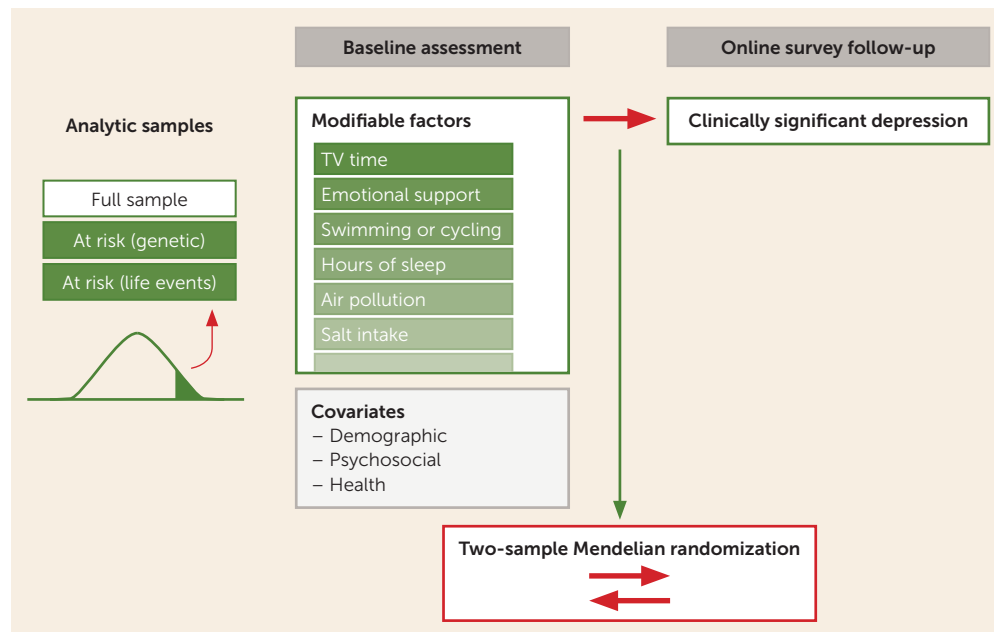
Conclusions: Using a two-stage approach, this study validates several actionable targets for preventing depression. It also demonstrates that not all factors associated with depression in observational research may translate into robust targets for prevention. A large-scale exposure-wide approach combined with genetically informed methods for causal inference may help prioritize strategies for multimodal prevention in psychiatry.

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Depression is the leading cause of disability worldwide (1), but knowledge of actionable strategies that could mitigate depression risk remains relatively limited. A number of critical research gaps have remained. First, the literature to date has focused on validating a limited set of hypothesized modifiable factors for prevention of depression, such as physical activity (2, 3) and social support (4). Without broader investigation, additional factors may be overlooked or unknown. Investigating a wide range of factors could help confirm existing relationships and also identify novel potential prevention targets. Systematically testing the relationship between many variables and a single outcome for hypothesis-free discovery is now common practice in other fields in the form of genome- or phenome-wide association studies and has led to new insights about

underlying associations (5, 6), but has not yet been applied to identifying modifiable factors for prevention of depression.

Second, few studies, to our knowledge, have appraised the relative influences of multiple modifiable factors within the same population. Some factors (e.g., specific nutrients or foods) that show statistically significant effects when studied alone may not prove robust or as clinically relevant when considered alongside other factors (7). Understanding the relative importance of different modifiable factors that could be integrated into prevention packages has been limited by modest sample sizes for multiple testing and lack of comprehensive measurements in a single study. The availability of large cohort studies, such as UK Biobank (8), now make comprehensive and well-powered inquiries possible.

FIGURE 1. Overview of two-stage analytic design^a

^a Associations between modifiable factors and incident depression were tested in three analytic samples: the full sample, individuals at risk based on polygenic risk, and individuals at risk based on reported traumatic life events. To reduce bias in associations from contemporaneous reporting, modifiable factors were selected from those indexed to the baseline assessment, and subsequent depression was assessed at the follow-up survey approximately 6 to 8 years later, after removing individuals with elevated depressive symptoms at baseline. Relationships between identified factors and depression risk were then examined in bidirectional Mendelian randomization analyses.

Third, we do not know which modifiable factors may help prevent depression among individuals at elevated risk. Two of the best substantiated risk factors for depression—genetic vulnerability and early-life adversity (9, 10)—are effectively unmodifiable in adults. What generally helps prevent depression in most people may not necessarily be most relevant for those with specific risk profiles (11) and vice versa. Depression is now recognized as a polygenic condition (12)—influenced by many variants across the genome with individually small effects (13). As we are increasingly able to quantify polygenic risk for depression (14) and may even communicate polygenic risk information to individuals in the future (15), it becomes vital to expand knowledge of effective actionable measures for those identified as having an elevated risk. Similarly, life history factors such as traumatic events are known to increase risk for depression (16). As we more systematically assess established sources of genetic and environmental risk in a precision medicine framework (17), evidence of modifiable factors that benefit high-risk individuals could guide recommendations to offset preexisting vulnerabilities for depression (18).

Finally, modifiable factors may be associated with depression for noncausal reasons, including unmeasured third variables (i.e., residual confounding) and reverse causation (e.g., whereby depression risk influences behavioral patterns). To strengthen conclusions about which modifiable factors may be high-priority intervention targets, Mendelian randomization analyses can be used to further test

relationships between identified factors and depression. Mendelian randomization is an alternative strategy for causal inference that uses genetic variants inherited at birth as statistical “instruments” to approximate a natural experiment in which individuals are assigned to varying average lifetime levels of an exposure (e.g., social affiliation) in relation to an outcome of interest (e.g., depression) (19). This use of genetic data bypasses typical sources of confounding in observational data and allows for triangulation of findings (20). We previously leveraged Mendelian randomization to validate a protective relationship between objectively measured physical activity and depression risk (3). Here, we extend the Mendelian randomization

approach to evaluate a wide range of possible modifiable factors.

In this study, using phenotypic and genomic data from over 100,000 UK Biobank participants without active depressive symptoms at baseline, we used an exposure-wide association study design to test the relationship between 106 modifiable factors and clinically significant depression at follow-up (Figure 1). Given the established role of genetics and traumatic life events on depression risk, we also aimed to identify factors that may influence depression even in the context of these risks. Finally, we used two-sample Mendelian randomization to further assess directional effects and potential causal relationships between identified factors and depression.

METHODS

Our initial sample consisted of 123,794 adults of white British ancestry who enrolled in UK Biobank, had high-quality genomic data (for quality control procedures, see the Supplementary Methods in the online supplement), and completed an online follow-up mental health survey approximately 6 to 8 years after their initial enrollment (Figure 1). Data analytic procedures were approved by the institutional review board at Partners HealthCare and conducted as part of UK Biobank application 32568. Primary data processing and statistical analyses were conducted between October 2018 and August 2019.

Measures

Incident depression. Participants who endorsed depressed mood and/or anhedonia (for details, see the Supplementary Methods in the online supplement) for more than half the days in the past 2 weeks at baseline (N=5,416) were considered to have elevated depressive symptoms (21) and were excluded from this study, leaving 118,378 participants. At follow-up, symptoms of depression were measured using all nine items of the Patient Health Questionnaire–9 (PHQ-9) (22), summed to create an overall score ranging from 0 to 27. To derive predicted probabilities of depression to stratify at-risk groups, we created a binary variable for clinically significant incident depression based on a score cut-off of ≥ 10 (23).

Modifiable factors. We curated data on 106 potentially modifiable factors (see Table S1A in the online supplement) as measured or derived at baseline. These factors included behavioral (e.g., exercise, sleep, media use, diet), social (e.g., activities, support), and environmental (e.g., green space, pollution) variables. We selected these variables by inspecting the UK Biobank data showcase (<http://biobank.ctsu.ox.ac.uk/crystal/index.cgi>). After review by three authors (K.W.C., J.W.S., K.M.N.), we included any variables in a domain that were 1) unlikely to be a close comorbidity of mental health problems (e.g., excluding substance use and cognitive functioning); 2) putatively modifiable at an individual or societal level (e.g., including behavioral and environmental factors); and 3) largely available for most participants and not just collected for a small subset (e.g., excluding branched questions that were only administered to individuals who had endorsed an earlier item). Potentially correlated variables within a category (e.g., 16-hour and 24-hour noise pollution) were retained to assess the relative influences of all available variables. As negative controls, we also selected two nonmodifiable variables hypothesized to be unrelated to depression—natural hair color and skin tanning ability. Data processing was performed on all variables, as described in the Supplementary Methods and Table S1A in the online supplement.

Traumatic life experiences. In the online follow-up, participants reported on their history of traumatic life experiences, including childhood physical, sexual, and emotional abuse; partner-based physical, sexual, and emotional abuse; and other traumatic events, including exposure to sexual assault, violent crime, life-threatening accident, and witnessing violent death (for details, see the Supplementary Methods).

Covariates. Baseline variables were extracted for participant characteristics (sex, age, assessment center), sociodemographic factors (socioeconomic deprivation, employment status, household income, completion of higher education, urbanicity, household size), and physical health factors (body mass index and reported physical illness or disability) (for

details and inclusion rationale, see the Supplementary Methods in the online supplement).

Polygenic Risk Scoring

Polygenic risk scores (PRSs) were generated from large-scale genome-wide association results for major depression (12). Specifically, we used summary statistics (discovery genome-wide association study [GWAS], N=431,394) from the Psychiatric Genomics Consortium, leaving out UK Biobank data to minimize sample overlap and including 23andMe data for improved statistical power. We retained single-nucleotide polymorphisms (SNPs) with minor allele frequency > 0.01 and INFO quality score > 0.80 . To generate PRSs, we applied PRS-CS (24)—a Bayesian polygenic prediction method that places a continuous shrinkage (CS) prior on effect sizes for all HapMap3 SNPs and infers posterior SNP weights using GWAS summary statistics combined with an external linkage disequilibrium reference panel, such as the 1000 Genomes Project European sample (for more details and comparison with conventional clumping and thresholding, see the Supplementary Methods in the online supplement). We set the global shrinkage parameter at 0.01 to reflect the likely polygenic architecture of major depression. Scores were calculated by summing the number of risk alleles at each SNP multiplied by the posterior SNP weight inferred using PRS-CS, with a total of 1,090,207 included SNPs. (For the distribution of scores, see the Supplementary Methods.) We then extracted residuals from a model in which PRSs were regressed on the top 10 European ancestry principal components provided by UK Biobank for use as stratification-adjusted PRSs in subsequent analyses.

Stratifying Participants at Risk for Incident Depression

Among individuals with available data on later depression and risk variables (i.e., polygenic risk and reported traumatic life events) (N=113,589; 4.3% with incident depression), we removed a holdout training sample of 1,000 participants consisting of an even split of randomly selected case and control subjects for incident depression (for the rationale, see the Supplementary Methods in the online supplement). In this holdout training sample, we regressed incident depression against polygenic risk or reported traumatic life events (for descriptive distributions, see Table S1B in the online supplement). Here, each traumatic life event was entered as a separate independent variable within a multivariable model to estimate relative weights of each event on depression risk, rather than assuming equal influences. We obtained regression coefficients for each set of risk variables from the training sample (see the Supplementary Methods) and used these coefficients as weights to generate predicted probability scores for incident depression for individuals in the testing sample (N=112,589), based on polygenic risk or reported traumatic life events. Selecting individuals with high predicted probability scores (> 90 th percentile), we obtained three groups: individuals in the full sample unselected for risk (maximum N=112,589), individuals at risk

based on genetic factors (the PRS group; maximum $N=11,258$), and individuals at risk based on reported traumatic life events (maximum $N=11,258$). Only 1,563 individuals belonged to both the PRS and traumatic life events groups (13.9% of each), suggesting modest overlap and potentially distinct influences on depression (for exploratory results in this reduced sample, see Tables S2J–L and Figures S4A–C in the online supplement).

Exposure-Wide Association Scan

Using an exposure-wide association approach with logistic regression (see the Supplementary Methods in the online supplement), we tested associations between each baseline modifiable factor and incident depression in each of these samples (Figure 1), with a conservative Bonferroni-corrected significance threshold for establishing top hits (0.05 divided by 106 tests across three main analytic samples, or 0.000157). All associations were adjusted for sex, baseline age, and assessment center (model 0). We further adjusted for the sociodemographic factors described earlier (model 1) and also added physical health factors (model 2). All analytic samples were restricted to participants who had not withdrawn from UK Biobank as of February 2020 and had full covariate data (full sample: maximum $N=100,517$; PRS group: maximum $N=10,093$; traumatic life events group: maximum $N=10,154$) to ensure that differences in results between successively adjusted models reflected the addition of covariates rather than varying sample size. We also descriptively assessed the overlap between significant factors in each at-risk sample compared with the full sample and between at-risk samples.

Mendelian Randomization Analyses

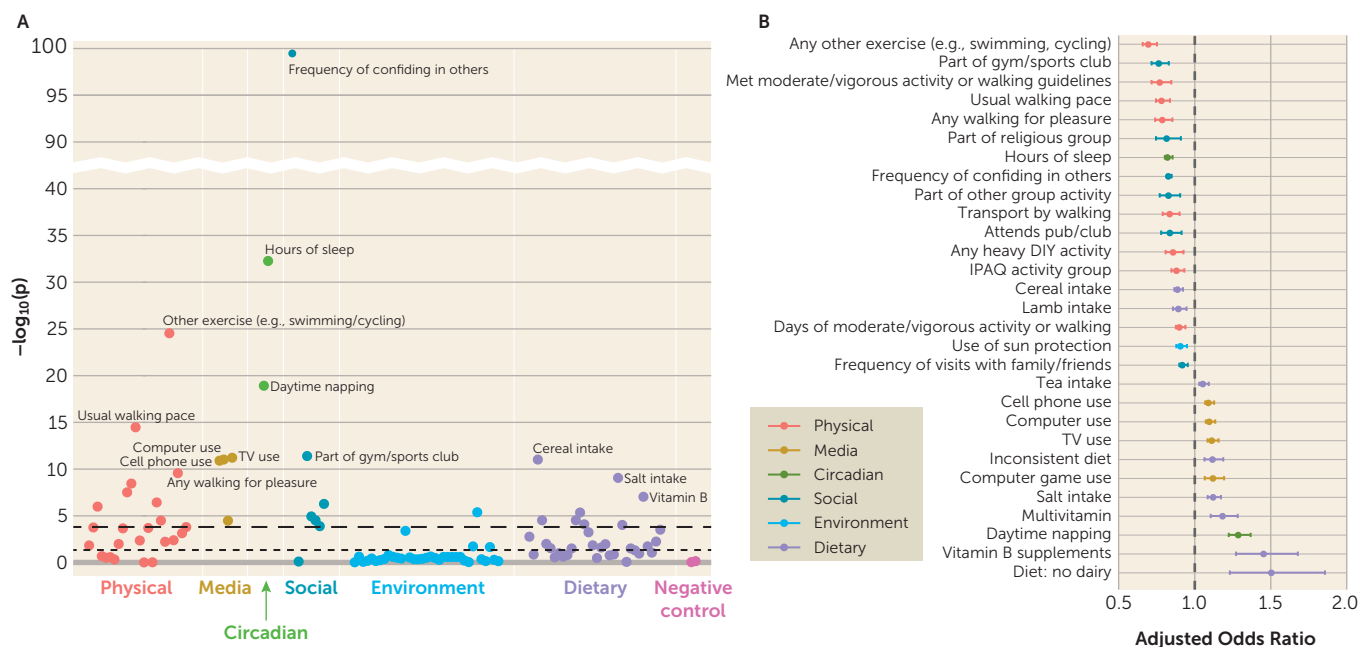
We performed bidirectional two-sample Mendelian randomization analyses (see the Supplementary Methods in the online supplement) between depression and modifiable factors identified in the fully adjusted exposure-wide association scan (model 2) in the overall sample. For each factor, we accessed the GWAS Atlas database (25) (<https://atlas.ctglab.nl>) to obtain publicly available UK Biobank-based summary statistics. For depression, we retained the Psychiatric Genomics Consortium summary statistics used for polygenic scoring (12). As instruments for each factor, we extracted highly associated SNPs ($p < 5 \times 10^{-7}$; for the rationale, see the Supplementary Methods) that were clumped for independence at $r^2 > 0.001$. Using the TwoSampleMR package in R (26), we conducted Mendelian randomization analyses to estimate the effect of each modifiable factor on the risk of depression and vice versa. For primary Mendelian randomization analyses, we combined per-SNP effects using inverse-variance weighted meta-analysis, where the resulting estimate represents the slope of a weighted regression of SNP-outcome effects on SNP-exposure effects in which the intercept is constrained to zero. We applied MR-PRESSO (27) with additional tests (i.e., Cook's distance, studentized residuals, Q-value outliers) to detect statistical outliers

reflecting potential bias (28), and removed these outliers to generate reported estimates. We relaxed the instrument p threshold ($p < 5 \times 10^{-6}$) for several traits lacking sufficient SNPs (≤ 3) after outlier removal (e.g., vitamin B supplementation, walking frequency). We then compared the pattern of inverse-variance weighted results to other established Mendelian randomization methods—the weighted median approach (29) and Mendelian randomization-Egger (MR-Egger) regression (30)—whose estimates rely on different assumptions and are relatively robust to horizontal pleiotropy, i.e., violation of the assumption that genetic instruments act on the outcome only via their effects on the exposure. For significant results, we further assessed horizontal pleiotropy using leave-one-SNP-out analyses, the modified Cochran's Q statistic, the MR-Egger intercept test (31), and manual SNP lookups (further details are provided in the Supplementary Methods in the online supplement). Reported estimates were converted to odds ratios where the outcome was binary, and interpreted using a conservative p threshold (0.05/number of factors with available summary statistics).

RESULTS

Modifiable Factors Prospectively Associated With Incident Depression in the Full Sample

In the full sample (for descriptive data, see the Supplementary Methods and Table S1C in the online supplement), 49 factors spanning multiple domains (e.g., physical activity, media use, sleep, social, environmental, and dietary variables) were significantly associated with depression (model 0) (see Figure S1A,C and Table S2A in the online supplement). After adjusting for sociodemographic factors (model 1), 39 factors were significantly associated with depression (see Figure S1B,D and Table S2B in the online supplement). After further adjusting for physical health factors (model 2), 29 factors remained significantly associated with depression (Figures 2 and 3; see also Figure S1E and Table S2C in the online supplement). Of these, 18 factors were associated with reduced odds of depression and 11 were associated with increased odds of depression (all continuous factors were standardized to mean of zero and a standard deviation of 1; for variable types, see Table S1A in the online supplement). The top 10 included six factors that appeared protective: confiding in others (adjusted odds ratio=0.83, 95% CI=0.82, 0.85, $p=9.66 \times 10^{-100}$), sleep duration (adjusted odds ratio=0.83, 95% CI=0.80, 0.85, $p=5.37 \times 10^{-33}$), engaging in exercises like swimming or cycling (adjusted odds ratio=0.70, 95% CI=0.66, 0.75, $p=2.91 \times 10^{-25}$), walking pace (adjusted odds ratio=0.79, 95% CI=0.74, 0.84, $p=3.37 \times 10^{-15}$), being part of a sports club or gym (adjusted odds ratio=0.77, 95% CI=0.72, 0.83, $p=3.98 \times 10^{-12}$), and cereal intake (adjusted odds ratio=0.89, 95% CI=0.87, 0.92, $p=9.57 \times 10^{-12}$). The remaining four factors appeared to increase risk: daytime napping (adjusted odds ratio=1.29, 95% CI=1.22, 1.37, $p=1.20 \times 10^{-19}$), computer use time (adjusted odds ratio=1.10, 95% CI=1.07, 1.13, $p=9.36 \times 10^{-12}$), television watching time (adjusted odds

FIGURE 2. Association results between modifiable factors and incident depression in the full sample, adjusted for all covariates^a

^a Panel A is an association plot for modifiable factors in relation to incident depression, with the x-axis organized by conceptual domains and the y-axis showing statistical significance as $-\log_{10}$ of the p value; the long-dash horizontal line indicates the significance threshold corrected for multiple testing, and the short-dash horizontal line indicates the $p < 0.05$ threshold. A selection of top factors are annotated for legibility; the full set of association results is provided in Tables S2A–C in the online supplement. Panel B presents the adjusted odds ratios for significant factors, in ascending order (i.e., from risk-reducing to risk-increasing). IPAQ=International Physical Activity Questionnaire classification of physical activity level (low, moderate, high).

ratio=1.12, 95% CI=1.08, 1.16, $p=6.07 \times 10^{-12}$), and cell phone use time (adjusted odds ratio=1.10, 95% CI=1.07, 1.13, $p=1.25 \times 10^{-11}$).

Factors Associated With Depression Among At-Risk Individuals Based on Polygenic Risk

Among individuals at high predicted probability of depression based on PRS, 12 factors were identified to be significantly associated with depression (model 0) (see Figure S2A,E and Table S2D in the online supplement). These were reduced to 10 (model 1; see Figure S2B,F and Table S2E) and four top factors (model 2; see Figure S2C,G and Table S2F) after adjustment for sociodemographic and health factors, respectively. Notably, these factors had been identified in the full sample. Of these, two appeared to be protective: frequency of confiding in others (adjusted odds ratio=0.85, 95% CI=0.81, 0.89, $p=2.87 \times 10^{-13}$) and sleep duration (adjusted odds ratio=0.81, 95% CI=0.75, 0.88, $p=4.07 \times 10^{-7}$). The other two appeared to increase risk: computer use time (adjusted odds ratio=1.17, 95% CI=1.09, 1.26, $p=1.19 \times 10^{-5}$) and salt intake (adjusted odds ratio=1.21, 95% CI=1.10, 1.33, $p=1.31 \times 10^{-4}$).

Factors Associated With Depression Among Individuals at Risk Based on Traumatic Life Events

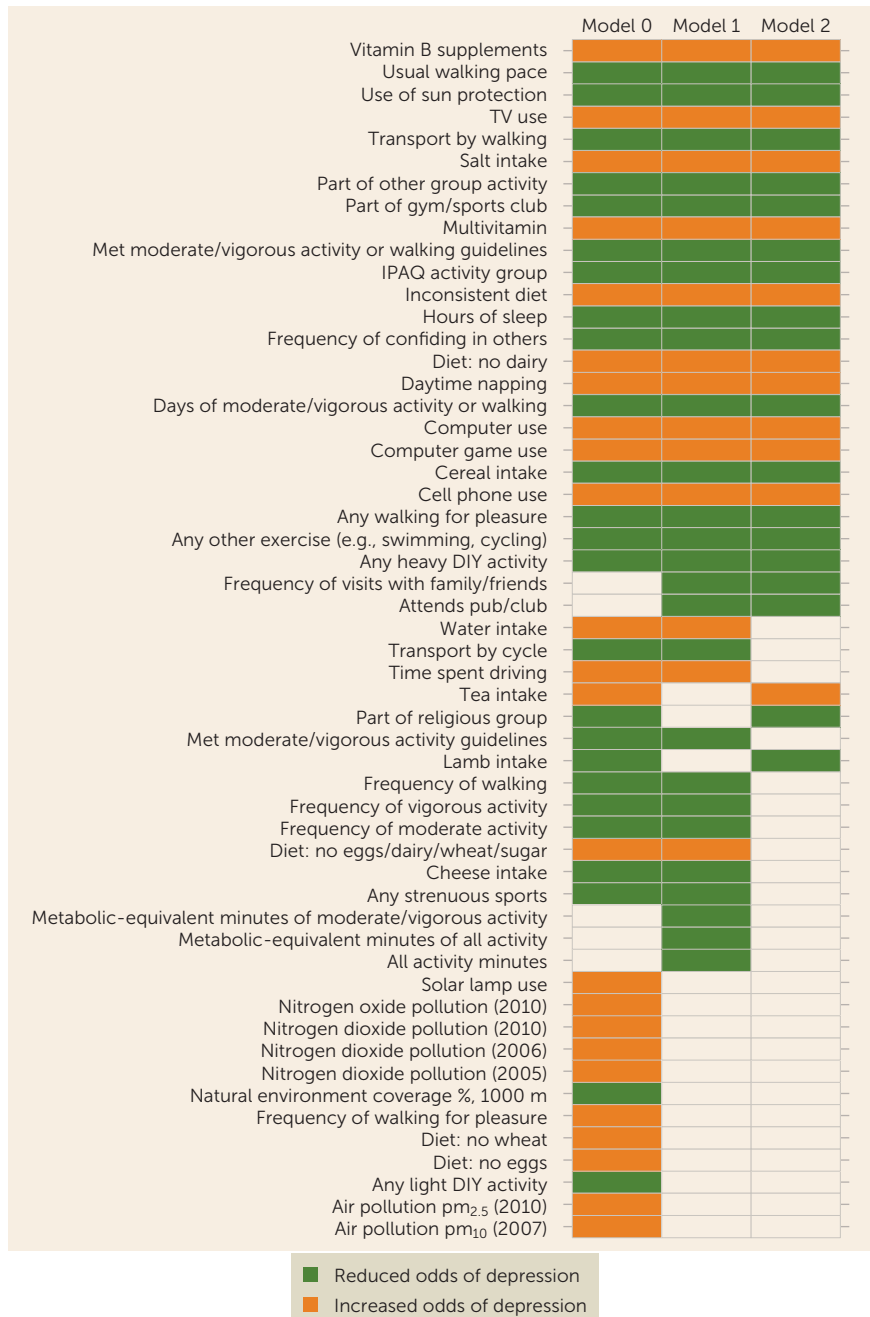
Among individuals with high predicted probability of depression based on their reported traumatic life events, 18 factors were significantly associated with depression

(model 0) (see Figure S3A,E and Table S2G in the online supplement). These were reduced to 16 (model 1; see Figure S3B,F and Table S2H) and four top factors (model 2; see Figure S3C,G and Table S2I) after adjustment for socio-demographic and health factors, respectively. Again, these factors had been identified in the full sample. Of these, three appeared to be protective: frequency of confiding in others (adjusted odds ratio=0.85, 95% CI=0.82, 0.88, $p=2.00 \times 10^{-22}$), engaging in exercises like swimming or cycling (adjusted odds ratio=0.66, 95% CI=0.59, 0.75, $p=2.31 \times 10^{-10}$), and sleep duration (adjusted odds ratio=0.83, 95% CI=0.79, 0.89, $p=3.93 \times 10^{-9}$). One factor appeared to increase risk: television watching time (adjusted odds ratio=1.15, 95% CI=1.08, 1.23, $p=5.85 \times 10^{-6}$). Two of these factors (confiding in others and sleep duration) had also been identified as top factors in the PRS group, and television watching time showed a similar estimate in the PRS group (adjusted odds ratio=1.17, 95% CI=1.08, 1.27) as well. The remaining top factors (computer use, salt intake, and exercises like swimming or cycling) showed overlapping confidence intervals between the PRS and traumatic life events groups, suggesting that associations may be relatively comparable across genetic or environmental risk despite not meeting the defined threshold.

Follow-Up Mendelian Randomization Analyses

We tested all modifiable factors identified in the adjusted full sample (model 2) with available GWAS summary statistics.

FIGURE 3. Top factors associated with incident depression across levels of covariate adjustment^a



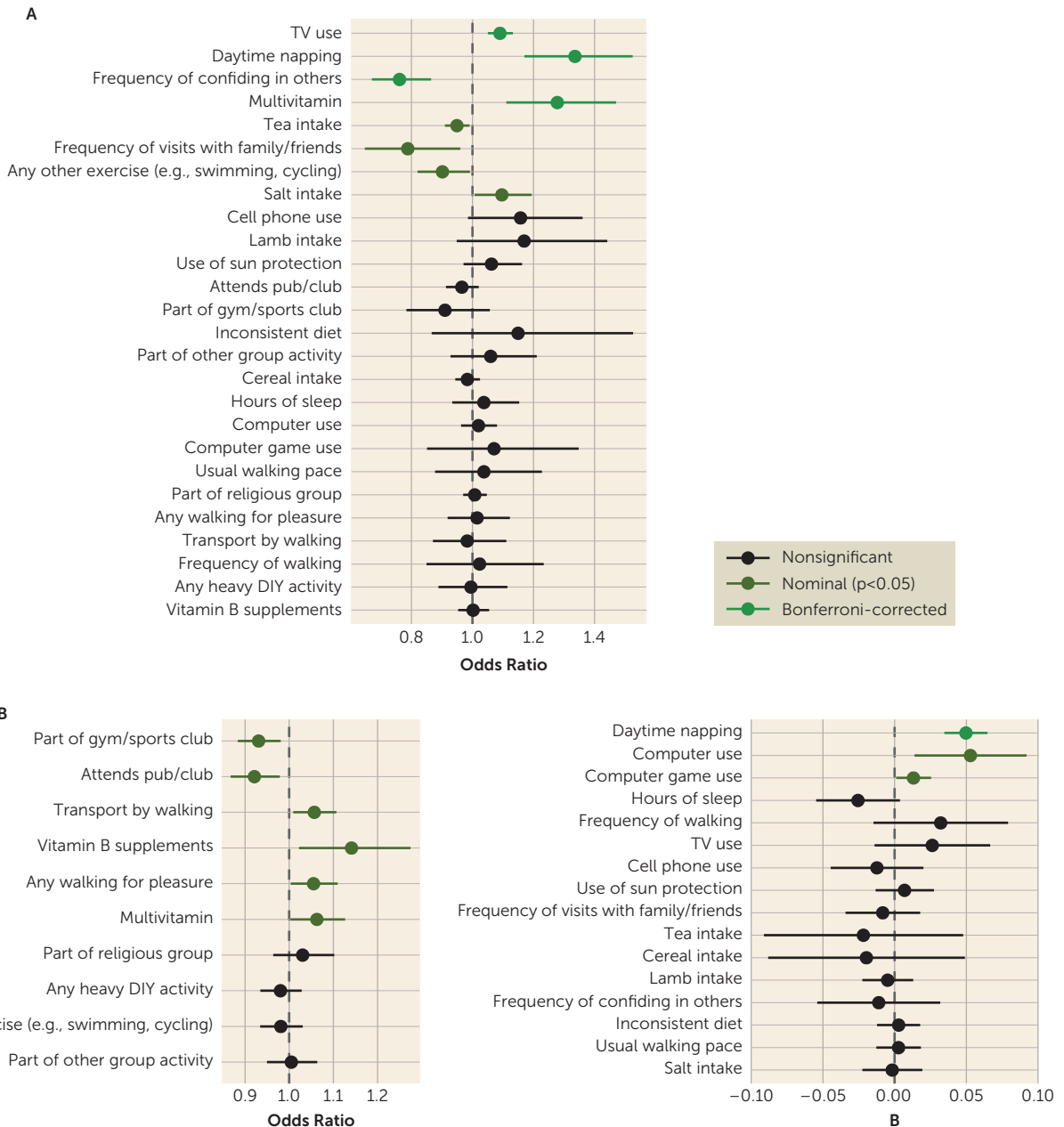
^a The top associated factors in the full sample are shown in order of consistency patterns across one, two, or three models, in descending alphabetical order within each pattern. Results are shown only for factors with significant associations in at least one model. (The full set of association results is provided in Tables S2A–C in the online supplement.) Model 0=adjusted for participant characteristics; model 1=model 0 further adjusted for socio-demographic factors; model 2=model 1 further adjusted for health factors; IPAQ=International Physical Activity Questionnaire classification of physical activity level (low, moderate, high).

Bidirectional Mendelian randomization analyses between each factor and depression revealed a number of findings suggesting possible causal relationships (see Figure 4 for inverse-variance weighted results; weighted median results are shown in Figures S5A,B and all estimates in Table S3 in the online supplement).

number of SNPs tested, this effect was notably attenuated when the instrument SNP threshold was further relaxed to $p < 5 \times 10^{-6}$ (odds ratio=1.07, 95% CI=1.0, 1.14, $p=0.0498$; 30 SNPs). Depression was also nominally associated with increased intake of multivitamins (odds ratio=1.06, 95% CI=1.003, 1.13, $p=0.0407$; 44 SNPs).

Mendelian randomization supported a beneficial effect of confiding in others on depression risk (odds ratio=0.76, 95% CI=0.67, 0.86, $p=2.53 \times 10^{-5}$; 10 SNPs; see Figure S6A in the online supplement), with nonsignificant effects in the reverse direction. We also found Mendelian randomization evidence supporting a deleterious effect of television use on depression risk (odds ratio=1.09, 95% CI=1.05, 1.13, $p=6.81 \times 10^{-6}$; 145 SNPs; see Figure S6B in the online supplement), with nonsignificant effects in the reverse direction. No evidence of effect heterogeneity or horizontal pleiotropy was observed for either factor (see the Supplementary Methods in the online supplement). Daytime napping showed bidirectional effects with depression, such that it was linked to higher odds of depression (odds ratio=1.34, 95% CI=1.17, 1.53, $p=1.82 \times 10^{-5}$; 91 SNPs; see Figure S6C in the online supplement), but depression was also associated with increased daytime napping ($\beta=0.05$, 95% CI=0.03, 0.06, $p=8.45 \times 10^{-11}$; 43 SNPs), with no evidence of effect heterogeneity or horizontal pleiotropy in either direction. Surprisingly, Mendelian randomization evidence suggested that multivitamin use was also linked to increased odds of depression (odds ratio=1.28, 95% CI=1.11, 1.47, $p=6.04 \times 10^{-4}$; six SNPs; see Figure S6D in the online supplement). Given the lower

FIGURE 4. Mendelian randomization estimates of top modifiable factors in relation to depression risk^a



^a Panel A presents Mendelian randomization estimates of the relationship between modifiable factors (exposures) and the risk of depression (outcome), based on the inverse-variance weighted method with outliers removed (for the weighted median method, see Figure S26 in the online supplement). Panel B presents Mendelian randomization estimates of the relationship between depression (exposure) and modifiable factors (outcomes), based on the inverse-variance weighted method with outliers removed (for the weighted median method, see Figure S27 in the online supplement). Odds ratio estimates are shown on the left for dichotomous factors as outcomes, and beta estimates on the right for nondichotomous factors as outcomes.

Other nominal results at the $p < 0.05$ threshold included potential risk-reducing effects of tea intake, visits with family and friends, and exercises such as swimming or cycling, and risk-increasing effects of salt intake on depression, and, in the reverse direction, potential effects of depression risk on reducing social participation and increasing tendencies for computer-related behavior and walking (Figure 4 and Table S3; see also the Supplementary Methods in the online supplement).

DISCUSSION

Although depression is a major source of suffering and lost productivity globally, successful prevention remains challenging. Using phenotypic and genomic data from UK Biobank, we used a novel two-stage approach to screen and validate a broad panel of modifiable factors as potential prevention targets. Consistent with the multifactorial nature of depression (32), we first identified a range of factors across

social, media, sleep, dietary, and physical activity–related domains that were associated with incident depression over the course of study participation, both in general and among at-risk individuals. In subsequent Mendelian randomization analyses, we identified factors with convergent support across both methods, and others with discrepant evidence that may require further validation before they are targeted in resource-intensive trials or policy.

Among factors with convergent support, confiding in others showed the strongest phenotypic associations, even among at-risk individuals, and these associations were substantiated by robust Mendelian randomization results, validating the impact of trusted social connections as causally protective for depression. Visiting with family and friends was also supported by nominally significant Mendelian randomization results, pointing to frequent social interactions as an additional key facet of social engagement that may be protective. Findings align with the literature on social connections and mental well-being (4) and with our recent study in military personnel demonstrating that greater social cohesion was linked to reduced risk of incident depression despite high genetic or environmental risk (33). Emergence of social factors as the most robust among many other modifiable targets suggests that efforts to counteract disconnection at the societal and individual levels—whether by social activity prescriptions (34) or reducing the stigma of seeking emotional support—should be central to an effective depression prevention agenda. Our two-stage analyses also validated television use as a risk factor for depression (35). Further work is needed to determine whether this effect is due to screen time or media exposure per se, or whether television watching time serves more generally as a proxy for sedentary behavior, which was not explicitly measured in the full sample but has been identified as a risk factor for depression (36). Regardless, our findings suggest that health care provider assessment of media use patterns in adult patients and providing psychoeducation on the potential mood impacts of excess television watching could represent another effective component of depression prevention. Finally, daytime napping emerged unexpectedly with bidirectional influences in the Mendelian randomization context; that is, a tendency for daytime napping in adults appeared to increase risk of depression, but depression itself may be a cause of increased napping.

A substantial number of associated factors were not supported by current Mendelian randomization evidence, for several possible reasons. First, not all modifiable factors—even those prospectively related to depression—may be causal in their effects on depression risk and thus represent weaker targets for prevention. For example, bidirectional Mendelian randomization evidence suggested that factors such as increased computer use and vitamin B supplementation are more likely to be consequences of depression than causes, such that depressed individuals may tend to spend more time on the computer or be more likely to take supplements. It may be useful to leverage these factors as early

indicators of depression rather than direct modifiers of depression risk. Causality notwithstanding, the co-occurrence of depression risk with a range of health-relevant behaviors highlights a potential mechanism for physical morbidities (e.g., cardiometabolic disease, premature mortality) often associated with depression, which could inform preventive interventions to reduce health disparities in individuals with or at risk of depression (37).

Second, the relationship between certain modifiable factors and depression may not be straightforward, and more nuanced study is required. For example, overall reported sleep duration, which was related to incident depression but not substantiated by current Mendelian randomization evidence, may have complex and nonlinear effects (38) that could not be fully explored in this study but could be probed in future studies with more detailed sleep-related phenotypes (39). Geocoded environmental exposures such as pollution and natural space also showed associations that did not persist after adjusting for sociodemographic factors and were thus not tested in Mendelian randomization. It may be that such environmental exposures exert stronger influences earlier in development (40) or their effects depend on heterogeneous features (e.g., tree canopy versus grass coverage [41]).

Third, although we adjusted for sociodemographic and health factors, residual confounding could explain some observed associations. For example, various dietary factors associated with depression (e.g., cereal consumption, lamb intake, vitamin B supplementation) were not supported in Mendelian randomization and may instead reflect behavioral patterns such as daily routines, social rituals, or health concerns that affect mental health more broadly. Despite popular views of vitamin B as a mood-boosting supplement, our findings align with a current lack of randomized trial evidence supporting beneficial effects on depression risk (42). Among the more surprising findings, multivitamin use was not only associated with increased depression but also supported by Mendelian randomization evidence, although it was attenuated in sensitivity analyses. Given sparse evidence to date (43), this finding should be interpreted with caution unless supported by additional data, although an intriguing but nonsignificant association of multivitamin supplementation with higher odds of depression was recently observed in a multisite randomized trial for depression prevention (44). We also found evidence suggesting reverse causation, whereby depressed individuals may be more likely to take multivitamins.

Fourth, the strength of current genetic instruments may have contributed to discrepancies between phenotypic and Mendelian randomization associations, and results may require updating as new genetic discoveries emerge. Although physical activity variables showed some of the largest protective relationships with incident depression, their effects were not bolstered in Mendelian randomization. We previously observed that while influences of objectively measured physical activity (not included here) on depression

were validated in Mendelian randomization (3), self-report measures did not show these patterns. Objective measures—capturing a broad tendency for movement—demonstrate higher heritability (45) and may yield more powerful genetic instruments. Indeed, self-reported activity variables, as well as dietary factors, tended to have fewer genome-wide significant SNPs than other traits (e.g., media use). Nonetheless, nominal Mendelian randomization results suggested that liability to engaging in exercises like swimming or cycling (protective) and salt intake (risk) may affect depression risk, meriting further inquiry.

Our study should be evaluated in light of several limitations. First, while we considered a wide array of lifestyle and environmental factors, we were limited by available variables in the UK Biobank database. These did not include modifiable psychological factors (e.g., coping styles) that could also influence depression risk. Second, although the exposure-wide design is a major strength, some associations—potentially noteworthy if studied alone—may be obscured by correction for multiple testing. For instance, physical activity variables (e.g., exercises like swimming and cycling, or heavy outdoor chores) were protectively associated with incident depression even among individuals at high genetic risk, as shown elsewhere (46), but not interpreted as “top” factors for this group because of conservative thresholds. While we highlight some of the most strongly associated factors, the full results should be reviewed in Table S2 in the online supplement. Third, our study relied largely on self-report measures, which can be subject to reporting biases. Our assessment of depression was based on a survey measure that, while widely used, does not constitute a clinical diagnostic interview. In addition, a self-reported outcome could explain stronger associations with factors that were also self-reported and have an emotional component (e.g., social factors). Given that depression may occur across the life course and that this was a sample of only older adults, we focused on any clinically significant incident depression over the follow-up period; however, future longitudinal research could distinguish between new-onset depression and relapse. Fourth, confirmation of causal effects may require randomized controlled trials of preventive interventions. In some cases, such trials might be prohibitively costly, require long follow-up periods, or be otherwise unfeasible. Mendelian randomization provides an important alternative for verifying effects; however, estimates reflect lifelong average effects of genetic variants and should not be interpreted in the same way as effects from a discrete intervention trial or within a briefer period. Moreover, absence of a Mendelian randomization result does not disconfirm the potential importance of a factor operating within shorter time frames, but points to a need to further investigate discrepancies. As mentioned above, horizontal pleiotropy is a common threat to the validity of Mendelian randomization estimates, which we attempted to rule out using multiple sensitivity analyses; notably, significant results for confiding in others, television watching

time, and daytime napping persisted even when retaining genetic instruments with no known associations with other phenotypes including depression-relevant traits. Finally, this study was restricted to an older white British sample that volunteered for research and thus represents a more engaged and healthy population (47) and may not be generalizable to other populations.

CONCLUSIONS

Systematic large-scale research on modifiable factors for prevention of depression has thus far been limited. In this study, in over 100,000 individuals for whom genomic and wide-ranging lifestyle and environmental measures were available, we screened more than 100 potentially modifiable factors for their association with incident depression, including among at-risk individuals, and then tested potential causal effects in a Mendelian randomization framework. Our two-stage results prioritize an array of potential targets for prevention—most robustly, social support factors, media use, and circadian habits—with the potential to reduce the risk of depression even in the face of genetic or environmental vulnerability. Not all factors associated with depression in observational research may represent potent targets for prevention. A large-scale systematic approach combined with genetically informed methods for causal inference could help prioritize candidates for multimodal prevention in psychiatry.

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Supplementary Methods

Methods S0. 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., 2019, pre-print), 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., 2019, pre-print). 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.

Methods S1. Genomic quality control

We performed quality control on the genomic data based on metrics provided by the UK Biobank²³. 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.

Methods S2. 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”).

B. Reported traumatic life events

Exposure to childhood trauma was measured using items from a short form of the Childhood Trauma Questionnaire²⁷, 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 binary items assessed other lifetime traumatic events at any point prior to follow-up (i.e., exposure to sexual assault, physically violent crime, serious/life-threatening accident, and witnessing sudden violent death).

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, which was 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 options ranging from <18K to

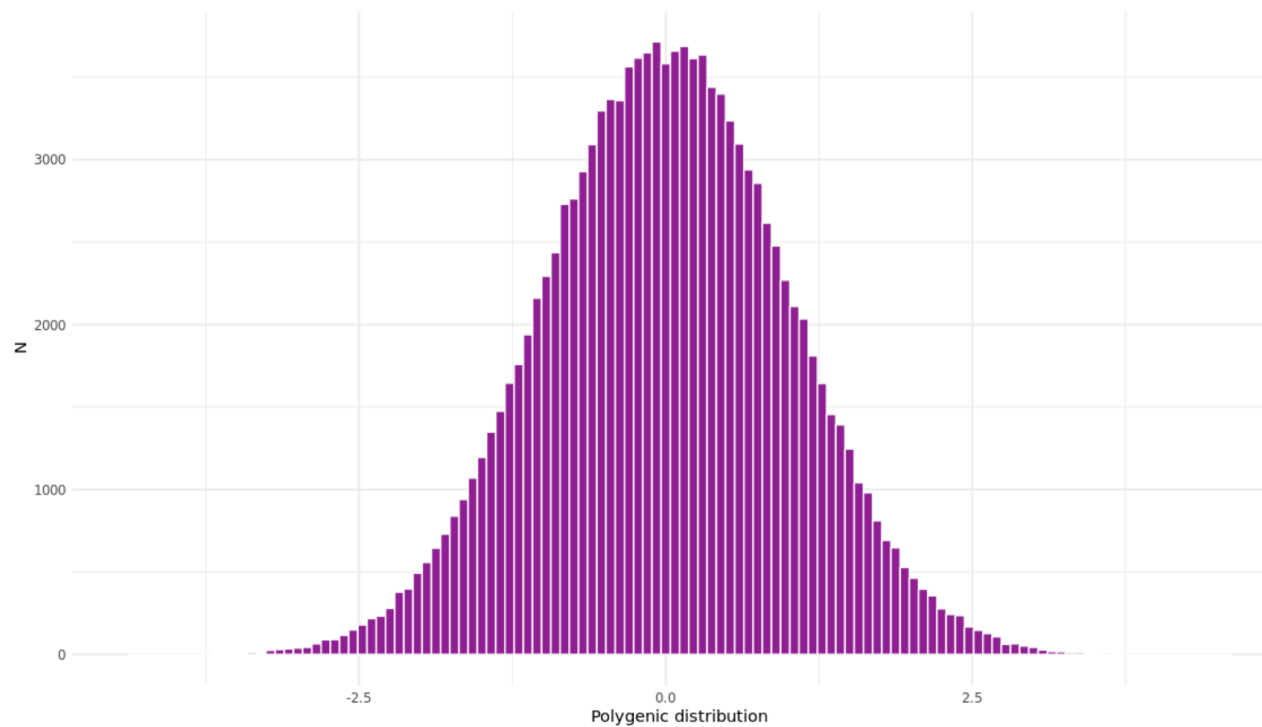
>100K. Individuals reported their educational qualifications and we derived a binary variable indicating the completion of higher education (i.e., college or university-level degree) as in previous research (Davies et al., 2016). Urbanicity was classified based on whether the participant was coded as 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 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.

Methods S3. Data cleaning and processing

We performed data cleaning on all variables and excluded variables 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 we dummy coded into separate binary variables (i.e., yes/no for a given type of activity, assigning NA to those missing on the initial 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.

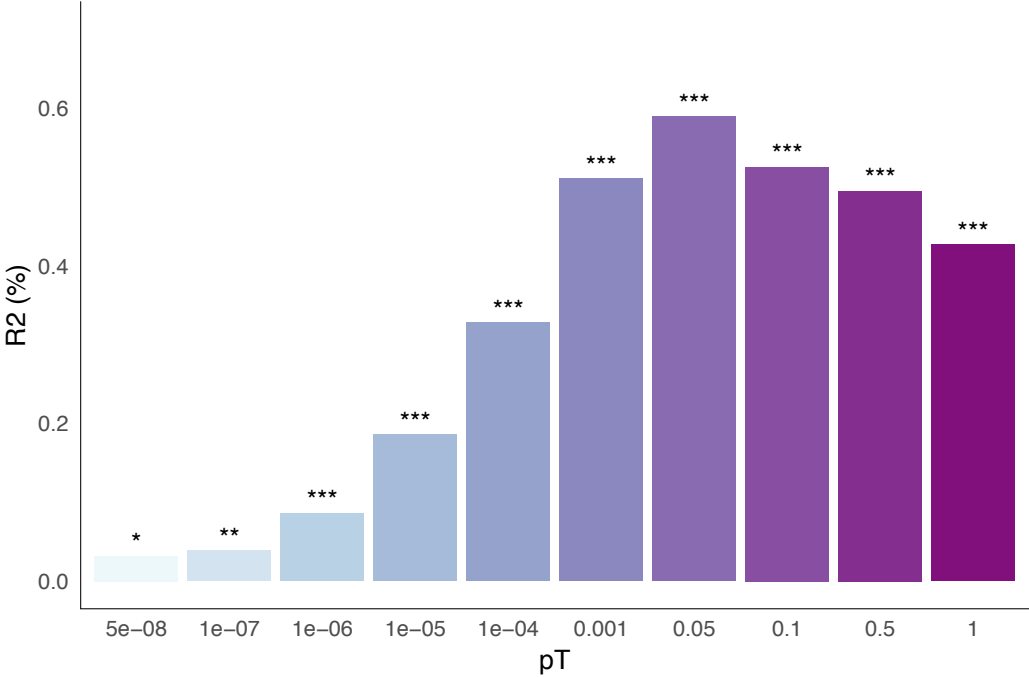
Methods S4. Polygenic scoring

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

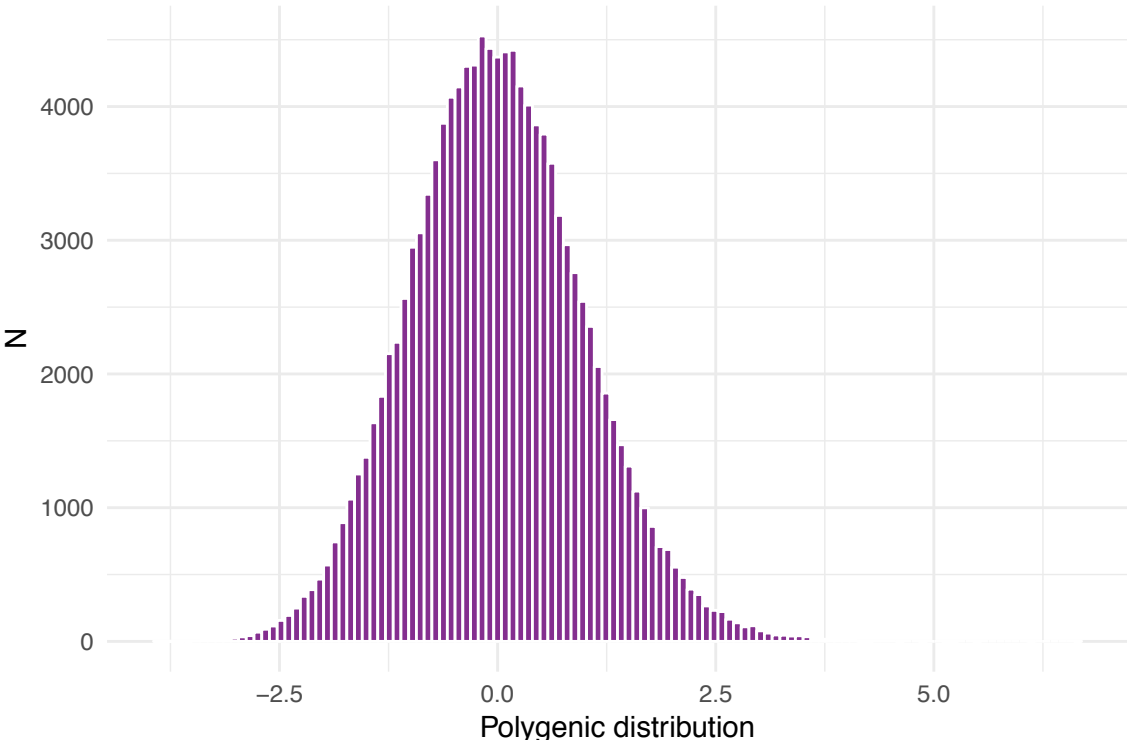


For comparison with the PRS-CS method (see distribution above and Methods in main manuscript), conventional clumping and thresholding procedures for polygenic risk scoring were performed using PRSice2 software. The below figures show PRSice2 estimates of explanatory R^2 of PRS across varying p-value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

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



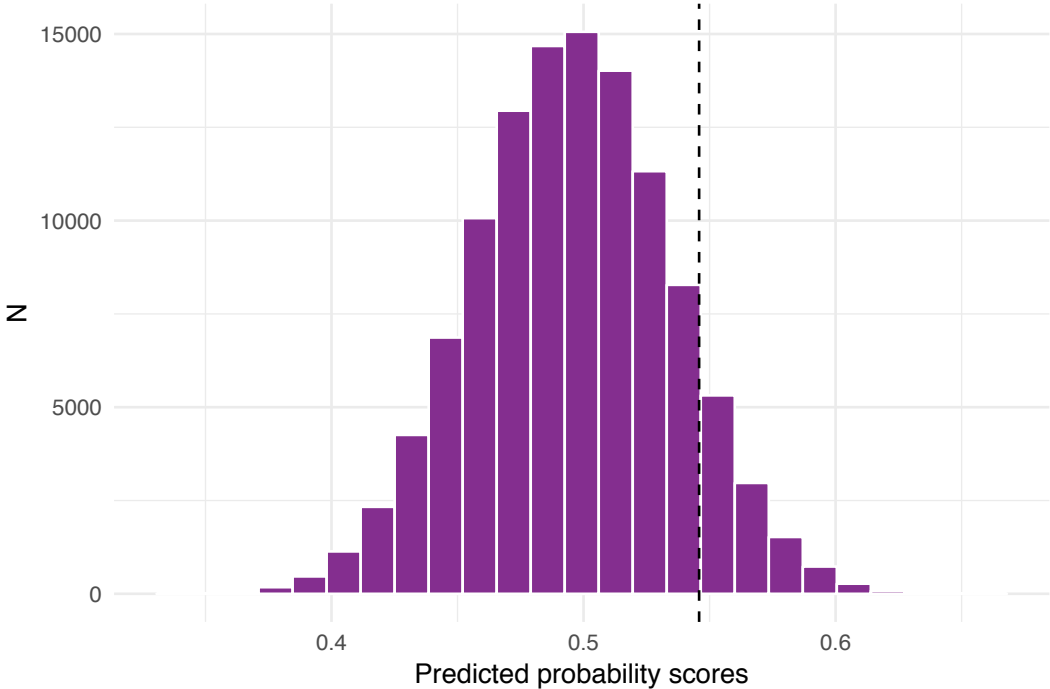
Distribution of scores for the top conventional PRS (pT=0.05)



Methods S5. Stratifying participants based on polygenic risk and reported traumatic life events

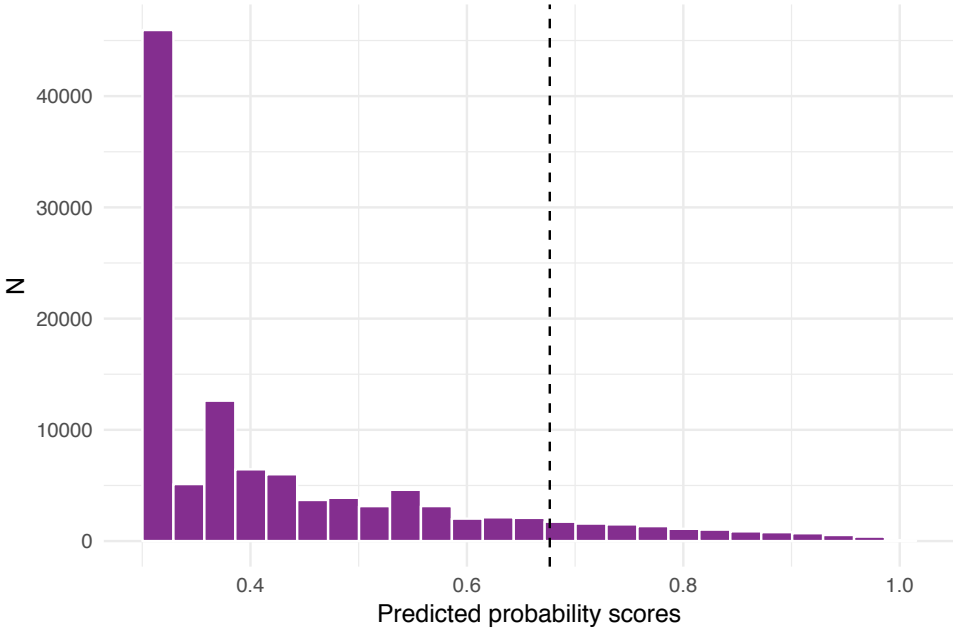
As described in Methods (main manuscript), we randomly sampled a holdout training sample of 1,000 participants with an even split of cases and controls on follow-up depression. The rationale for a holdout sample of this size and case distribution was to derive predicted probabilities using the available 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 (binary variable) as the 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 or (b) the set of reported traumatic life events. The weights used for variables in each risk set are reported below, along with the distribution.

Predicted probability scores for polygenic risk and stratification point



Predicted probability scores derived from training variable weights: Polygenic risk score (0.15867). 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 (0.10080), childhood emotional abuse (0.44014), childhood sexual abuse (0.11032), physical partner violence (0.07844), partner emotional abuse (0.48091), partner sexual interference (0.07409), lifetime exposure to sexual assault (0.31809), lifetime exposure to sudden violent crime (0.25048), life-threatening accident (0.44122), and witnessing sudden violent death (0.32587). Dashed line indicates cut-point for establishing at-risk group (> 90th percentile).

Methods S6. Factors-wide association analyses

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 predictor variables were dummy coded for each model, while non-dichotomous (continuous or ordinal) variables were entered as predictors with linear assumptions. The analytic sample sizes for each tested association are summarized with all results in **Supplementary Tables 1a-i**.

Methods S7. 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 database²⁶ (<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 MR framework; however, related traits (e.g., walking frequency) were examined as possible. For depression, we retained the same set of summary statistics¹² 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 $< 1 \times 10^{-7}$) for the exposure of interest.

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 major 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 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.

C. Nominal MR results

Other findings were nominally significant at the traditional $p < 0.05$ threshold, which suggested potential beneficial effects of tea intake (OR=0.95, 95% CI [0.91-0.99], $p=1.63E-2$); more frequent social visits (OR=0.79, 95% CI [0.65-0.96], $p=1.80E-2$; non-significant WM estimate though directionally consistent) and engaging in exercises like swimming and cycling (OR=0.89, 95% CI [0.81-0.98], $p=1.95E-2$; non-significant WM estimate though directionally consistent), as well as deleterious effects of salt intake (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/club use (OR=0.93, 95% CI [0.88-0.98], $p=7.10E-3$), attendance at pubs/social clubs (OR=0.92, 95% CI [0.87-0.98], $p=8.03E-3$), and time spent driving (beta=-0.05, 95% CI [-0.09, -0.015], $p=6.67E-3$), as well as increased computer use (beta=0.04, 95% CI [0.14-0.09], $p=7.97E-3$) and playing computer games (beta=0.01, 95% CI [0.001-0.03], $p=3.27E-2$; non-significant WM estimate and also directionally inconsistent), and supplementation not only with multivitamins (as noted earlier) but also vitamin B (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 (OR=1.05, 95% CI [1.004-1.11], $p=3.61E-2$, non-significant WM estimate though directionally consistent; OR=1.06, 95% CI [1.009-1.11], $p=1.87E-2$, respectively).

Supplementary Figures

Modifiable factors associated with depression in the full sample

Figure S1. Top hits for Model 0 (adjusted for base factors)

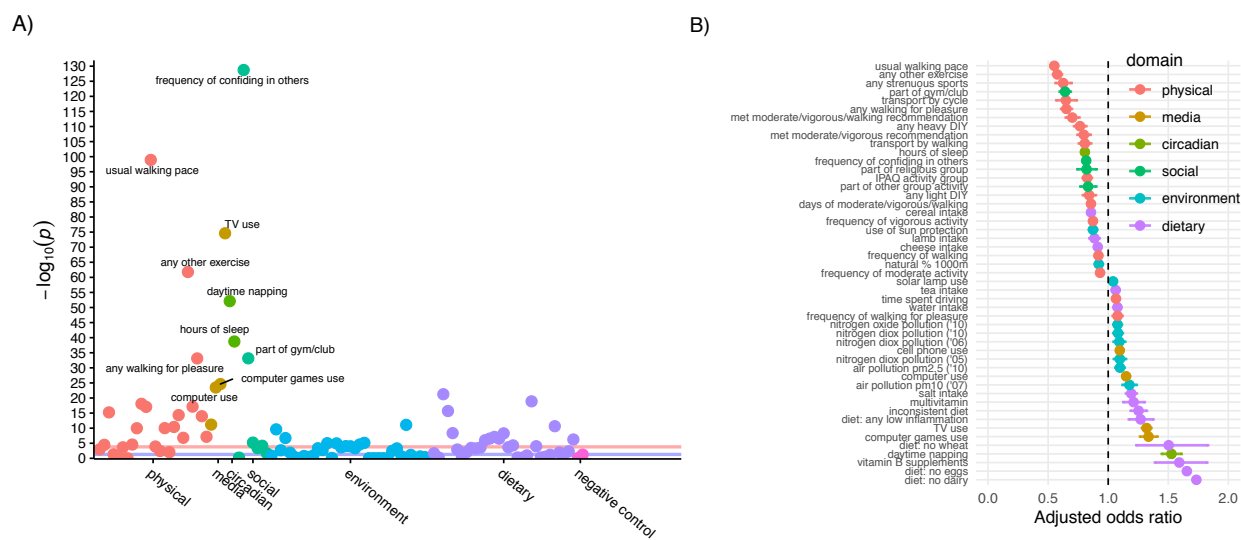
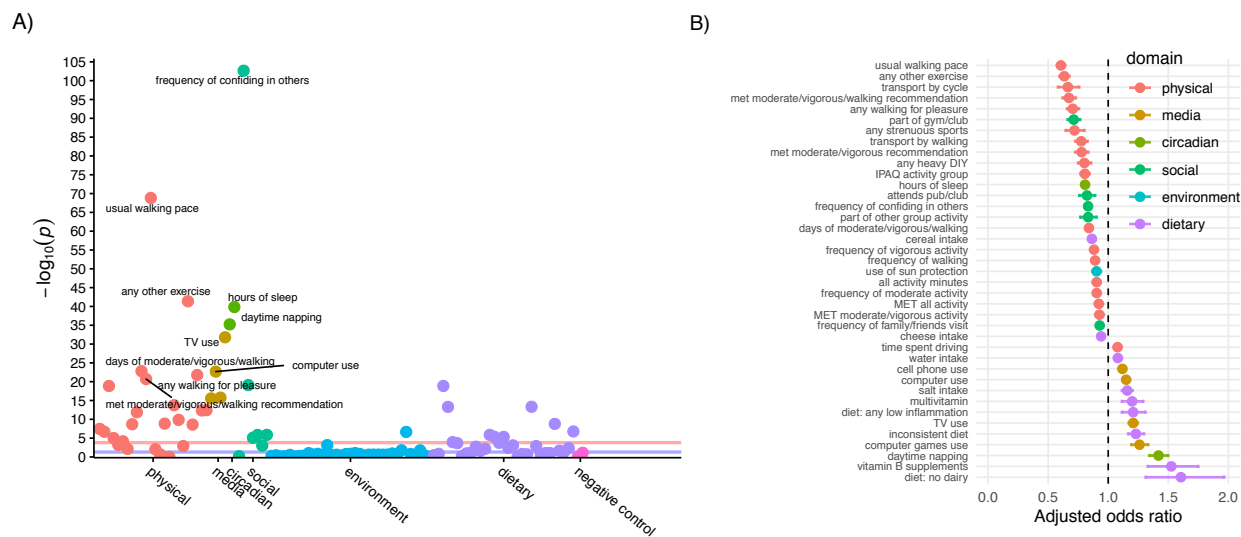


Figure S2. Top hits for Model 1 (adjusted for sociodemographic factors)



Top hits for Model 2 (further adjusted for sociodemographic and health factors)

Shown in main manuscript

Figure S3. All results for Model 0 (adjusted for base factors)



Figure S4. All results for Model 1 (further adjusted for sociodemographic factors)

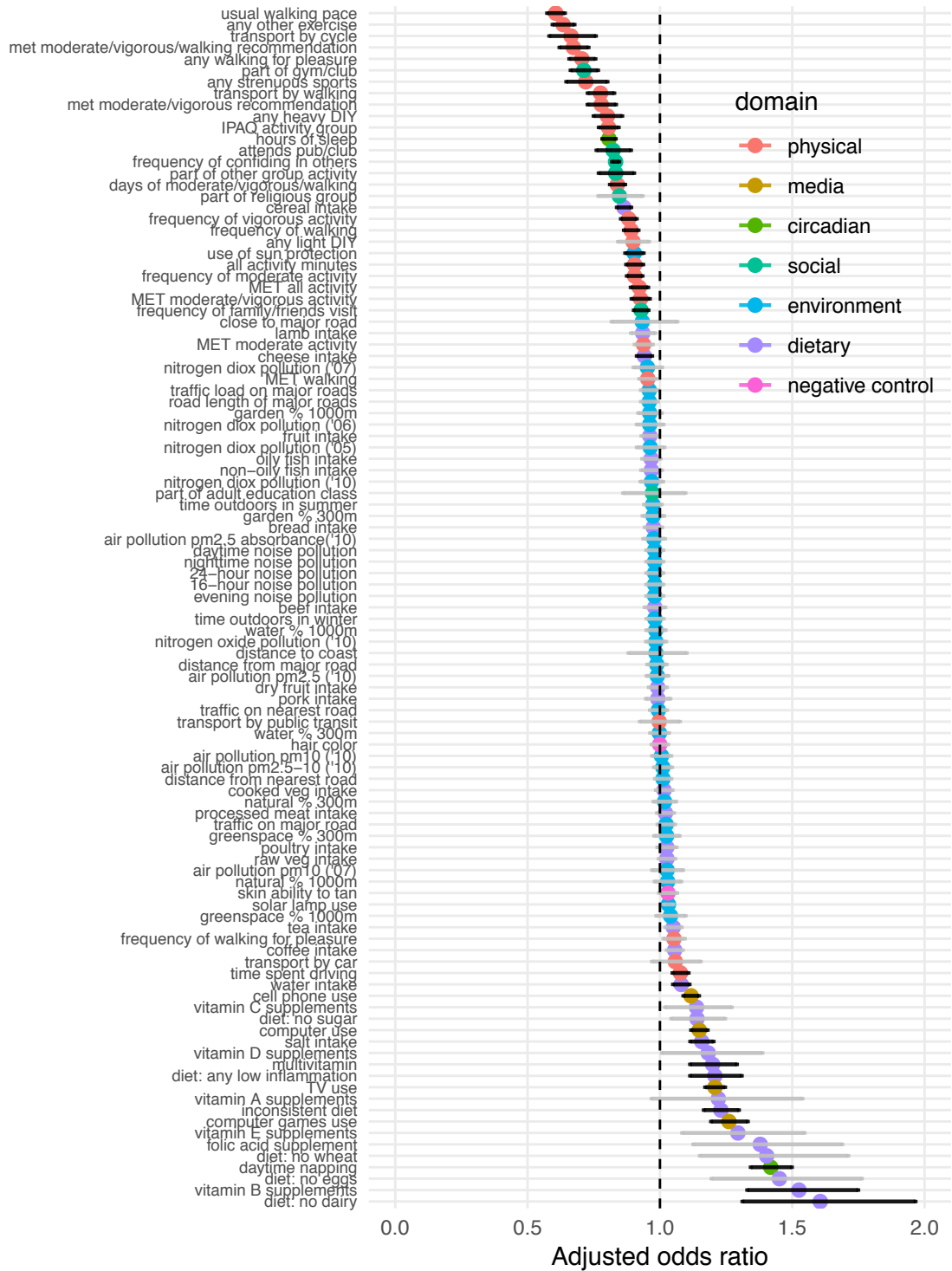


Figure S5. All results for Model 2 (further adjusted for sociodemographic and health factors)



Factors associated with depression among at-risk individuals (based on polygenic risk)

Figure S6. Top hits for Model 0 (adjusted for base factors)

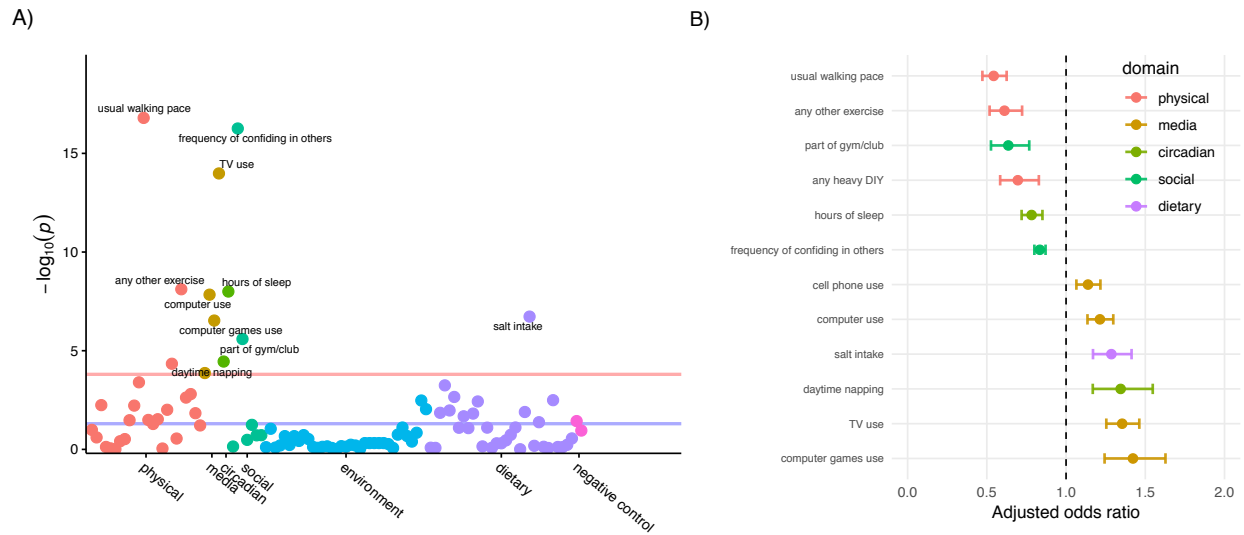


Figure S7. Top hits for Model 1 (further adjusted for sociodemographic factors)

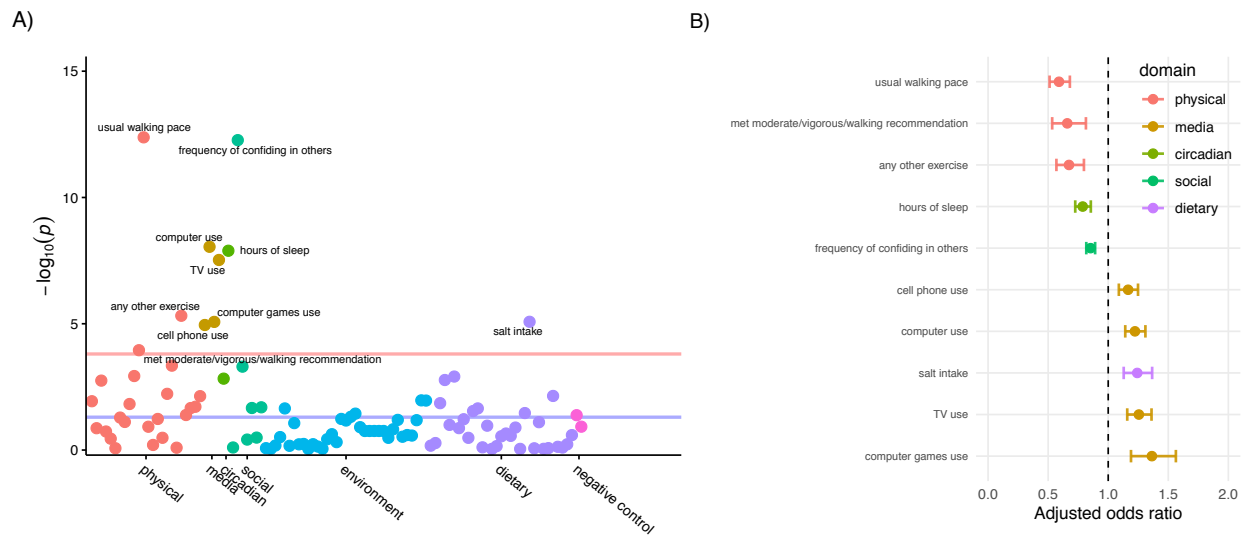


Figure S8. Top hits for Model 2 (further adjusted for sociodemographic and health factors)

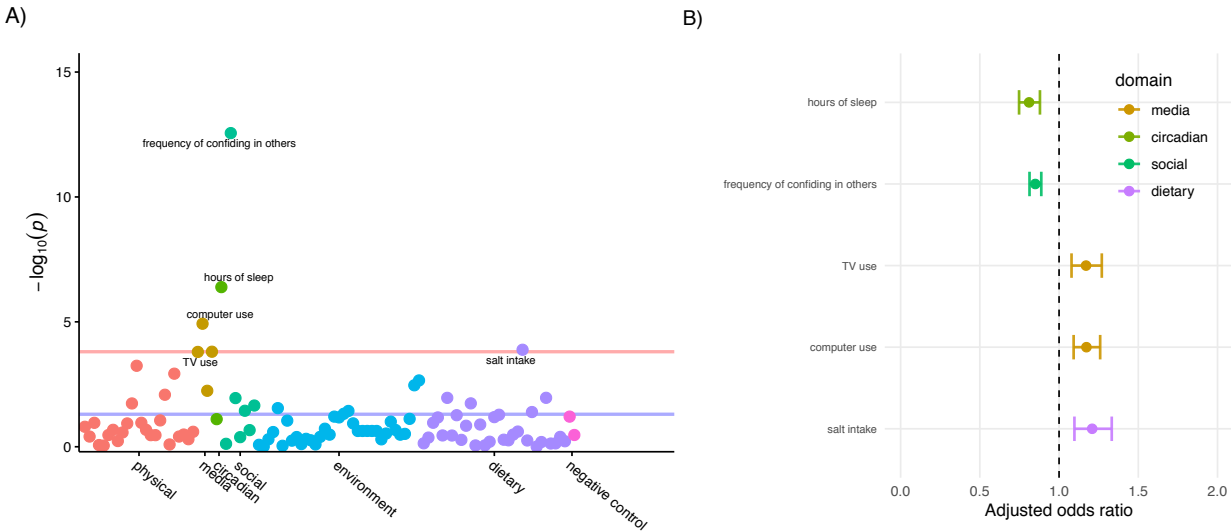


Figure S9. Consistency of associated factors across levels of covariate adjustment. Blue = protective direction of association; red = risk-increasing direction of association.

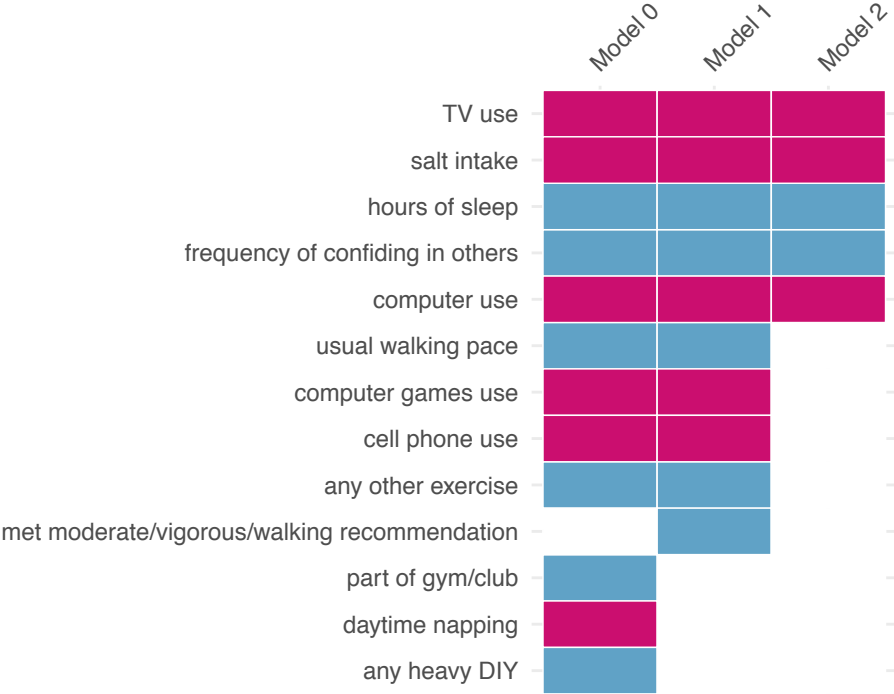


Figure S10. All results for Model 0 (adjusted for base factors)

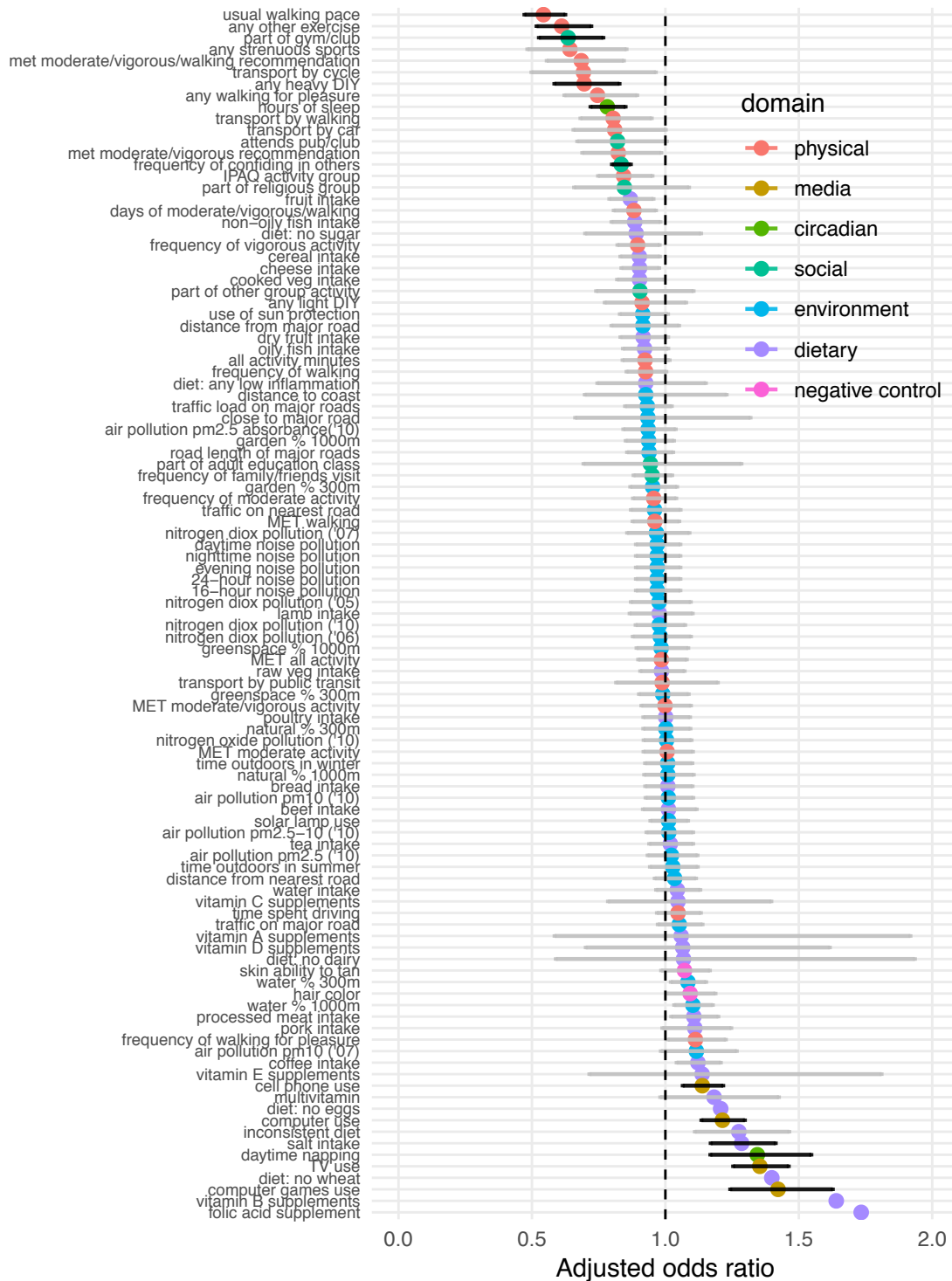


Figure S11. All results for Model 1 (further adjusted for sociodemographic factors)

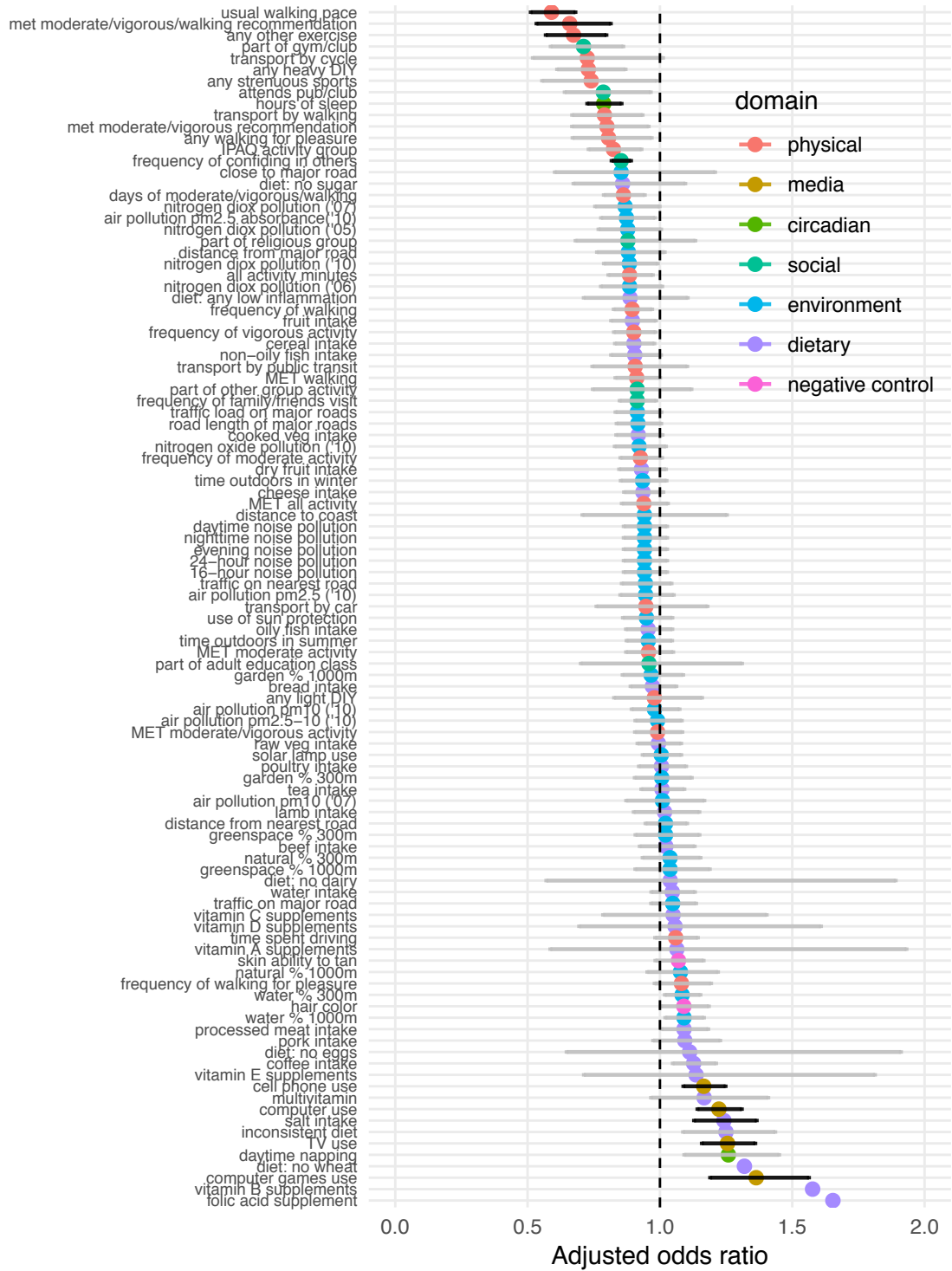


Figure S12. All results for Model 2 (further adjusted for sociodemographic and health factors)



Factors associated with depression among at-risk individuals (based on traumatic life events)

Figure S13. Top hits for Model 0 (adjusted for base factors)

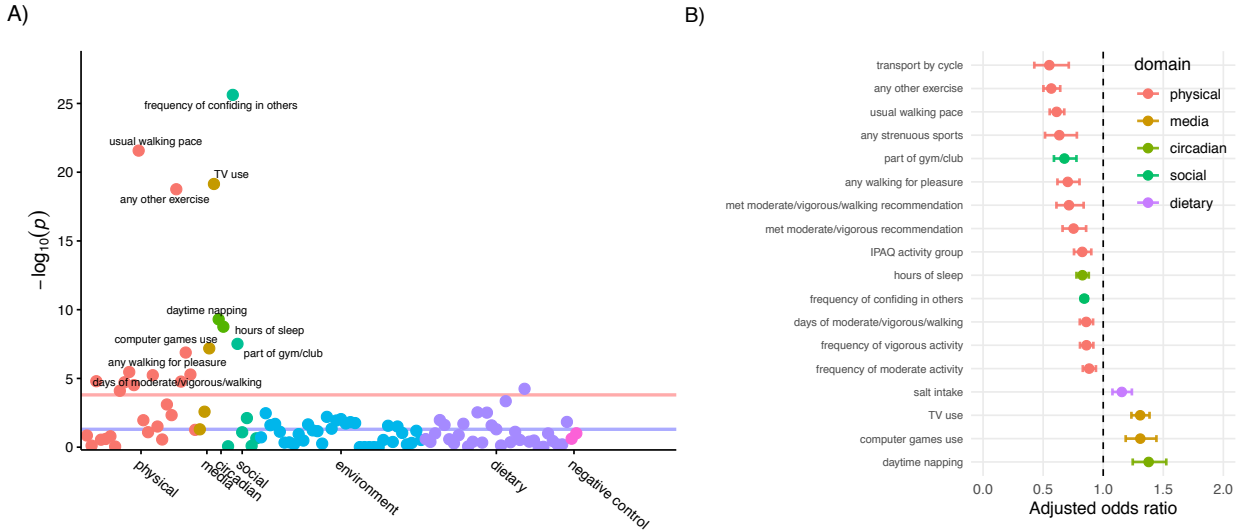


Figure S14. Top hits for Model 1 (further adjusted for sociodemographic factors)

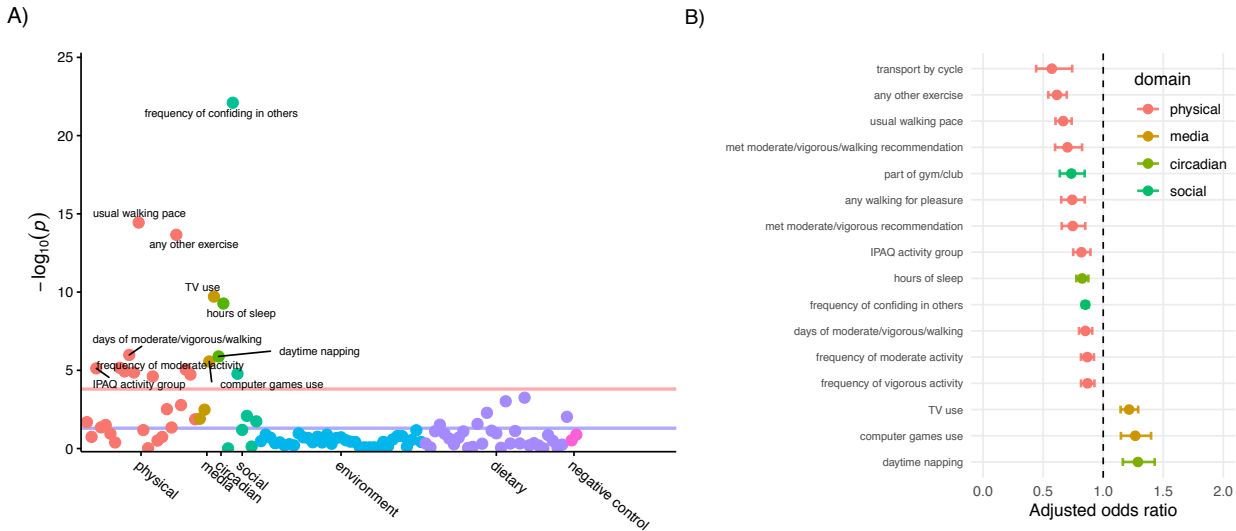


Figure S15. Top hits for Model 2 (further adjusted for sociodemographic and health factors)

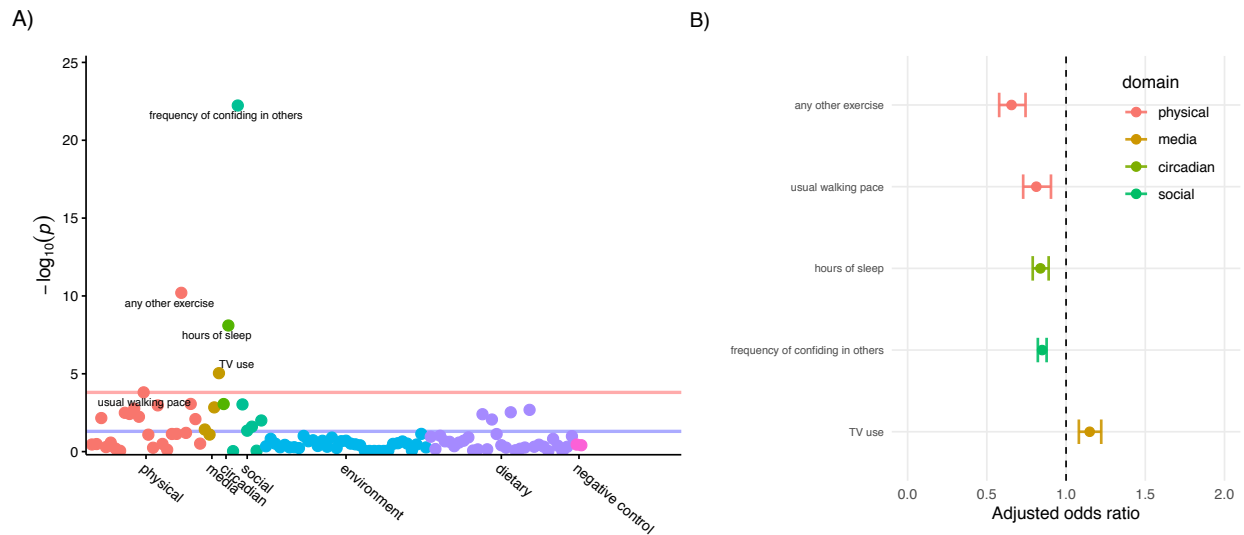


Figure S16. Consistency of associated factors across levels of covariate adjustment. Blue = protective direction of association; red = risk-increasing direction of association.

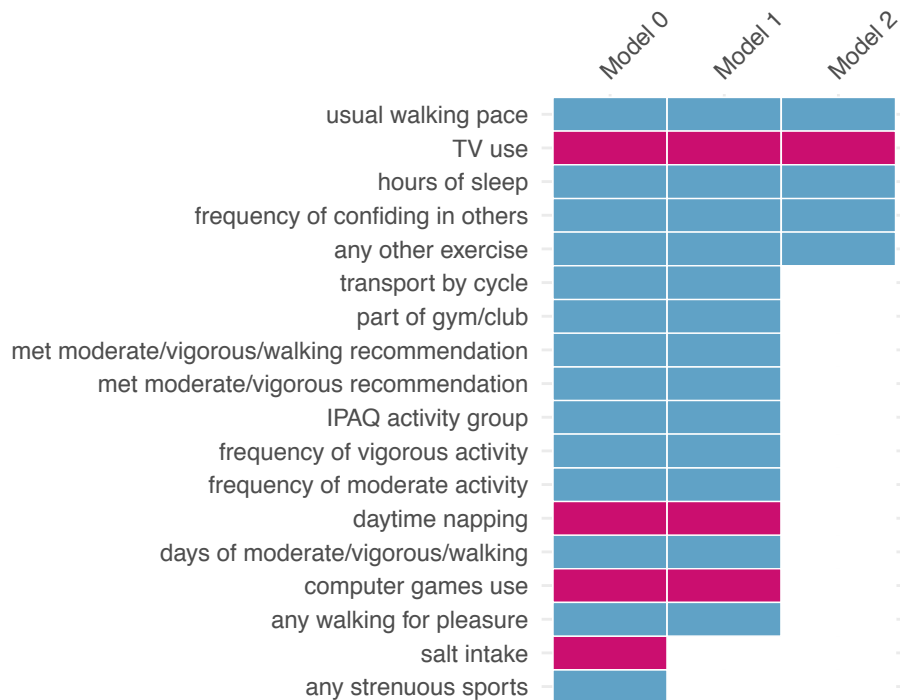


Figure S17. All results for Model 0 (adjusted for base factors)



Figure S18. All results for Model 1 (further adjusted for sociodemographic factors)

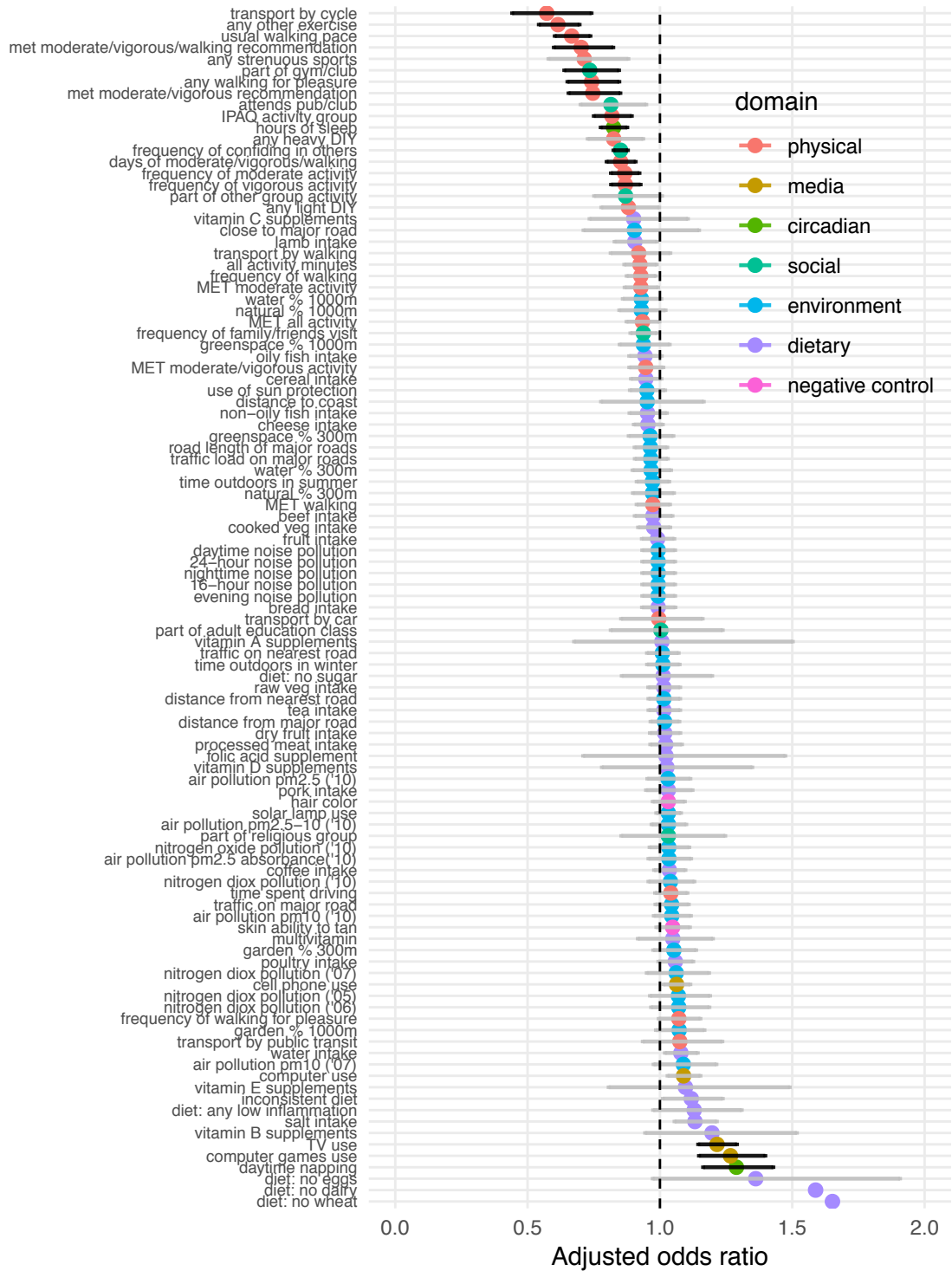


Figure S19. All results for Model 2 (further adjusted for sociodemographic and health factors)



Exploratory factors associated with depression among at-risk individuals (based on being at-risk on both polygenic risk and traumatic life events, maximum n=1,558)

Figure S20. Top hits for Model 0 (adjusted for base factors)

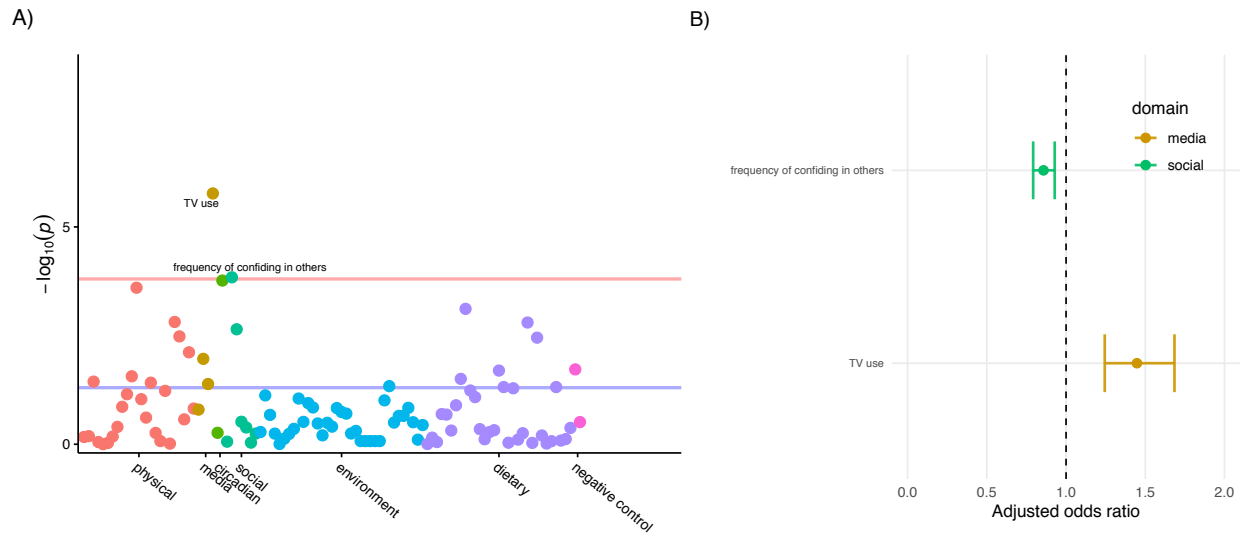


Figure S21. Top hits for Model 1 (further adjusted for sociodemographic factors)

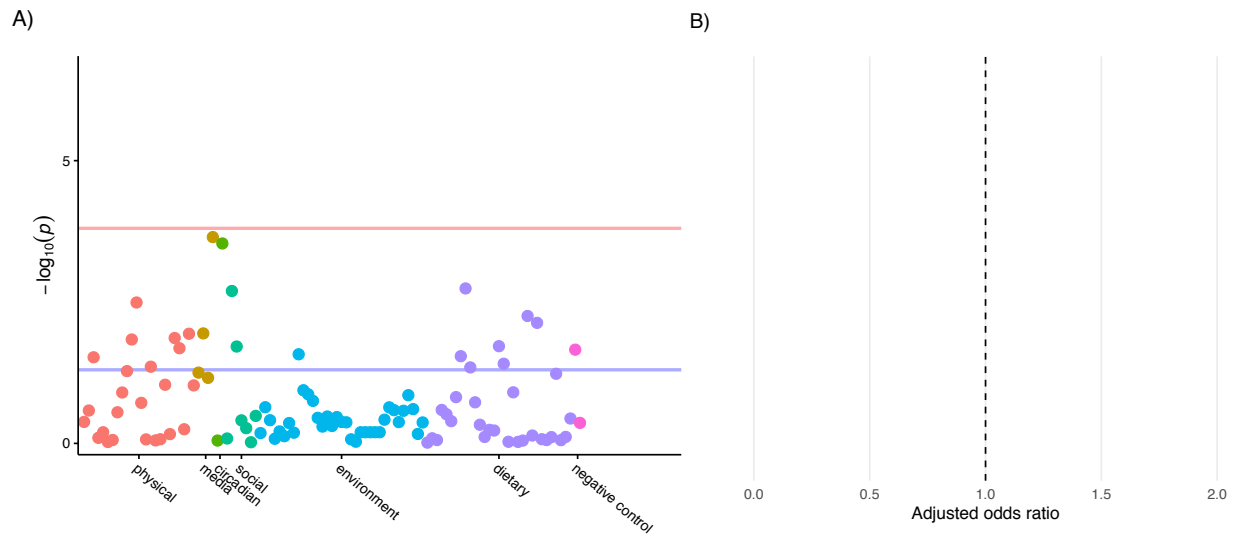


Figure S22. Top hits for Model 2 (further adjusted for sociodemographic and health factors)

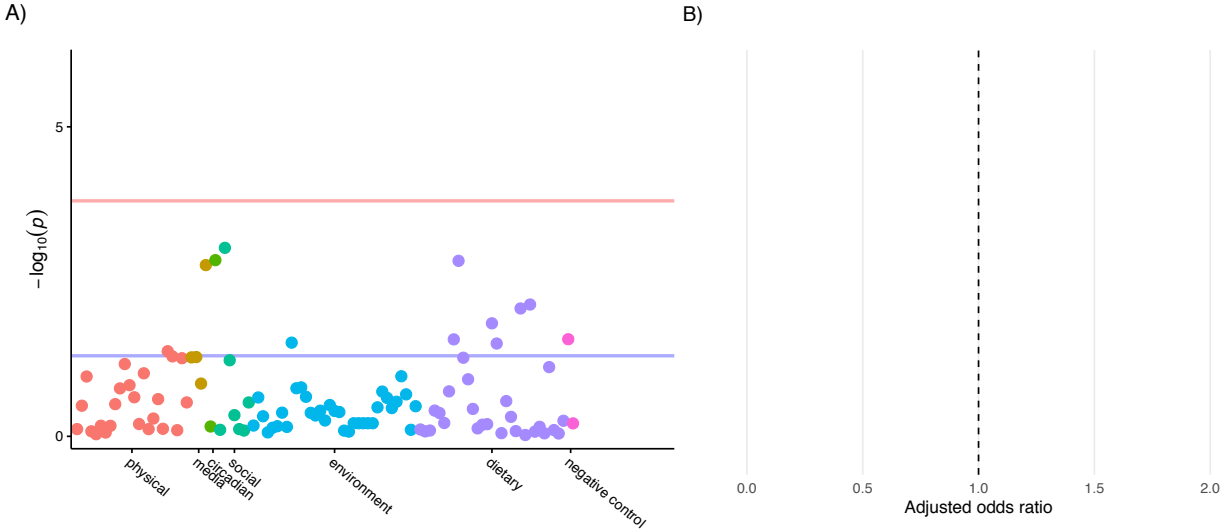


Figure S23. All results for Model 0 (adjusted for base factors)

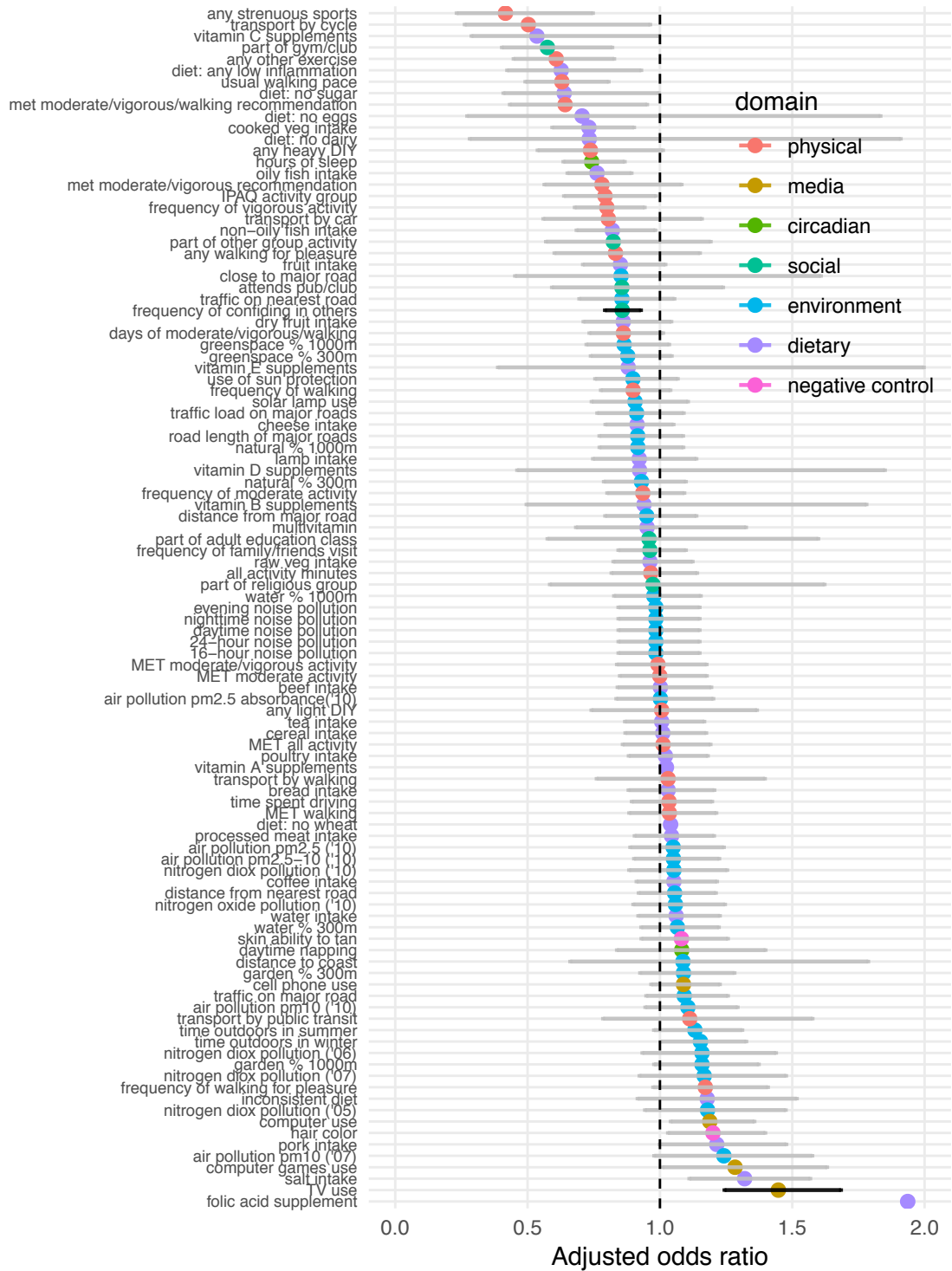


Figure S24. All results for Model 1 (further adjusted for sociodemographic factors)



Figure S25. All results for Model 2 (further adjusted for sociodemographic and health factors)



Figure S26. MR estimates of top modifiable factors → the risk of depression with outliers removed, based on the weighted median method

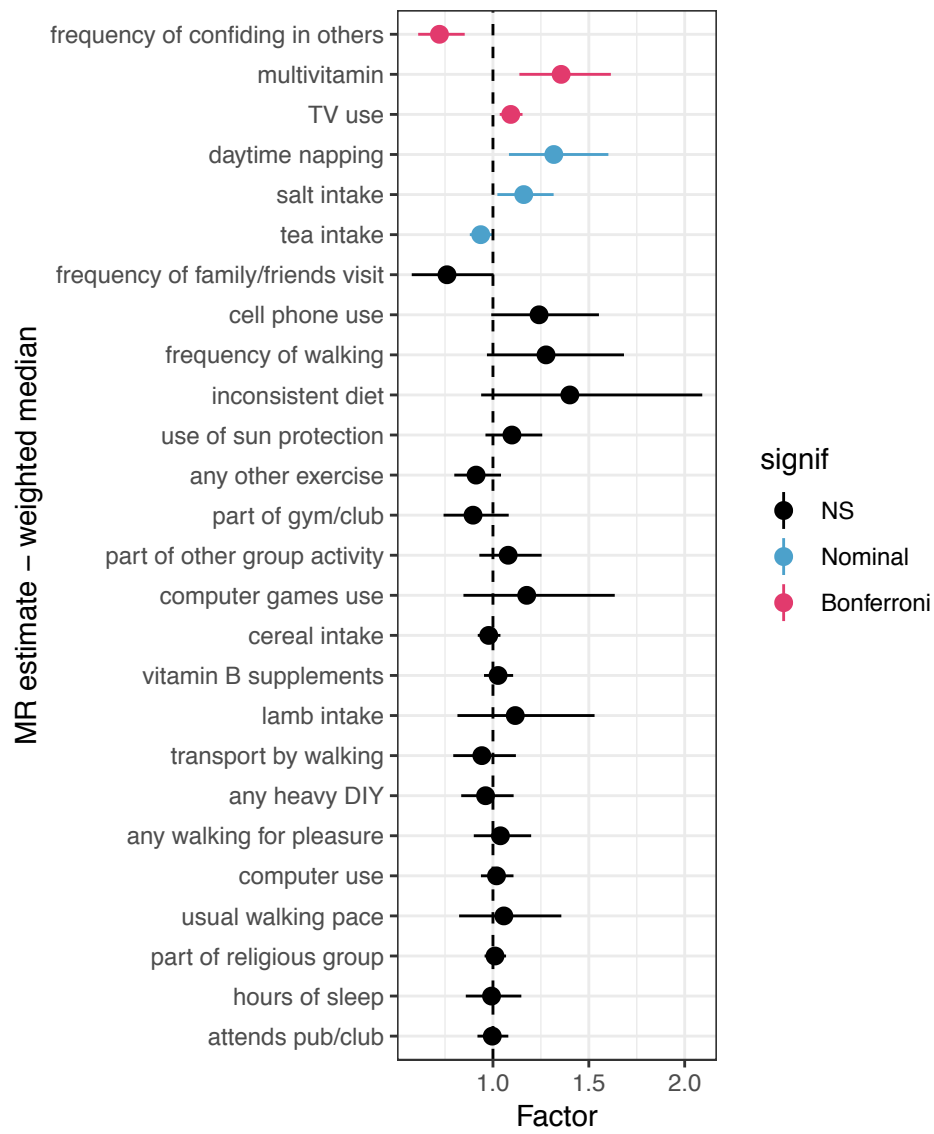


Figure 27. MR estimates of depression → top modifiable factors with outliers removed, based on the weighted median method. Odds ratio estimates on left shown for dichotomous factors as outcomes, and beta estimates on right shown for non-dichotomous factors as outcomes.

