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Triangulated evidence provides no support for bidirectional causal pathways between diet/physical activity and depression/anxiety

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Original Article

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Abstract

Background. Previous studies (various designs) present contradicting insights on the potential causal effects of diet/physical activity on depression/anxiety (and vice versa). To clarify this, we employed a triangulation framework including three methods with unique strengths/limitations/potential biases to examine possible bidirectional causal effects of diet/physical activity on depression/anxiety.

Methods. Study 1: 3-wave longitudinal study (n = 9,276 Dutch University students). Using random intercept cross-lagged panel models to study temporal associations. Study 2: cross-sectional study (n = 341 monozygotic and n = 415 dizygotic Australian adult twin pairs). Using a co-twin control design to separate genetic/environmental confounding. Study 3: Mendelian randomization utilizing data (European ancestry) from genome-wide association studies (n varied between 17,310 and 447,401). Using genetic variants as instrumental variables to study causal inference.

Results. Study 1 did not provide support for bidirectional causal effects between diet/physical activity and symptoms of depression/anxiety. Study 2 did provide support for causal effects between fruit/vegetable intake and symptoms of depression/anxiety, mixed support for causal effects between physical activity and symptoms of depression/anxiety, and no support for causal effects between sweet/savoury snack intake and symptoms of depression/anxiety. Study 3 provides support for a causal effect from increased fruit intake to the increased likelihood of anxiety. No support was found for other pathways. Adjusting the analyses including diet for physical activity (and vice versa) did not change the conclusions in any study.

Conclusions. Triangulating the evidence across the studies did not provide compelling support for causal effects of diet/physical activity on depression/anxiety or vice versa.

Introduction

Mental health disorders (particularly depression and anxiety), along with unhealthy lifestyle behaviours (such as poor diet and physical inactivity) are pressing challenges in today's society (GBD 2019 Diseases and Injuries Collaborators, 2020; NCD Countdown 2030 collaborators, 2018; World Health Organization, 2022). Between 1990 and 2019, the estimated past-year global prevalence of depression and anxiety increased from 171 to 280 million and from 195 to 301 million, respectively (GBD Mental Disorders Collaborators, 2022). Additionally, the global prevalence of insufficient physical activity[1] has increased from 23% in 2000 to 26% in 2010 and 31% in 2022 (Strain et al., 2024) and over several decades dietary quality has worsened globally (e.g., increased uptake of processed foods, away-from-home meals and sugar-sweetened beverages) (Popkin, Adair, & Ng, 2012). Accordingly, understanding factors contributing to the development and recovery of these conditions/behaviours is important.

Previous studies have suggested that mental health and lifestyle behaviours might be interconnected and possibly influence each other (although results are mixed). Several studies have found support for bidirectional or unidirectional causal pathways between diet or physical activity and depression or anxiety (Choi et al., 2019; Iob et al., 2023; Liu, Yan, Li, & Zhang, 2016; Mammen & Faulkner, 2013; McDowell, Dishman, Gordon, & Herring, 2019; Molendijk,

[1]Insufficient physical activity is defined as not adhering to 150 minutes of moderate-intensity activity, 75 minutes of vigorous-intensity activity, or an equivalent combination per week.

Molero, Sánchez-Pedreño, Van der Does, & Martínez-González, 2018; Pasman et al., 2024; Pearce et al., 2022; Rebar et al., 2015; Roshanaei-Moghaddam, Katon, & Russo, 2009; Saghafian et al., 2018; Schuch et al., 2019; Schuch et al., 2018; Tuck, Farrow, & Thomas, 2019; Wanjau et al., 2023; Yan, Xu, Li, & Liu, 2023), while others have not (Appleton, Boxall, Adenuga-Ajayi, & Seyar, 2024; T. T. Chen, Chen, Fang, Cheng, & Lin, 2022; Choi et al., 2019; De Moor, Boomsma, Stubbe, Willemsen, & de Geus, 2008; Iob et al., 2023; Moreno-Peral et al., 2022; Pasman et al., 2024; Yan et al., 2023). It must be noted that these studies focussed on either diet or physical activity in relation to mental health. None of these studies took into account that diet might confound the relationship between physical activity and mental health, and vice versa that physical activity might confound the relationship between diet and mental health. Consequently, this limits the ability to provide more robust estimates on direct effects between diet/physical activity and depression/anxiety. Additionally, not all pathways have been thoroughly investigated. For example, studies involving diet have mostly focused on the intake of healthy foods (e.g., fruits and vegetables) but neglected studying the intake of unhealthy foods (e.g., sweet or savoury snacks).

Various research designs have been employed in previous studies (e.g., randomized controlled trials, prospective cohort studies, co-twin control designs (CTCDs)[2] and Mendelian randomization (MR)[3]). Given that no single-methodology approach can provide definite evidence for causal pathways on its own (Hammerton & Munafò, 2021), the ultimate approach to gain more robust insights on this complex causal question is to apply "triangulation" (Munafò & Davey Smith, 2018; Patton, 1999). This refers to using various study designs, each with unique strengths and potential weaknesses, to address the same research question. In a triangulation framework, the results across the included methods are compared to help overcome the biases arising from the use of one single method, to focus on overarching patterns, and to help achieve empirical consensus (Munafò & Davey Smith, 2018; Patton, 1999).

Consequently, in this study, we aimed to unravel the potential causal effects of diet (intake of sweet snacks, savoury snacks, fruits and vegetables)/physical activity on depression/anxiety and vice versa. This was done in unadjusted models (including one lifestyle and one mental health measure) and adjusted models (including one diet, one physical activity and one mental health measure; to explore possible confounding by diet/physical activity and obtain more robust direct effect estimates of the exposure of interest on the outcome). We employed a triangulation framework including three distinct lines of evidence, to utilise the different strengths and acknowledge potential weaknesses and sources of bias of each method. We focused on: (1) exploring temporal associations using random intercept cross-lagged panel models (RI-CLPMs), (2) separating genetic and environmental confounding using CTCD mixed-effects models, and (3) utilising genetic variants as instrumental variables with MR. Study 1 used longitudinal data from the Healthy Student Life (HSL) project (n = 9,276 Dutch University students) (van Hooijdonk, Simons, van Noorden, Geurts, & Vink, 2023). Study 2 used cross-sectional data from the Brisbane Longitudinal Twin Study (BLTS; n = 341 monozygotic and n = 415 dizygotic Australian adult twin pairs) (Mitchell et al., 2019). Study 3 used summary statistics from genome-wide association studies (GWASs; n varied between 17,310 and 447,401).

Methods

Triangulation framework

In the current study, we employed a triangulation framework to examine causal pathways between diet/physical activity and depression/anxiety. This involves answering the same causal question by integrating results from different statistical methods which have different strengths, limitations and (preferably) unrelated sources of potential bias (Lawlor, Tilling, & Davey Smith, 2016; Munafò, Higgins, & Davey Smith, 2021). In the current triangulation framework, we used three complementary methods (referred to as Studies 1, 2 and 3), that provide insight on potential causal effects form different perspectives (as illustrated in Figure 1):

- RI-CLPMs (Study 1). We estimated individual-level temporal associations which show how changes in one variable might predict changes in another variable over time.
- CTCD (Study 2). We separated genetic and environmental confounding by examining and comparing the association between an exposure and outcome at population-level and within twin pairs (who have overlap in genes and shared early environment).
- MR (Study 3). We leveraged genetic variants as instrumental variables to estimate the potential population-level causal effect of an exposure on an outcome.

When the findings in a triangulation framework converge, this provides greater confidence in the conclusions and potential causal effect, since it is unlikely that the same bias effects all three methods. Divergent findings will help to identify sources of bias which require further investigation (Munafò et al., 2021). Table 1 provides a detailed comparison of how the three methods in the triangulation framework complement each other in addressing different sources of potential bias. To investigate converge/divergence in our triangulation framework, we evaluated the magnitude, direction and margin

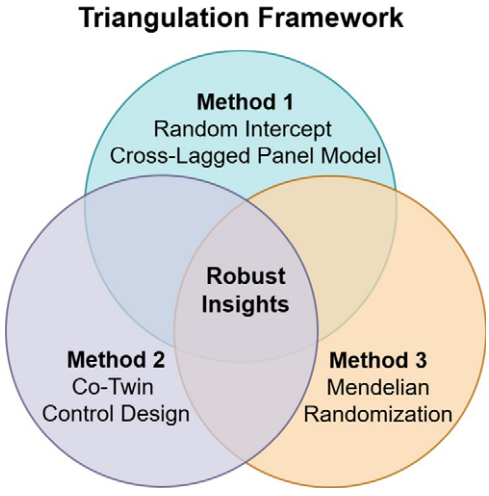

Figure 1. Concept of triangulation.
Note. Illustration of how our three complementary methods help to strengthen causal inference.

[2]In co-twin control designs monozygotic and dizygotic twin pairs are leveraged to account for genetic and environmental confounding (Gonggrijp, van de Weijer, Bijleveld, van Dongen, & Boomsma, 2023).

[3]In Mendelian randomization studies genetic variants robustly associated with an exposure are used as instrumental variables to study its causal effects on an outcome (Davey Smith & Ebrahim, 2003).

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Table 1. Overview of the studies included in the triangulation framework

Study	Short description	Strengths compared to other studies	Potential bias/limitation
Study 1: Random Intercept Cross-Lagged Panel Models (observational longitudinal study)	Statistical approach used to examine the individual-level temporal associations between ≥2 variables.	In contrast to Studies 2 and 3, in Study 1 within-person and between-person effects can be decomposed. This allows to control for all time-invariant unobserved heterogeneity. Compared to Study 2, this design can provide insights on the direction of effects.	Unmeasured confounding could bias the findings.
Study 2: Co-Twin Control Design (observational cross-sectional study)	Statistical approach used to separate genetic and environmental confounding (and indirectly infer possible causation) by examining and comparing the association between an exposure and outcome (1) at population-level (without considering zygosity/discordance), (2) within same-sex DZ twin pairs discordant for the exposure and (3) within MZ twin pairs discordant for the exposure.	In contrast to Studies 1 and 3, comparing discordant same-sex DZ and MZ twins enables controlling for factors shared within twins of the same twin pair, e.g., unobserved and unmeasured genetic and shared (early) environmental factors.	Although Study 2 naturally controls for confounding factors which are shared within twin pairs, unmeasured confounding by non-shared environmental factors could still bias the findings. Additionally, this design cannot distinguish between causation and reverse causation.
Study 3: Mendelian randomization (genetically informed study)	Statistical approach which leverages genetic variants (robustly associated with an exposure) as instrumental variables to estimate the potential population-level causal effect of an exposure on an outcome.	Compared to Studies 1 and 2, Study 3 is less susceptible for unmeasured confounding. Compared to Study 2, MR can distinguish between causation and reverse causation.	Weak instrument bias (occurs when the instrumental variable is weakly associated with the exposure of interest) and horizontal pleiotropy (occurs when a genetic variant directly and independently influences ≥2 traits) could bias the findings.

Note. All studies use observational studies to some extend which has known potential biases like reporting/recall bias, measurement errors, selection bias, and social-desirability bias. DZ = dizygotic. MZ = monozygotic.

of error of all effect estimates and compared these across the three methods.

All methods in the triangulation framework were preregistered in the Open Science Framework: https://osf.io/e4d5b/ (Supplementary Material A describes deviations). Analyses were performed in R version 4.3.1 (R Core Team, 2023). Reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and STROBE using mendelian randomisation (STROBE-MR) guidelines (Skrivankova et al., 2021; Von Elm et al., 2007). Details of the methods per study have been provided below.

Study 1: random intercept cross-lagged panel models

The RI-CLPM is a structural equation modelling approach used to model within-person directional effects of one variable on another variable over time, and vice versa (Hamaker, Kuiper, & Grasman, 2015). In the RI-CLPM, observed scores of all constructs are decomposed into (1) grand means (time-varying or fixed means over all individuals per occasion; the paths from the triangles (constants, with value fixed at 1) to the squares (observed scores) in Figure 2); (2) stable between-person variance (random intercepts, an individual's time-invariant deviation from the grand means, see "Between" in Figure 2) and (3) fluctuating within-person variance (differences between an individual's observed measurements and their expected score based on the grand means and random intercept, see "Within" in Figure 2) (Mulder & Hamaker, 2021). The within-person cross-lagged effects (red arrows Figure 2) illustrate how one variable potentially influences another variable over time within a person and are of interest when studying possible causal effects.

Procedure and participants

Data from the HSL project were used (van Hooijdonk et al., 2023). This questionnaire study follows Dutch Radboud University students and assesses their mental health and lifestyle. In this study, we utilized data from Wave 1 (October–November 2021, collected during the COVID-19 pandemic; $N_{invited}$ = 25,035), Wave 2 (May–July 2022; $N_{invited}$ = 23,994) and Wave 3 (May–July 2023; $N_{invited}$ = 23,425). The analytical sample included 9,276 students (6,004 participated in one questionnaire; 2,208 in two; 1,064 in all). The study was independently reviewed by Radboud University's Social Sciences Ethics Committee, and there is no formal objection to this study (ECSW-2021-086). Supplementary Material B includes additional information.

Measures (self-reported)

For the main analyses, we used continuous data on sweet snack intake (van den Broek, Larsen, Verhagen, Burk, & Vink, 2020), savoury snack intake (van den Broek et al., 2020), fruit intake (van den Broek et al., 2020), vegetable intake (van den Broek et al., 2020), physical activity (IPAQ Research Committee, 2005), depressive symptoms (Van de Velde, Levecque, & Bracke, 2009), anxiety symptoms (Donker, van Straten, Marks, & Cuijpers, 2011) and age. Additionally, information on gender (male/female/other) was used. For descriptive purposes, we also used data on living situation, relationship status, parental educational type, body mass index (BMI; kg/m^2), and overall perceived physical and mental health. Supplementary Material C includes additional information.

Statistical analyses

Descriptive statistics were used to explore all measures. Additionally, intraclass correlation (ICCs) were calculated using the lme4 package (Bates et al., 2009b) to gain insight in the proportion of variance explained between persons (ICC) and within persons (1-ICC) across the waves (Aarts, Verhage, Veenvliet, Dolan, & Van Der Sluis, 2014). Next, RI-CLPMs were applied to the data using the lavaan package (Rosseel, 2012). We ran ten RI-CLPMs including one diet/physical activity and one mental health measure

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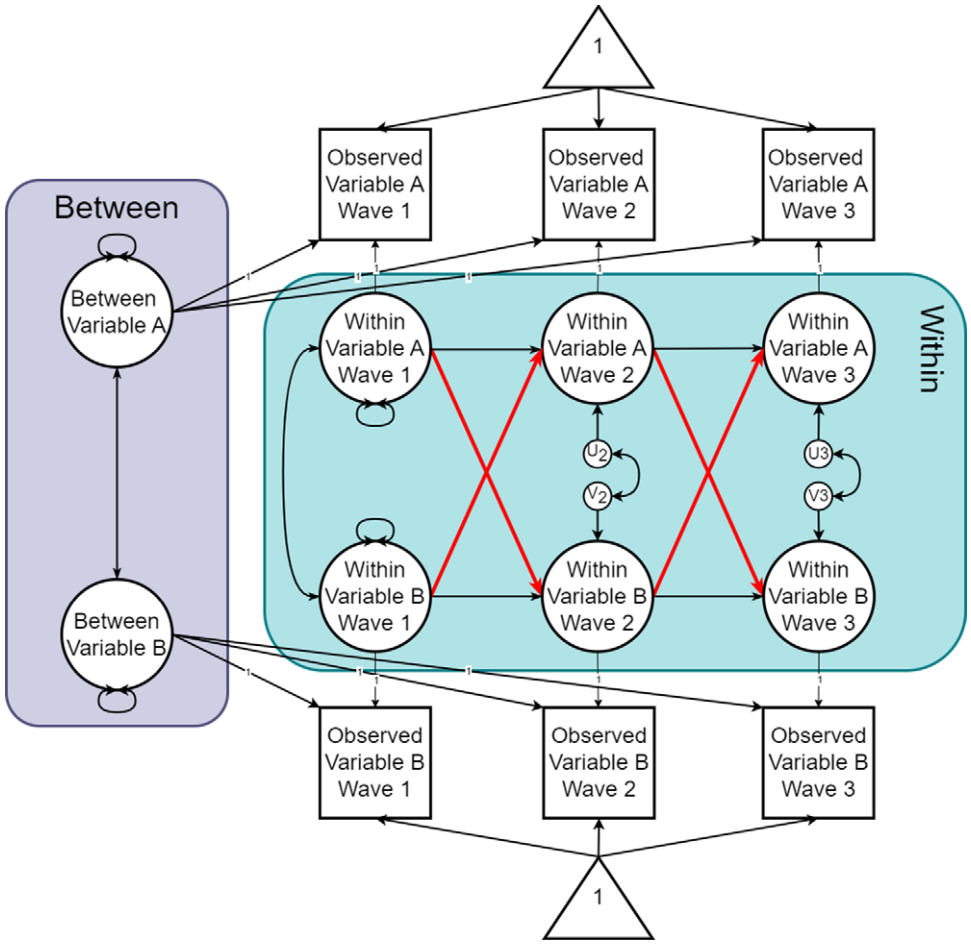

Figure 2. Example of a random intercept cross-lagged panel model (RI-CLPM) assessing the bidirectional pathways between variable A and variable B, including between-person and within-person components at three survey waves.
Note. The squares indicate observed variables, while the circles represent latent (unobserved) variables. U and V represent the residual variance. The triangles represent constants for the mean structure. To improve readability, no covariates are presented. Based on Hamaker et al. (2015) and Mulder and Hamaker (2021).

(Supplementary Table ST1). In the results, we refer to these analyses as unadjusted models. Moreover, we ran eight RI-CLPMs where the unadjusted temporal associations were adjusted for either diet (when unadjusted model included physical activity) or physical activity (when unadjusted model included diet), taking into account potential confounding by diet/physical activity (Supplementary Table ST2). Each model included one diet measure, physical activity, and one mental health measure. In the results, we refer to these models as adjusted models.

In all models, five parameters were estimated: (1) between-person covariance random intercepts, (2) within-person stability (or autoregressive) effects, (3) within-person cross-lagged effects, (4) within-person concurrent covariance, and (5) time-invariant covariate associations of gender (male/female) and Wave 1 age (extension 1 in Mulder and Hamaker (2021)). When participants joined after Wave 1, Wave 1 age was estimated and gender reported at first participation was used. Full information maximum likelihood (FIML) was used to handle missing data and the robust estimator maximum likelihood with robust standard errors (MLR) was used to handle non-normality (Enders, 2001; Graham, 2009). Per model, the fit was assessed and considered acceptable when: (1) the scaled chi-square test was non-significant ($p > .05$), (2) root-mean-square error of approximation < .06, (3) standardized root mean square residual < .08, and (4) comparative fit index > .90 (Hu & Bentler, 1999; Kline, 2023). To investigate potential support for causal effects, the magnitude, direction and margin of error of the within-person cross-lagged effects were studied.

Last, sensitivity analyses to examine the robustness of the findings were performed using complete cases for all RI-CLPMs (n varied between 776 and 841). These were added as a large proportion of HSL participants only joined one wave and these might be different from participants who participated every time (e.g., healthier lifestyle/better mental health).

Study 2: co-twin control design

The CTCD is applied on the assumption that monozygotic (MZ) twins share 100% of their genetic material and 100% of their shared (early) environment (e.g., prenatal exposures, childhood environment and other family influences), and that dizygotic (DZ) twins share, on average, 50% of their genetic material and 100% of their shared (early) environment (Vitaro, Brendgen, & Arseneault, 2009). In population-level observational studies, the association between exposure and outcome can be confounded by multiple factors. This limits the possibility of drawing valid conclusions on causal inference. In contrast, equivalent association

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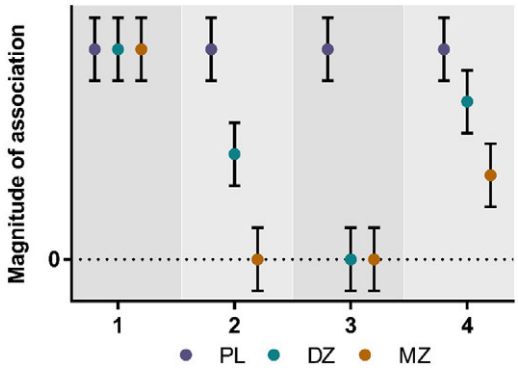

Figure 3. Hypothetical outcome scenarios of a co-twin control design (CTCD).
Note. Population-level (PL) = the mean difference in the magnitude of association between exposed and unexposed individuals; DZ = the mean difference in the magnitude of association within dizygotic same-sex twin pairs discordant for the exposure; MZ = the mean difference in the magnitude of association within monozygotic twin pairs discordant for the exposure. Scenario 1: the magnitude of the association is similar across all groups (regardless of shared genes or (early) environment), inferring possible causality. Scenario 2: the association between exposure and outcome is entirely inferred by genetic confounding, as the association within same-sex DZ twins (who share 50% of their genetic material) is intermediate, and the association within MZ twins (who share 100% of their genetic material) is zero. Scenario 3: the association between exposure and outcome is entirely inferred by environmental confounding, as the association within same-sex DZ and MZ twins (who share 100% of their (early) environment) is zero. Scenario 4: the association between exposure and outcome is partly inferred by both genetic and environmental confounding. Based on Gonggrijp et al. (2023).

estimates in discordant[4] MZ and same-sex DZ twin pairs control for age, sex and varying degrees of familial confounding, thus helping to differentiate between causation and confounding (Eaton et al., 2012; Mosteller & Boruch, 2004; Shadish, Cook, & Campbell, 2002).

The CTCD consists of three sub-models, testing the association between an exposure and outcome: (1) at the population-level (using all data without considering zygosity/twin pair discordance), (2) within DZ same-sex twin pairs discordant for the exposure, and (3) within MZ twin pairs discordant for the exposure (Gonggrijp et al., 2023). The mean difference in the magnitude of the association between exposed and unexposed individuals in these sub-models can be compared to infer the contributions of unmeasured genetic and shared (early) environmental confounders and, thus, indirectly infer possible causation. Figure 3 further illustrates this. Scenario 1 points to possible causation, as the mean difference in the magnitude of the association between exposed and unexposed individuals is equal in all three sub-model (regardless of overlap in genes/shared (early) environment within the DZ and MZ twin pairs). Scenario 2 points to genetic confounding, as the mean difference in the magnitude of association between exposed and unexposed individuals is intermediate within DZ twin pairs (50% overlap in genes) and zero within MZ twins (100% overlap in genes). Scenario 3 points to environmental confounding, as the mean difference in the magnitude of association between exposed and unexposed individuals is zero within DZ and MZ twin pairs (both 100% overlap in shared (early) environment). Scenario 4 points to a combination of genetic and environmental confounding, given that the mean difference between exposed and unexposed individuals is not zero in all three sub-models and reduces depending on the degree of genetic overlap.

[4]Discordance refers to the fact that one member of the twin pair is exposed while the other person is unexposed to an exposure of interest.

Procedure and participants

We used data from the BLTS, 25UP project (Mitchell et al., 2019). The 25UP project utilized questionnaires to collect information on mental health conditions, general/physical health, psychosocial items, and general demographic information. Data were collected between 2016 and 2018, and participants included twins and their non-twin siblings from South-East Queensland (Australia). Recruitment details have been reported by Mitchell et al. (2019). For this study, data from complete twin pairs were used ($n_{total\ individuals}$ = 1,512, including 341 MZ, 217 DZ same-sex and 198 DZ opposite-sex twin pairs).

Measures (self-reported)

For the main analyses, we used data on sweet/savoury snack intake (dichotomized) (Mitchell et al., 2019), fruit/vegetable intake (dichotomized) (Mitchell et al., 2019), physical activity (continuous and dichotomized) (IPAQ Research Committee, 2005) and symptoms of depression/anxiety (continuous and dichotomized) (Andrews & Slade, 2001). Additionally, age and gender (male/female) were used. For descriptive purposes, we also used information on living situation, study/work status, highest level of education, current relationship status, BMI (kg/m^2), and overall perceived physical and mental health. Supplementary Material D includes additional information.

Selection of twins per sub-model

For sub-model 1 (population-level), we selected all available data without considering zygosity or twin pair con/discordance on the exposure of interest (dichotomized sweet/savoury snack intake, fruit/vegetable intake, physical activity and symptoms of depression/anxiety). For sub-model 2, we selected data from DZ same-sex twin pairs who were discordant on the exposure of interest (within one pair: one twin exposed and one twin unexposed to the exposure of interest). For sub-model 3, we selected data from MZ twin pairs who were discordant on the exposure of interest.

Statistical analyses

Descriptive statistics were used to explore all measures. Next, the CTCD was utilized by running linear (lmer) and logistic (glmer) mixed-effects models using the lme4 package (Bates et al., 2009a). We fitted six mixed-effects models, each including the three sub-models (mentioned above), including one diet/physical activity measure and the combined measure for symptoms of depression/anxiety (Supplementary Table ST3). In the results, we refer to these models as unadjusted models. Moreover, we fitted eight mixed-effects models to adjust the unadjusted models for either diet (when unadjusted models included physical activity) or physical activity (when unadjusted models included diet), taking into account potential confounding by diet/physical activity (Supplementary Table ST4). In case this variable was continuous, the variable was standardized. Again, each model consisted of three sub-models and each sub-model included one diet measure, physical activity, and symptoms of depression/anxiety. In the results, we refer to these models as adjusted models. In all models, family clustering was taken into account (by adding family as a random effect). Sub-models 1 were corrected for age and gender, Supplementary Material E provides additional information on model settings, calculations of *p*-values and confidence intervals. To investigate potential causal effects, the magnitude, direction and error margin of the association between exposure and outcome across the three sub-models in each model were studied.

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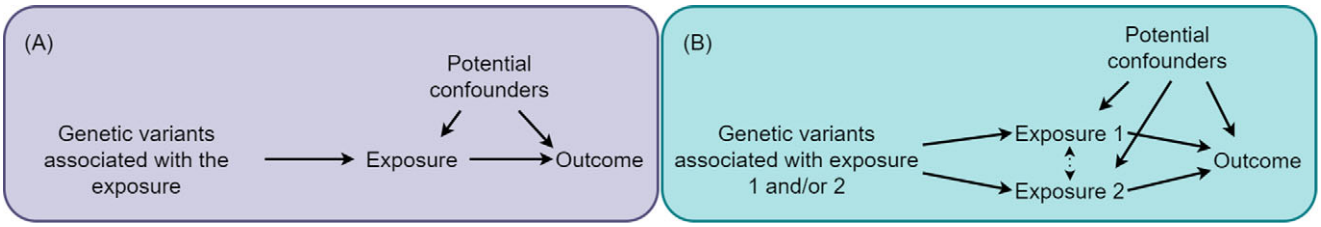

Figure 4. Directed acyclic graphs for (A) Univariable mendelian randomization and (B) Multivariable mendelian randomization.

Sensitivity analyses were performed for all models to assess the reliability of the chosen discordance thresholds (Supplementary Material D). In these analyses, slightly different discordance criteria were used (given that no set cut-offs were available).

Study 3: mendelian randomization

In two-sample univariable Mendelian randomization (UVMR), genetic variants (single nucleotide polymorphisms; SNPs) robustly associated with an exposure are leveraged as instrumental variables to estimate the potential population-level causal effect of an exposure on an outcome (Davey Smith & Ebrahim, 2003), see Figure 4A. The basis of MR is built on Mendel's laws of random segregation[5] and independent assortment[6] (Evans & Davey Smith, 2015). MR is less prone to unmeasured confounding or reverse causation than observational studies as genetic variants are randomly assigned during conception and typically unaffected by environmental/lifestyle factors later in life (Carnegie et al., 2020; Gupta, Walia, & Sachdeva, 2017). To gain valid estimates, several core assumptions need to be satisfied: (1) the genetic instrumental variable is robustly associated with the exposure (relevance assumption), (2) there is no confounding between the genetic instrumental variable and the outcome (independence assumption), and (3) the instrumental variable is not associated with the outcome other than via the exposure (exclusion restriction) (Lawlor, Harbord, Sterne, Timpson, & Davey Smith, 2008). Multiple MR methods exist that evaluate these assumptions. The consistency of effect estimates across these methods strengthens the evidence.

Multivariable Mendelian randomization (MVMR) is an extension of UVMR which facilitates using multiple exposures (e.g., diet and physical activity) to estimate the direct independent effects of multiple exposures on an outcome (Burgess & Thompson, 2015), conditional on the effect of the other exposure on the outcome (Figure 4B).

Data sources

Publicly available summary statistics from GWASs (European ancestry) were used to select SNPs associated with sweet snack intake (Elsworth et al., 2020), savoury snack intake (Elsworth et al., 2020), fruit intake (Cole, Florez, & Hirschhorn, 2020), vegetable intake (Elsworth et al., 2020), physical activity (Klimentidis et al., 2018), depression[7] (Howard et al., 2019), and anxiety[8] (Otowa et al., 2016). See Supplementary Table ST5 and Supplementary Material F for information per phenotype.

Statistical analyses

Supplementary Material G explains the SNPs selection and Supplementary Table ST6 (UVMR) and ST7 (MVMR) contain all selected SNPs. First, twenty UVMR analyses were run using the TwoSampleMR package (Hemani, Zheng, et al., 2018). Each model included one diet/physical activity and one mental health measure (Supplementary Table ST8). The inverse-variance weighted (IVW) method was used as the main method (Burgess, Butterworth, & Thompson, 2013), providing valid estimates when horizontal pleiotropy is balanced or absent (Hemani, Bowden, & Davey Smith, 2018). Next, several sensitivity analyses (mostly available in the TwoSampleMR package) were performed (Supplementary Material H): MR-Egger (Bowden, Davey Smith, & Burgess, 2015), weighted median (Bowden, Davey Smith, Haycock, & Burgess, 2016), simple mode (Hartwig, Davey Smith, & Bowden, 2017), weighted mode (Hartwig et al., 2017), MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) (Verbanck, Chen, Neale, & Do, 2018), MR using the robust adjusted profile score (MR-RAPS) (Zhao, Wang, Hemani, Bowden, & Small, 2018)) and, MRlap (Mounier & Kutalik, 2023). The mean *F*-statistic was calculated to evaluate instrument strength ($F < 10$ may indicate a weak instrument (Burgess & Thompson, 2011)), IVW and MR-Egger heterogeneity tests and MR-Egger pleiotropy tests were performed to assess horizontal and directional pleiotropy, respectively (Hemani, Zheng, et al., 2018).

Moreover, twenty-four MVMR analyses were run using the TwoSampleMR package (Hemani, Zheng, et al., 2018). This extension of the UVMR allows for adjustment of potential confounders, in this case adjusting the UVMR analyses including diet for physical activity and adjusting the UVMR analyses including physical activity for diet. Each model included one diet measure, physical activity and one mental health measure (Supplementary Table ST9). The MVMR-IVW method was used as the main method (Sanderson, Davey Smith, Windmeijer, & Bowden, 2018) and several sensitivity analyses were performed (Supplementary Material H): MVMR-Egger[9] (Rees, Wood, & Burgess, 2017) and MVMR-PRESSO (Verbanck et al., 2018). The *F*-statistic was calculated to evaluate instrument strength and pleiotropy tests were performed using the MVMR package to assess heterogeneity (Sanderson, Spiller, & Bowden, 2021). For both UVMR and MVMR, the magnitude,

[5]Mendel's law of random segregation: alleles separate at meiosis, and a randomly selected allele is passed from the parents to the offspring (Evans & Davey Smith, 2015).

[6]Mendel's law of independent assortment: alleles for separate traits are transmitted independently of one another (Evans & Davey Smith, 2015).

[7]Including three depression-related phenotypes: broad depression, probable major depressive disorder (MDD), and International Classification of Diseases (ICD, version 9 or 10)-coded MDD.

[8]Including lifetime diagnosis for any of the five core anxiety disorders: generalized anxiety disorder, panic disorder, social phobia, agoraphobia, and specific phobias.

[9]MVMR-Egger was performed twice, once oriented so that the exposure 1 SNPs were positive and once oriented so that exposure 2 SNPs were positive (Sanderson et al., 2018). For each exposure, only the results for the relevant (positive) orientation have been reported.

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Table 2. Triangulated evidence of all unadjusted/univariable analyses

Causal path	Study 1: random intercept-cross lagged panel models[a]				Study 2: co-twin control design[b]			Study 3: univariabele mendelian randomization[c]	
	b W1 → W2	SE	*b* W2 → W3	SE	Group	b	95% CI	N SNPs	OR (95% CI)
Sweet snack intake → Depression	−0.05	0.06	0.03	0.07	PL	1.03	0.34, 1.69	21	1.00 (0.83, 1.20)
Sweet snack intake → Anxiety	−0.02	0.03	0.00	0.03	DZ	0.28	−1.10, 1.70	12	1.41 (0.39, 5.14)
Savoury snack intake → Depression	0.03	0.11	0.06	0.13	MZ	0.17	−1.16, 1.50	15	1.04 (0.85, 1.27)
Savoury snack intake → Anxiety	−0.07	0.05	−0.07	0.05				11	0.61 (0.14, 2.57)
Depression → Sweet snack intake	0.03	0.04	0.00	0.04	PL	0.40	0.11, 0.67	72	0.99 (0.96, 1.02)
Anxiety → Sweet snack intake	−0.07	0.08	0.05	0.10	DZ	0.09	−0.70, 0.89	15	1.00 (0.99, 1.01)
Depression → Savoury snack intake	0.04	0.02	0.02	0.02	MZ	0.20	−0.50, 0.91	72	1.00 (0.97, 1.02)
Anxiety → Savoury snack intake	−0.03	0.05	0.00	0.04				15	1.01 (0.99, 1.02)
Fruit intake → Depression	0.21	0.13	0.10	0.14	**PL**	**1.84**	**1.19, 2.50**	79	0.93 (0.83, 1.05)
Fruit intake → Anxiety	0.08	0.06	0.01	0.06	**DZ**	**1.33**	**−0.57, 3.17**	**76**	**1.99 (1.19, 3.34)**
Vegetable intake → Depression	0.08	0.09	−0.03	0.08	**MZ**	**2.06**	**0.98, 3.25**	19	1.06 (0.86, 1.30)
Vegetable intake → Anxiety	0.05	0.04	−0.02	0.03				14	1.12 (0.22, 5.66)
Depression → Fruit intake	0.13	0.02	0.02	0.02	**PL**	**0.56**	**0.30, 0.79**	73	1.00 (0.95, 1.04)
Anxiety → Fruit intake	−0.03	0.04	0.03	0.05	**DZ**	**0.46**	**−0.28, 1.15**	19	1.00 (0.99, 1.00)
Depression → Vegetable intake	0.00	0.03	0.04	0.03	**MZ**	**0.66**	**0.03, 1.32**	72	0.99 (0.97, 1.01)
Anxiety → Vegetable intake	−0.03	0.07	−0.04	0.08				15	1.00 (0.99, 1.01)
Physical activity → Depression	−0.01	0.01	0.01	0.01	PL	1.05	0.19, 1.88	19	1.08 (0.81, 1.43)
Physical activity → Anxiety	−0.01	0.04	0.04	0.04	DZ	0.12	−2.43, 2.67	17	1.54 (0.54, 4.33)
					MZ	0.43	−1.31, 2.14		
Depression → Physical activity	0.09	0.27	−0.52	0.29	**PL**	**−4.29**	**−7.90, −0.70**	72	0.99 (0.96, 1.03)
Anxiety → Physical activity	0.02	0.06	−0.02	0.06	**DZ**	**−7.03**	**−16.19, 1.84**	15	0.99 (0.99, 1.00)
					MZ	**−9.46**	**−16.40, −2.20**		

Note. Findings highlighted in bold present pathways were support was found for that potential causal path. *b* = unstandardized estimate, *SE* = standard error, b = regression coefficient for the exposure, 95% CI = 95% confidence interval, OR = odds ratio, SNPs = single nucleotide polymorphisms, W1 = Wave 1, W2 = Wave 2, W3 = Wave 3, PL = population-level, MZ = monozygotic twin pairs, DZ = same-sex dizygotic twin pairs.

[a]Only the cross-lagged within-person effects have been presented. Full results can be found in Supplementary Tables ST12–ST29.

[b]Only the regression coefficients of the exposure of interest have been presented. Full results can be found in Supplementary Tables ST32–ST45. In Study 2, combined measures of sweet and savoury snack intake, fruit and vegetable intake, and depression and anxiety were used.

[c]Only the results from the inverse-variance weighted (IVW) method have been presented. Full results can be found in Supplementary Tables ST47–48.

direction and confidence intervals of the odds ratios (ORs) were studied to evaluate potential causal effects.

Results

Triangulated evidence

Table 2 provides a summary of all effect estimates and the magnitude, direction and margin of error of the effect estimates for Studies 1, 2 and 3 for the analyses performed with one lifestyle behaviour (diet/physical activity) and one mental health measure (depression/anxiety); unadjusted models. The findings of most assessed pathways across the three methods did not provide strong support for causal pathways between diet/physical activity and depression/anxiety (or vice versa). This is reflected by the magnitude of the effect estimates which were considerably small, pointing to weak or non-existing causal pathways. Converge for all three methods was observed for the models testing bidirectional causal effects between sweet/savoury snack intake and depression/anxiety, and the models testing causal effects of physical activity on depression/anxiety. The convergence across the three methods provides greater confidence in the conclusions and absence of causal pathways.

Some divergence was observed in the models assessing bidirectional causal effects between fruit/vegetable intake and depression/anxiety. Study 1 did not provide support (i.e., the (un)standardized betas are close to zero), Study 2 did provide support (i.e., the regression coefficients across the three sub-models are roughly equal), Study 3 did not provide support in most assessed pathways (i.e., the ORs are close to one), except for the pathway fruit intake on anxiety (OR = 1.99, 95% CI = 1.19–3.34). Additionally, some divergence was observed in the models assessing causal effects of depression/anxiety on physical activity. Studies 1 and 3 did not provide support (i.e., in Study 1 the (un)standardized betas are close to zero and in Study 3 the OR are close to one), while Study 2 did provide support (i.e., the regression coefficients of the MZ/DZ sub-models are larger than of the population-level submodel). A further reflection on how potential biases might have impacted these findings and contributed to the divergence is required, and has

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been provided in the discussion. Below, we discuss the findings from Studies 1, 2 and 3 in more detail.

Supplementary Table ST10 provides a summary of effect estimates and the magnitude, direction and margin of error of the effect estimates from Studies 1, 2 and 3 for the analyses were the causal pathways were adjusted for a potential confounder (the other lifestyle behaviour; diet or physical activity); adjusted models. Conclusions were in line with the unadjusted models.

Study 1: random intercept cross-lagged panel models

Sample description and intraclass correlations (ICC)

At Wave 1, the mean age of the sample was 23 years (*SD* = 4.2), 72% were female, 86% were not living alone, and 49% were single. The mean BMI score was 22.5 kg/m^2 (*SD* = 3.5) and overall physical and mental health was perceived as very good or excellent by 32% and 25%, respectively. Descriptives for Wave 2 and 3 were similar (Supplementary Table ST11).

The ICC for depressive symptoms was 0.63, which shows that 63% of the variance in the three measurements of depressive symptoms can be explained by differences between persons (i.e., stable trait level) and the remaining 37% of the variance can be explained by fluctuations within persons (i.e., change over time). For anxiety symptoms the ICC was 0.53, for sweet snack intake the ICC was 0.64, the ICC for savoury snack intake was 0.64, the ICC for fruit intake was 0.73, the ICC for vegetable intake was 0.66, and the ICC for physical activity was 0.52.

Random intercept cross-lagged panel models

Table 3 shows all within-person cross-lagged effects. Supplementary Tables ST12-ST29 provide all estimates. The fit indices per model were acceptable (Supplementary Table ST30).

The within-person cross-lagged effects (unadjusted models) did not provide support for causal effects of diet or physical activity on depressive or anxiety symptoms, given that the (un)standardized estimates were close to zero with relatively large error margins. Similarly, the within-person cross-lagged effects (unadjusted models) did not provide support for causal effects of depressive or anxiety symptoms on diet or physical activity. This means that participants' changes in depressive/anxiety symptoms, relative to their own expected scores, were not predicted by participants' diet/physical activity at the previous wave (or vice versa). This pattern was consistent with the adjusted models and sensitivity analyses.

Study 2: co-twin control design

Sample description

The mean age of the total sample was 30 years (SD = 4.2), 62% were male, 53% lived with a partner (and/or children), 66% worked full-time, and 70% had a relationship (Supplementary Table ST31). The mean BMI score was 24.7 kg/m^2 (*SD* = 4.8) and overall physical and mental health was perceived as (very) good by 76% and 72%, respectively. A total of 64% of the participants were "exposed" to sweet/savoury snack intake, 47% to insufficient fruit/vegetable intake, 19% to physical inactivity and 29% to symptoms of depression/anxiety.

Mixed-effects models

All results are reported in Supplementary Tables ST32-ST45 and patterns in regression coefficients are shown in Figure 5 and compared to the scenarios in Figure 3. Information on the DZ/MZ discordance rate per model has been provided in Supplementary Table ST46.

Our results do not support causal pathways between sweet/savoury snack intake and symptoms of depression/anxiety (Figure 5A/5B). The association between exposure and outcome was present at the population-level (unadjusted models) but not within DZ/MZ twin pairs, and the regression coefficients within DZ/MZ twins were roughly equal with overlapping error bars. This suggests that Scenario 3 (confounding by shared (early) environment) most closely represents the observed patterns in regression coefficients (unadjusted/adjusted models). Although this pattern was observed in some sensitivity analyses, these findings were not fully consistent with the sensitivity analyses (Supplementary Tables ST32-ST33, ST38-ST39).

Our results support causal pathways between fruit/vegetable intake and symptoms of depression/anxiety (Figure 5C/5D). The patterns in regression coefficients (unadjusted/adjusted models) most closely represent Scenario 1, as the regression coefficients across the three groups were roughly equal. In most sub-models, the association between exposure and outcome was present (except for one within MZ and all within DZ twins sub-models). These findings were consistent with the sensitivity analyses (Supplementary Tables ST34-ST35, ST40-ST41).

Our results provided mixed support for causal pathway between symptoms of depression/anxiety and physical activity. In the models where symptoms of depression/anxiety were the exposure and physical activity was the outcome (Figure 5F), the pattern in regression coefficients (unadjusted/adjusted models) between the three groups most closely represents Scenario 1, supporting causal effects. In most sub-models, the association between exposure and outcome was present (except the population-level model adjusted for fruit/vegetable intake and all within DZ models). These findings were consistent with the sensitivity analyses (Supplementary Tables ST37, ST44-ST45). In the models where physical activity was the exposure and symptoms of depression/anxiety were the outcome (Figure 5E), the pattern in regression coefficients (unadjusted/adjusted models) between the three groups most closely represents Scenario 3 (confounding by shared (early) environment). The pattern observed in the sensitivity analyses pointed more towards genetic confounding (Scenario 2) (Supplementary Tables ST36, ST42-ST43).

Study 3: mendelian randomization

Univariable and multivariable mendelian randomization

Supplementary Tables ST47-ST48 provide all UVMR and MVMR results. Figure 6 presents results from the IVW method. UVMR did not provide support for the hypothesis that the genetic liability for unhealthy diet/physical inactivity causally increases the risk of depression (Figure 6A) or anxiety (Figure 6C), given that most of the ORs were close to one with confidence intervals including one. Likewise, our results do not support the hypothesis that the genetic liability of depression (Figure 6B) or anxiety (Figure 6D) causally increases unhealthy diet/physical inactivity. One exception, UVMR does suggest fruit intake might causally increase the risk of anxiety (Model 11A$_{UVMR}$; OR$_{IVW}$ = 1.99; 95% confidence interval (CI) = 1.19 to 3.34; p = .009). This effect was consistent across all sensitivity analyses (Supplementary Table ST47). The UVMR IVW (p = .023) and MR-Egger (p = .019) heterogeneity tests for Model 11A did provide evidence for heterogeneity (Supplementary Table ST49), while the MR-Egger pleiotropy test (p = .918) did not provide evidence for directional pleiotropy (Supplementary Table ST50). The MVMR findings were in line with the UVMR findings (Supplementary Tables ST48, ST51). Most instruments were sufficiently strong (F-statistics >10; Supplementary Tables ST52 (UVMR) and ST53 (MVMR)).

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Table 3. Results within-person cross-lagged effects

	Unadjusted models								Adjusted models							
	W1 → W2				W2 → W3				W1 → W2				W2 → W3			
Pathways	*b*	*SE*	β	*p*	*b*	*SE*	β	*p*	*b*	*SE*	β	*p*	*b*	*SE*	β	*p*
Sweet snack intake → Depressive symptoms[a]	−0.05	0.06	−0.04	.401	0.03	0.07	0.03	.610	−0.06	0.06	−0.05	.334	0.03	0.07	0.03	.621
Depressive symptoms → Sweet snack intake[a]	0.03	0.04	0.03	.543	0.00	0.04	0.01	.920	0.02	0.04	0.02	.676	−0.01	0.04	−0.02	.790
Sweet snack intake → Anxiety symptoms[a]	−0.02	0.03	−0.03	.552	0.00	0.03	0.01	.896	−0.02	0.03	−0.03	.538	0.00	0.03	0.01	.881
Anxiety symptoms → Sweet snack intake[a]	−0.07	0.08	−0.04	.410	0.05	0.10	0.03	.656	−0.08	0.09	−0.04	.336	0.03	0.10	0.02	.746
Savoury snack intake → Depressive symptoms[a]	0.03	0.11	0.01	.822	0.06	0.13	0.03	.615	0.00	0.11	0.00	.978	0.06	0.13	0.03	.622
Depressive symptoms → Savoury snack intake[a]	0.04	0.02	0.08	.094	0.02	0.02	0.05	.325	0.03	0.02	0.07	.161	0.01	0.02	0.03	.484
Savoury snack intake → Anxiety symptoms[a]	−0.07	0.05	−0.08	.116	−0.07	0.05	−0.08	.198	−0.08	0.05	−0.08	.098	−0.07	0.05	−0.08	.200
Anxiety symptoms → Savoury snack intake[a]	−0.03	0.05	−0.02	.592	0.00	0.04	0.00	.968	−0.04	0.05	−0.03	.450	0.00	0.04	0.00	.932
Fruit intake → Depressive symptoms[a]	0.21	0.13	0.08	.120	0.10	0.14	0.05	.359	0.22	0.13	0.08	.105	0.12	0.14	0.05	.412
Depressive symptoms → Fruit intake[a]	0.13	0.02	−0.04	.483	0.02	0.02	0.05	.410	0.00	0.02	−0.01	.817	0.02	0.02	0.06	.293
Fruit intake → Anxiety symptoms[a]	0.08	0.06	0.07	.170	0.01	0.06	0.01	.871	0.08	0.06	0.07	.178	0.00	0.06	0.00	.972
Anxiety symptoms → Fruit intake[a]	−0.03	0.04	−0.03	.541	0.03	0.05	0.04	.555	−0.01	0.04	−0.02	.752	0.03	0.05	0.04	.522
Vegetable intake → Depressive symptoms[a]	0.08	0.09	0.05	.343	−0.03	0.08	−0.02	.687	0.09	0.09	0.05	.325	−0.03	0.08	−0.02	.723
Depressive symptoms → Vegetable intake[a]	0.00	0.03	0.01	.910	0.04	0.03	0.07	.253	0.00	0.03	0.00	.969	0.04	0.04	0.06	.315
Vegetable intake → Anxiety symptoms[a]	0.05	0.04	0.06	.224	−0.02	0.03	−0.03	.584	0.05	0.04	0.06	.221	−0.02	0.03	−0.03	.590
Anxiety symptoms → Vegetable intake[a]	−0.03	0.07	−0.02	.629	−0.04	0.08	−0.03	.606	−0.04	0.07	−0.03	.586	−0.05	0.08	−0.04	.545
Physical activity → Depressive symptoms[b]	−0.01	0.01	−0.07	.175	0.01	0.01	0.04	.467	Not presented here as multiple adjusted models were estimated.							
Depressive symptoms → Physical activity[b]	0.09	0.27	0.02	.734	−0.52	0.29	−0.10	.075								
Physical activity → Anxiety symptoms[b]	−0.01	0.04	−0.01	.829	0.04	0.04	0.04	.367								
Anxiety symptoms → Physical activity[b]	0.02	0.06	0.02	.701	−0.02	0.06	−0.01	.794								

Note. Other model estimates (between-person covariance random intercepts, within-person stability (or autoregressive) effects, within-person concurrent covariance, and time-invariant covariate associations of gender and age) per model are presented in Supplementary Tables S11-S28. W1 = Wave 1, W2 = Wave 2, W3 = Wave 3, b = unstandardized estimate, β = standardized estimate, *SE* = standard error.

[a]Adjusted models were corrected for physical activity.

[b]Adjusted models were corrected for all diet measures and these cross-lagged effects have been presented in Supplementary Tables S22–S29.

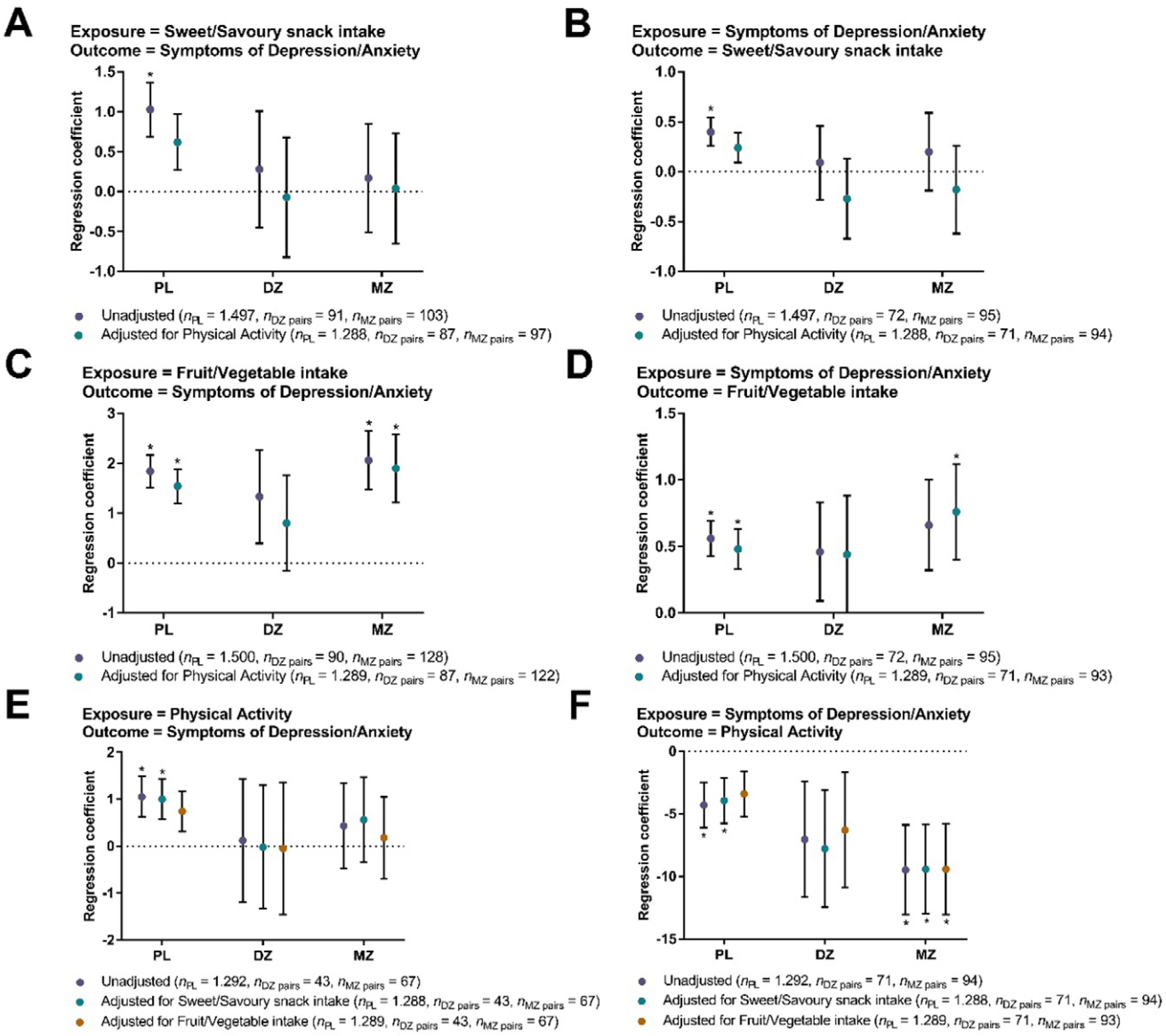

Figure 5. Results mixed-effects models - patterns in regression coefficients at population-level (PL), within dizygotic (DZ) same-sex twins and within monozygotic (MZ) twins. Asterisks represent associations between exposure and outcome per subgroup where $p < .05$.

Discussion

Principal findings

Triangulating evidence from three distinct methods did not provide compelling support for causal effects of diet/physical activity on depression/anxiety (or vice versa). These conclusions remained when adjusting the analyses including diet and depression/anxiety for physical activity and when adjusting the analyses including physical activity and depression/anxiety for diet.

Comparison with previous studies

Sweet/savoury snack intake and depression/anxiety

Convergent evidence from our triangulation framework did not support causal effects of sweet/savoury snack intake on depression/anxiety (both in unadjusted and adjusted models). No previous studies focused on these specific pathways, although our results are in line with an MR study that did not find a causal effect of "Never eating sugar or foods/drinks containing sugar" on depression (Du et al., 2023). In contrast, meta-analyses of prospective/cohort studies did support causal effects of Western-style dietary patterns (including high consumption of sweets), sugar-sweetened beverages and ultra-processed foods on increased depression/anxiety (Lane et al., 2024; Li et al., 2017; Y. Wang et al., 2022). These effects could be enhanced by unmeasured confounders or differences could be explained by using different measurements and including participants with different ancestries or from different cultures (with different eating habits).

Convergent evidence from our triangulation framework did not support causal effects of depression/anxiety on sweet/savoury snack intake (both in unadjusted and adjusted models). This is in line with some studies focusing on the relationship between sugar intake and negative mood (Cardi, Leppanen, & Treasure, 2015; Knüppel, Shipley, Llewellyn, & Brunner, 2017), although it is in contrast with previous work indicating that some individuals cope with negative emotions by overeating energy-dense, nutrient-poor and palatable

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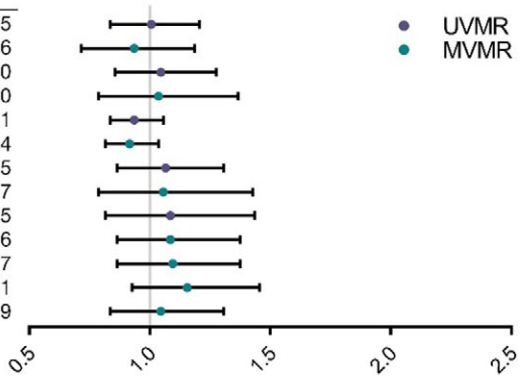
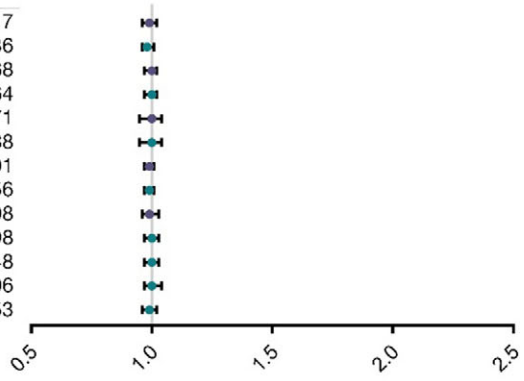
(A)

Exposure	Outcome	*n* snp	OR	95% CI	*p*
Sweet snack intake	Depression	21	1.00	0.83, 1.20	.975
with adj. for physical activity		40	0.93	0.74, 1.18	.556
Savoury snack intake	Depression	15	1.04	0.85, 1.27	.720
with adj. for physical activity		34	1.03	0.78, 1.36	.840
Fruit intake	Depression	79	0.93	0.83, 1.05	.261
with adj. for physical activity		98	0.91	0.81, 1.03	.144
Vegetable intake	Depression	19	1.06	0.86, 1.30	.605
with adj. for physical activity		39	1.05	0.78, 1.42	.727
Physical activity	Depression	19	1.08	0.81, 1.43	.615
with adj. for sweet snack intake		40	1.08	0.86, 1.37	.506
with adj. for savoury snack intake		34	1.09	0.86, 1.37	.497
with adj. for fruit intake		98	1.15	0.92, 1.45	.231
with adj. for vegetable intake		39	1.04	0.83, 1.30	.709



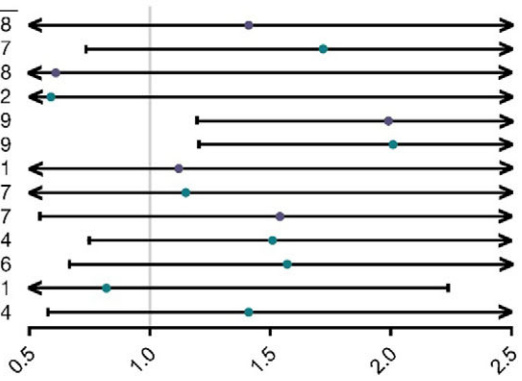
(B)

Exposure	Outcome	*n* snp	OR	95% CI	*p*
Depression	Sweet snack intake	72	0.99	0.96, 1.02	.417
with adj. for physical activity		91	0.98	0.96, 1.01	.236
Depression	Savoury snack intake	72	1.00	0.97, 1.02	.768
with adj. for physical activity		91	1.00	0.97, 1.02	.764
Depression	Fruit intake	73	1.00	0.95, 1.04	.871
with adj. for physical activity		91	1.00	0.95, 1.04	.888
Depression	Vegetable intake	72	0.99	0.97, 1.01	.401
with adj. for physical activity		91	0.99	0.97, 1.01	.456
Depression	Physical activity	72	0.99	0.96, 1.03	.708
with adj. for sweet snack intake		93	1.00	0.97, 1.03	.798
with adj. for savoury snack intake		87	1.00	0.97, 1.03	.748
with adj. for fruit intake		151	1.00	0.97, 1.04	.906
with adj. for vegetable intake		91	0.99	0.96, 1.02	.653



(C)

Exposure	Outcome	*n* snp	OR	95% CI	*p*
Sweet snack intake	Anxiety	12	1.41	0.39, 5.14	.598
with adj. for physical activity		29	1.72	0.73, 4.05	.227
Savoury snack intake	Anxiety	11	0.61	0.14, 2.57	.498
with adj. for physical activity		28	0.59	0.19, 1.85	.372
Fruit intake	Anxiety	76	1.99	1.19, 3.34	.009
with adj. for physical activity		93	2.01	1.20, 3.36	.009
Vegetable intake	Anxiety	14	1.12	0.22, 5.66	.891
with adj. for physical activity		31	1.15	0.29, 4.53	.847
Physical activity	Anxiety	17	1.54	0.54, 4.33	.417
with adj. for sweet snack intake		29	1.51	0.74, 3.06	.264
with adj. for savoury snack intake		28	1.57	0.66, 3.72	.316
with adj. for fruit intake		93	0.82	0.30, 2.24	.701
with adj. for vegetable intake		31	1.41	0.57, 3.46	.464



(D)

Exposure	Outcome	*n* snp	OR	95% CI	*p*
Anxiety	Sweet snack intake	15	1.00	0.99, 1.01	.736
with adj. for physical activity		32	1.00	0.99, 1.01	.962
Anxiety	Savoury snack intake	15	1.01	0.99, 1.02	.389
with adj. for physical activity		32	1.00	0.99, 1.02	.434
Anxiety	Fruit intake	19	1.00	0.99, 1.00	.375
with adj. for physical activity		32	1.00	0.99, 1.02	.620
Anxiety	Vegetable intake	15	1.00	0.99, 1.01	.725
with adj. for physical activity		32	1.00	0.99, 1.01	.701
Anxiety	Physical activity	15	0.99	0.99, 1.00	.276
with adj. for sweet snack intake		27	0.99	0.99, 1.00	.215
with adj. for savoury snack intake		26	1.00	0.99, 1.00	.256
with adj. for fruit intake		89	0.99	0.98, 1.00	.113
with adj. for vegetable intake		29	0.99	0.99, 1.00	.221

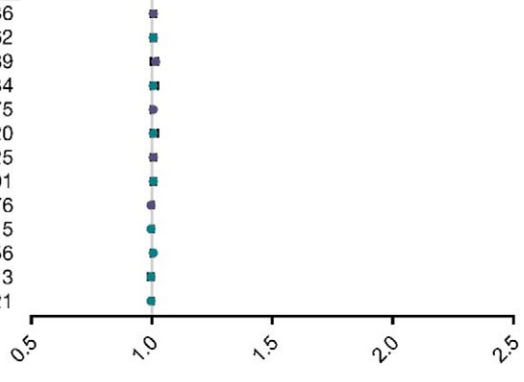


Figure 6. Results of the univariable and multivariable mendelian randomization.

Note. (A) Exposure = diet (sweet snack intake, savoury snack intake, fruit intake, vegetable intake) or physical activity. Outcome = depression. (B) Exposure = depression. Outcome = diet or physical activity. (C) Exposure = diet or physical activity. Outcome = anxiety. (D) Exposure = anxiety. Outcome = diet or physical activity. Method = Inverse variance weighted. UVMR = Univariable Mendelian randomization; MVMR = Multivariable Mendelian randomization; OR = odds ratio; 95% CI = 95% confidence interval; SNP = single nucleotide polymorphism.

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foods (Burnatowska, Surma, & Olszanecka-Glinianowicz, 2022; Dakanalis et al., 2023). Assessment of foods (for example high in sugar) might not reflect an individual's general diet, which requires more nuanced assessments to shed new light on potential causal effects.

Fruit/vegetable intake and depression/anxiety

Consistent in the unadjusted and adjusted models, Study 1 did not support causal effects of fruit/vegetable intake on depression/anxiety, while Study 2 did support causal effects between increased fruit intake and increased depression/anxiety and Study 3 did support a causal effect from increased fruit/vegetable intake to increased anxiety (Study 3). Contradicting insights were also observed in previous work (Appleton et al., 2024; T. T. Chen et al., 2022; Liu et al., 2016; Molendijk et al., 2018; Saghafian et al., 2018; Tuck et al., 2019; Q. Wang et al., 2024; Yan et al., 2023). Possibly, the time intervals in Study 1 (6–12 months) were too long to detect causation (Singh et al., 2024). Additionally, the variance in the study measures across all waves that could be explained by fluctuations within persons varied between 27% to 48%, which might limit the opportunity to detect possible temporal associations in Study 1.

Studies 1 and 3 did not provide support for causal effects of depression/anxiety on fruit/vegetable intake while Study 2 support causal effects between depression/anxiety and fruit/vegetable intake (both in unadjusted and adjusted models). When comparing these findings to previous literature, only two MR studies were identified which did not support a causal effect of depression on fruit intake and/or vegetable intake (T. T. Chen et al., 2022; Yan et al., 2023).

Possibly, limitations of the designs used in Studies 2 and 3 could explain the suggestive findings mentioned above. E.g., a small sample size, arbitrary discordance definitions or confounding by non-shared factors in Study 2 (Frisell, Öberg, Kuja-Halkola, & Sjölander, 2012) and potential violations of the MR assumptions (e.g., horizontal pleiotropy[10]) in Study 3 (Davies et al., 2019; Hemani, Bowden, & Davey Smith, 2018; Spiga et al., 2023). This emphasizes the need for triangulation and developing more complex methods where the strengths of different designs are combined (e.g., within-family MR).

Physical activity and depression/anxiety

Convergent evidence from our triangulation framework did not support causal effects of physical activity on depression/anxiety (both in unadjusted and adjusted models). Although this is in line with some studies (various designs, mostly using self-report) (Choi et al., 2019; De Moor et al., 2008; Iob et al., 2023; Moreno-Peral et al., 2022; Pasman et al., 2024), most existing studies do provide support for a protective causal effect of physical activity on depression and/or anxiety risk (Choi et al., 2019; Iob et al., 2023; Mammen & Faulkner, 2013; McDowell et al., 2019; Pearce et al., 2022; Rebar et al., 2015; Schuch et al., 2019; Schuch et al., 2018). Some of these studies (using MR) found different results for self-reported or accelerometer-based physical activity (Choi et al., 2019; Iob et al., 2023), which suggests future studies could explore this difference further using various other designs.

No support for causal effects of depression/anxiety on physical activity was provided by Studies 1 and 3 while Study 2 did support possible causal effects between increased depression/anxiety and decreased physical activity (both in unadjusted and adjusted models). Mixed results were also observed in previous work. For instance, a systematic review (longitudinal studies) showed that depression was associated with being less active over time (Roshanaei-Moghaddam et al., 2009). The authors suggested this might be due to lower motivation and energy to exercise. A recent MR study also found a causal effect of depression on decreased accelerometer-based physical activity (Pasman et al., 2024). In contrast, this was not found in other MR studies (including both self-reported and accelerometer-based physical activity) (Choi et al., 2019; Iob et al., 2023). Pasman et al. (2024) used a more recent and larger GWAS for depression (Als et al., 2023) (>1.3 million individuals including 371,184 cases; identifying 243 risk loci) compared to Choi et al. (2019) and Iob et al. (2023) who used a smaller GWAS (Wray et al., 2018) (including 344,901 controls and 135,458 cases; identifying 44 risk loci). Consequently, this may explain the differences in findings and suggest sufficient sample sizes are needed in future studies. Alternatively, other potential biases (described above) might also contribute to the divergent results.

Strengths, limitations & future research

Although triangulation is not new, triangulation in mental health research is limited (Hammerton & Munafò, 2021). To our knowledge, this study is the first to triangulate evidence to assess the causal pathways between diet, physical activity, depression, and anxiety. No single method can provide definite evidence for causal pathways on its own (Hammerton & Munafò, 2021). In our study, triangulation strengthened our conclusion of no causal effects for sweet and savoury snack intake, since this finding was consistent across methods that address different types of confounding. However, for fruit/vegetable intake and physical activity, divergent findings across methods revealed potential biases that single-method studies might have missed. This demonstrates triangulation's value in both confirming null effects and identifying method-specific biases needing further investigation. We also extended previous work by considering mutual confounding between diet and physical activity, since both play substantial roles in health maintenance and disease prevention, rather than treating them as independent behaviours.

However, several limitations exist. First, retrospective triangulation was applied using existing data. Although the measures across the three studies were aligned as much as possible, not all measures were exactly the same. Consequently, this could influence the comparability of the studies. In line with this, the three studies included in the triangulation framework used data originating from different countries (i.e., The Netherlands and Australia). It could be that country-specific dietary habits or physical activity norms have impacted the compatibility of the three studies, which could explain some divergence in the findings. However, we do not expect that the difference in the origin of the data had a major impact, given that all individuals were from European Ancestry. Future studies could adapt prospective triangulation approaches (Munafò et al., 2021; Treur, Lukas, Sallis, & Wootton, 2024), where study measures, sample populations and timing of data collections are aligned before data collection. This will result in even stronger confidence in the conclusions and help to avoid divergence in the results. Second, all studies used observational self-reported data to some extent. Therefore, reporting/recall bias[11], measurement errors and selection bias[12] could not fully be ruled out (Hammerton

[10]Horizontal pleiotropy: The SNPs employed might affect the outcome through pathways unrelated to the exposure.

[11]Reporting/recall bias: bias introduced by incomplete or inaccurate reporting.

[12]Selection bias: bias introduced by the selection of participants.

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& Munafò, 2021; Pandis, 2014). Future studies can consider additional/other approaches less prone to these biases (e.g., the MR and the Direction of Causation twin model (Castro-de-Araujo et al., 2023; Minică, Boomsma, Dolan, de Geus, & Neale, 2020) or within-family GWAS/MR). Third, Wave 1 of Study 1 was collected during the COVID-19 pandemic (Fall 2021). During this unique time, several measures aimed to reduce the spread of the coronavirus were implemented (e.g., working from home, limits on number of students in classrooms at schools/universities, 1.5-meter spacing rule, and wearing face masks; National Institute for Public Health and the Environment (n.d.)). These measures most likely impacted the lifestyle behaviours and mental health reported during Wave 1. E.g., other studies do report that physical activity levels reduced and depressive symptoms increased during the COVID-19 pandemic (Caroppo et al., 2021; P. J. Chen, Pusica, Sohaei, Prassas, & Diamandis, 2021; Park, Zhong, Yang, Jeong, & Lee, 2022). However, this does not necessarily imply that the associations between variables in this study are different during the COVID-19 pandemic compared to other periods, as in previous work physical activity-depressive symptoms associations before and during the pandemic could be constrained to be equal over time (van den Broek et al., 2024). Given the different time intervals between the waves in the RI-CLPMs in Study 1, we were unable to empirically test whether we could constrain during and after the pandemic. Despite this, we have little reason to suspect that the within-person effects would be different for the two time intervals, given that all effect sizes were considerably small/close to zero. Fourth, Studies 2 and 3 might have limited power. In Study 2, the sample sizes are relatively small (especially DZ twin pairs). Consequently, larger twin studies are needed. In Study 3, this is reflected by smaller GWASs of sweet snack intake, savoury snack intake, vegetable intake and, anxiety. Consequently, fewer robustly associated exposure SNPs were available at the genome-wide significance level and a less stringent *p*-value threshold was used to select exposure SNPs. This could have introduced weak instrument bias (Burgess & Thompson, 2011). Consequently, larger GWASs are needed. Fifth, sex-specific analyses were not included. However, it is known that depression/anxiety are more common among females than males (GBD Mental Disorders Collaborators, 2022) and a recent study in adolescents suggested sex-specific effects from physical activity on depressive symptoms (van den Broek et al., 2024). Future studies could investigate these possible sex-specific effects. Last, post-treatment bias might bias the results of the performed adjusted models, in case the exposure has an causal effect on the included confounder (Acharya, Blackwell, & Sen, 2016).

Implications

Integrating triangulation approaches (also beyond the scope of this study) in scientific work more systematically, instead of single-methodology approaches, will greatly impact the weight of scientific output (Hammerton & Munafò, 2021). Institutions, organisations and policymakers can also use triangulated evidence to make more confident decisions on policy/strategy development, innovations to foster and resource allocation. With regard to the implications of the current study, given the acknowledged limitations of our triangulation approach, it is too early to provide strong recommendations for practice. However, triangulating evidence adds an important piece of the bigger puzzle of finding the true answer to the question if causal pathways exist between diet/physical activity and depression/anxiety. Before we can provide clear practical recommendations, additional pieces of this bigger puzzle are needed. As mentioned, these can be obtained by e.g., using complementary methods with other unrelated sources of potential biases or conducting larger twin studies/GWASs. Although in the current study no strong support for causal pathways between diet/physical activity and depression/anxiety was found, offering prevention/intervention services to e.g., stimulate physical activity, healthy diet and mental health will remain important (regardless of potential causal pathways), given their role in the disease risk reduction of multiple chronic diseases (Afshin et al., 2019; Warburton, Nicol, & Bredin, 2006).

Conclusion

Triangulated evidence from three distinctive methods (with unique strengths, weaknesses and key sources of potential bias) did not provide strong support for causal effects of diet/physical activity on depression/anxiety or vice versa, neither in the unadjusted or adjusted models (where diet was adjusted for physical activity and vice versa). Future studies could apply prospective triangulation to gain even more robust insights and confidence in answering complex causal questions.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S0033291724003349.

Data availability. Data from the Healthy Student Life project, used in Study 1, will be available via the data repository of Radboud University. Data from the Brisbane Longitudinal Twin Study, used in Study 2, are available upon request via the co-author (nathan.gillespie@vcuhealth.org). Summary statistics from genome-wide association studies, used in Study 3, are publicly available (for access see Supplementary Table ST5).

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Code availability. Codes are available on the Open Science Framework (https://osf.io/e4d5b/).

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Competing interest. The author(s) declare none.

Ethical statement. This study was performed in line with the principles of the Declaration of Helsinki. The Healthy Student Life study (Study 1) has been reviewed by Radboud University's Social Sciences Ethics Committee, and there

was no formal objection to this research (ECSW-2021-086). The Brisbane Longitudinal Twin Study, 25UP project (Study 2) assessment protocols were approved by the QIMR Berghofer Medical Research Institute Human Research Ethics Committee. Additional ethics approval was not required for the current study.

References

Aarts, E., Verhage, M., Veenvliet, J. V., Dolan, C. V., & Van Der Sluis, S. (2014). A solution to dependency: Using multilevel analysis to accommodate nested data. *Nature Neuroscience*, **17**(4), 491–496. doi:10.1038/nn.3648

Acharya, A., Blackwell, M., & Sen, M. (2016). Explaining causal findings without bias: Detecting and assessing direct effects. *American Political Science Review*, **110**(3), 512–529. doi:10.1017/S0003055416000216

Afshin, A., Sur, P. J., Fay, K. A., Cornaby, L., Ferrara, G., Salama, J. S., … Murray, C. J. L. (2019). Health effects of dietary risks in 195 countries, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*, **393**(10184), 1958–1972. doi:10.1016/S0140-6736(19)30041-8

Als, T. D., Kurki, M. I., Grove, J., Voloudakis, G., Therrien, K., Tasanko, E., … Børglum, A. D. (2023). Depression pathophysiology, risk prediction of recurrence and comorbid psychiatric disorders using genome-wide analyses. *Nature Medicine*, **29**(7), 1832–1844. doi:10.1038/s41591-023-02352-1

Andrews, G., & Slade, T. (2001). Interpreting scores on the Kessler Psychological Distress Scale (K10). *Australian and New Zealand Journal of Public Health*, **25**(6), 494–497. doi:10.1111/j.1467-842x.2001.tb00310.x

Appleton, K. M., Boxall, L. R., Adenuga-Ajayi, O., & Seyar, D. F. (2024). Does fruit and vegetable consumption impact mental health? Systematic review and meta-analyses of published controlled intervention studies. *British Journal of Nutrition*, **131**(1), 163–173. doi:10.1017/s0007114523001423

Bates, D., Maechler, M., Bolker, B., Walker, S., Christensen, R. H. B., Singmann, H., … Grothendieck, G. (2009a). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, **67**(1), 1–48. doi:10.18637/jss.v067.i01

Bates, D., Maechler, M., Bolker, B., Walker, S., Christensen, R. H. B., Singmann, H., … Grothendieck, G. (2009b). Package 'lme4'. http://lme4.r-forge.r-project.org.

Bowden, J., Davey Smith, G., & Burgess, S. (2015). Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International Journal of Epidemiology*, **44**(2), 512–525. doi:10.1093/ije/dyv080

Bowden, J., Davey Smith, G., Haycock, P. C., & Burgess, S. (2016). Consistent estimation in mendelian randomization with some invalid instruments using a weighted Median estimator. *Genetic Epidemiology*, **40**(4), 304–314. doi:10.1002/gepi.21965

Burgess, S., Butterworth, A., & Thompson, S. G. (2013). Mendelian randomization analysis with multiple genetic variants using summarized data. *Genetic Epidemiology*, **37**(7), 658–665. doi:10.1002/gepi.21758

Burgess, S., & Thompson, S. G. (2011). Avoiding bias from weak instruments in Mendelian randomization studies. *International Journal of Epidemiology*, **40**(3), 755–764. doi:10.1093/ije/dyr036

Burgess, S., & Thompson, S. G. (2015). Multivariable Mendelian randomization: The use of pleiotropic genetic variants to estimate causal effects. *American Journal of Epidemiology*, **181**(4), 251–260. doi:10.1093/aje/kwu283

Burnatowska, E., Surma, S., & Olszanecka-Glinianowicz, M. (2022). Relationship between mental health and emotional eating during the COVID-19 pandemic: A systematic review. *Nutrients*, **14**(19). doi:10.3390/nu14193989

Cardi, V., Leppanen, J., & Treasure, J. (2015). The effects of negative and positive mood induction on eating behaviour: A meta-analysis of laboratory studies in the healthy population and eating and weight disorders. *Neuroscience & Biobehavioral Reviews*, **57**, 299–309. doi:10.1016/j.neubiorev.2015.08.011

Carnegie, R., Zheng, J., Sallis, H. M., Jones, H. J., Wade, K. H., Evans, J., … Martin, R. M. (2020). Mendelian randomisation for nutritional psychiatry. *The Lancet Psychiatry*, **7**(2), 208–216. doi:10.1016/S2215-0366(19)30293-7

Caroppo, E., Mazza, M., Sannella, A., Marano, G., Avallone, C., Claro, A. E., … Sani, G. (2021). Will nothing be the same again?: Changes in lifestyle during COVID-19 pandemic and consequences on mental health. *International Journal of Environmental Research and Public Health*, **18**(16), 8433.

Castro-de-Araujo, L. F. S., Singh, M., Zhou, Y., Vinh, P., Verhulst, B., Dolan, C. V., & Neale, M. C. (2023). MR-DoC2: Bidirectional causal modeling with instrumental variables and data from relatives. *Behavior Genetics*, **53**(1), 63–73. doi:10.1007/s10519-022-10122-x

Chen, P. J., Pusica, Y., Sohaei, D., Prassas, I., & Diamandis, E. P. (2021). An overview of mental health during the COVID-19 pandemic. *Diagnosis (Berl)*, **8**(4), 403–412.

Chen, T. T., Chen, C. Y., Fang, C. P., Cheng, Y. C., & Lin, Y. F. (2022). Causal influence of dietary habits on the risk of major depressive disorder: A diet-wide Mendelian randomization analysis. *Journal of Affective Disorders*, **319**, 482–489. doi:10.1016/j.jad.2022.09.109

Choi, K. W., Chen, C. Y., Stein, M. B., Klimentidis, Y. C., Wang, M. J., Koenen, K. C., & Smoller, J. W. (2019). Assessment of bidirectional relationships between physical activity and depression among adults: A 2-sample mendelian randomization study. *JAMA Psychiatry*, **76**(4), 399–408. doi:10.1001/jamapsychiatry.2018.4175

Cole, J. B., Florez, J. C., & Hirschhorn, J. N. (2020). Comprehensive genomic analysis of dietary habits in UK Biobank identifies hundreds of genetic associations. *Nature Communications*, **11**(1), 1467. doi:10.1038/s41467-020-15193-0

Dakanalis, A., Mentzelou, M., Papadopoulou, S. K., Papandreou, D., Spanoudaki, M., Vasios, G. K., … Giaginis, C. (2023). The association of emotional eating with overweight/obesity, depression, anxiety/stress, and dietary patterns: A review of the current clinical evidence. *Nutrients*, **15**(5). doi:10.3390/nu15051173

Davey Smith, G., & Ebrahim, S. (2003). 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *International Journal of Epidemiology*, **32**(1), 1–22. doi:10.1093/ije/dyg070

Davies, N. M., Howe, L. J., Brumpton, B., Havdahl, A., Evans, D. M., & Davey Smith, G. (2019). Within family Mendelian randomization studies. *Human Molecular Genetics*, **28** (R2), R170–R179. doi:10.1093/hmg/ddz204

De Moor, M. H., Boomsma, D. I., Stubbe, J. H., Willemsen, G., & de Geus, E. J. (2008). Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Archives Of General Psychiatry*, **65** (8), 897–905. doi:10.1001/archpsyc.65.8.897

Donker, T., van Straten, A., Marks, I., & Cuijpers, P. (2011). Quick and easy self-rating of generalized anxiety disorder: Validity of the Dutch web-based GAD-7, GAD-2 and GAD-SI. *Psychiatry Research*, **188**(1), 58–64. doi:10.1016/j.psychres.2011.01.016

Du, Z., Guo, S., Sun, Y., Zhou, Q., Jiang, Y., Shen, Y., … Zhou, H. (2023). Causal relationships between dietary habits and five major mental disorders: A two-sample Mendelian randomization study. *Journal of Affective Disorde*, **340**, 607–615. doi:10.1016/j.jad.2023.08.098

Eaton, N. R., Krueger, R. F., South, S. C., Gruenewald, T. L., Seeman, T. E., & Roberts, B. W. (2012). Genes, environments, personality, and successful aging: Toward a comprehensive developmental model in later life. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, **67**(5), 480–488. doi:10.1093/gerona/gls090

Elsworth, B., Lyon, M., Alexander, T., Liu, Y., Matthews, P., Hallett, J., … Hemani, G. (2020). The MRC IEU OpenGWAS data infrastructure. *bioRxiv, 2020.08.10.244293v1*. doi:10.1101/2020.08.10.244293

Enders, C. K. (2001). A primer on maximum likelihood algorithms available for use with missing data. *Structural Equation Modeling*, **8**(1), 128–141. doi:10.1207/S15328007SEM0801_7

Evans, D. M., & Davey Smith, G. (2015). Mendelian randomization: New applications in the coming age of hypothesis-Free causality. *Annual Review of Genomics and Human Genetics*, **16**, 327–350. doi:10.1146/annurev-genom-090314-050016

Frisell, T., Öberg, S., Kuja-Halkola, R., & Sjölander, A. (2012). Sibling comparison designs: Bias from non-shared confounders and measurement error. *Epidemiology*, **23**(5), 713–720. doi:10.1097/EDE.0b013e31825fa230

GBD 2019 Diseases and Injuries Collaborators. 2020 Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet*, **396**(10258), 1204–1222. doi:10.1016/s0140-6736(20)30925-9

GBD Mental Disorders Collaborators. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry*, **9**(2), 137–150. doi:10.1016/S2215-0366(21)00395-3

Gonggrijp, B. M., van de Weijer, S. G., Bijleveld, C. C., van Dongen, J., & Boomsma, D. I. (2023). The co-twin control design: Implementation and methodological considerations. *Twin Research and Human Genetics*, 1–8. doi:10.1017/thg.2023.35

Graham, J. W. (2009). Missing data analysis: Making it work in the real world. *Annual Review of Psychology*, **60**, 549–576. doi:10.1146/annurev.psych.58.110405.085530

Gupta, V., Walia, G., & Sachdeva, M. (2017). 'Mendelian randomization': An approach for exploring causal relations in epidemiology. *Public Health*, **145**, 113–119. doi:10.1016/j.puhe.2016.12.033

Hamaker, E. L., Kuiper, R. M., & Grasman, R. P. (2015). A critique of the cross-lagged panel model. *Psychological Methods*, **20**(1), 102–116. doi:10.1037/a0038889

Hammerton, G., & Munafò, M. R. (2021). Causal inference with observational data: the need for triangulation of evidence. *Psychological Medicine*, **51**(4), 563–578. doi:10.1017/S0033291720005127

Hartwig, F. P., Davey Smith, G., & Bowden, J. (2017). Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *International Journal of Epidemiology*, **46**(6), 1985–1998. doi:10.1093/ije/dyx102

Hemani, G., Bowden, J., & Davey Smith, G. (2018). Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Human Molecular Genetics*, **27** (R2), R195–r208. doi:10.1093/hmg/ddy163

Hemani, G., Zheng, J., Elsworth, B., Wade, K. H., Baird, D., Haberland, V., … Haycock, P. (2018). The MR-Base platform supports systematic causal inference across the human phenome. *elife*, **7**, e34408. doi:10.7554/eLife.34408

Howard, D. M., Adams, M. J., Clarke, T. K., Hafferty, J. D., Gibson, J., Shirali, M., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, **22**(3), 343–352. doi:10.1038/s41593-018-0326-7

Hu, L. t., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal*, **6**(1), 1–55. doi:10.1080/10705519909540118

Iob, E., Pingault, J. B., Munafò, M. R., Stubbs, B., Gilthorpe, M. S., Maihofer, A. X., & Danese, A. (2023). Testing the causal relationships of physical activity and sedentary behaviour with mental health and substance use disorders: a Mendelian randomisation study. *Molecular Psychiatry*, **28**(8), 3429–3443. doi:10.1038/s41380-023-02133-9

IPAQ Research Committee. (2005). Guidelines for data processing and analysis of the International Physical Activity Questionnaire (IPAQ)-short and long forms. https://sites.google.com/view/ipaq/score

Klimentidis, Y. C., Raichlen, D. A., Bea, J., Garcia, D. O., Wineinger, N. E., Mandarino, L. J., … Going, S. B. (2018). Genome-wide association study of habitual physical activity in over 377,000 UK Biobank participants identifies multiple variants including CADM2 and APOE. *International Journal of Obesity (Lond)*, **42**(6), 1161–1176. doi:10.1038/s41366-018-0120-3

Kline, R. B. (2023). *Principles and practice of structural equation modeling*. Guilford publications.

Knüppel, A., Shipley, M. J., Llewellyn, C. H., & Brunner, E. J. (2017). Sugar intake from sweet food and beverages, common mental disorder and depression: Prospective findings from the Whitehall II study. *Scientific Reports*, **7**(1), 6287. doi:10.1038/s41598-017-05649-7

Lane, M. M., Gamage, E., Du, S., Ashtree, D. N., McGuinness, A. J., Gauci, S., … Marx, W. (2024). Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses. *BMJ*, **384**, e077310. doi:10.1136/bmj-2023-077310

Lawlor, D. A., Harbord, R. M., Sterne, J. A., Timpson, N., & Davey Smith, G. (2008). Mendelian randomization: Using genes as instruments for making causal inferences in epidemiology. *Statistics in Medicine*, **27**(8), 1133–1163. doi:10.1002/sim.3034

Lawlor, D. A., Tilling, K., & Davey Smith, G. (2016). Triangulation in aetiological epidemiology. *International Journal of Epidemiology*, **45**(6), 1866–1886. doi:10.1093/ije/dyw314

Li, Y., Lv, M. R., Wei, Y. J., Sun, L., Zhang, J. X., Zhang, H. G., & Li, B. (2017). Dietary patterns and depression risk: A meta-analysis. *Psychiatry Research*, **253**, 373–382. doi:10.1016/j.psychres.2017.04.020

Liu, X., Yan, Y., Li, F., & Zhang, D. (2016). Fruit and vegetable consumption and the risk of depression: A meta-analysis. *Nutrition*, **32**(3), 296–302. doi:10.1016/j.nut.2015.09.009

Mammen, G., & Faulkner, G. (2013). Physical activity and the prevention of depression: a systematic review of prospective studies. *American Journal of Preventive Medicine*, **45**(5), 649–657. doi:10.1016/j.amepre.2013.08.001

McDowell, C. P., Dishman, R. K., Gordon, B. R., & Herring, M. P. (2019). Physical activity and anxiety: A systematic review and meta-analysis of prospective cohort studies. *American Journal of Preventive Medicine*, **57**(4), 545–556. doi:10.1016/j.amepre.2019.05.012

Minică, C. C., Boomsma, D. I., Dolan, C. V., de Geus, E., & Neale, M. C. (2020). Empirical comparisons of multiple Mendelian randomization approaches in the presence of assortative mating. *International Journal of Epidemiology*, **49**(4), 1185–1193. doi:10.1093/ije/dyaa013

Mitchell, B. L., Campos, A. I., Rentería, M. E., Parker, R., Sullivan, L., McAloney, K., … Scott, J. (2019). Twenty-five and up (25Up) study: A new wave of the Brisbane Longitudinal Twin Study. *Twin Research and Human Genetics*, **22**(3), 154–163.

Molendijk, M., Molero, P., Sánchez-Pedreño, F. O., Van der Does, W., & Martínez-González, M. A. (2018). Diet quality and depression risk: a systematic review and dose-response meta-analysis of prospective studies. *Journal of Affective Disorders*, **226**, 346–354. doi:10.1016/j.jad.2017.09.022

Moreno-Peral, P., Pino-Postigo, A., Conejo-Cerón, S., Bellón, D., Rodríguez-Martín, B., Martínez-Vizcaíno, V., & Bellón, J. (2022). Effectiveness of physical activity in primary prevention of anxiety: Systematic review and meta-analysis of randomized controlled trials. *The International Journal of Environmental Research and Public Health*, **19**(3). doi:10.3390/ijerph19031813

Mosteller, F. F., & Boruch, R. F. (2004). *Evidence matters: Randomized trials in education research*. Brookings Institution Press.

Mounier, N., & Kutalik, Z. (2023). Bias correction for inverse variance weighting Mendelian randomization. *Genetic Epidemiology*, **47**(4), 314–331. doi:10.1002/gepi.22522

Mulder, J. D., & Hamaker, E. L. (2021). Three extensions of the random intercept cross-lagged panel model. *Structural Equation Modeling: A Multidisciplinary Journal*, **28**(4), 638–648. doi:10.1080/10705511.2020.1784738

Munafò, M. R., & Davey Smith, G. (2018). Robust research needs many lines of evidence. *Nature*, **553**(7689), 399–401. doi:10.1038/d41586-018-01023-3

Munafò, M. R., Higgins, J. P. T., & Davey Smith, G. (2021). Triangulating evidence through the inclusion of genetically informed designs. *Cold Spring Harbor Perspectives in Medicine*, **11**(8). doi:10.1101/cshperspect.a040659

National Institute for Public Health and the Environment. (n.d.). Tijdlijn van coronamaatregelen 2021. https://www.rivm.nl/gedragsonderzoek/tijdlijn-van-coronamaatregelen-2021

NCD Countdown 2030 Collaborators. (2018). NCD Countdown 2030: Worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. *Lancet*, **392**(10152), 1072–1088. doi:10.1016/s0140-6736(18)31992-5

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry*, **21**(10), 1391–1399. doi:10.1038/mp.2015.197

Pandis, N. (2014). Bias in observational studies. *American Journal of Orthodontics and Dentofacial Orthopedics*, **145**(4), 542–543. doi:10.1016/j.ajodo.2014.01.008

Park, A. H., Zhong, S., Yang, H., Jeong, J., & Lee, C. (2022). Impact of COVID-19 on physical activity: A rapid review. *Journal of Global Health*, **12**, 05003.

Pasman, J. A., Bergstedt, J., Harder, A., Gong, T., Xiong, Y., Hägg, S., … Lu, Y. (2024). Causes and consequences of major depressive disorder: An encompassing Mendelian randomization study. *medRxiv*, 2024.2005.2021.24307678. doi:10.1101/2024.05.21.24307678

Patton, M. Q. (1999). Enhancing the quality and credibility of qualitative analysis. *Health Services Research*, **34** (5 Pt 2), 1189–1208.

Pearce, M., Garcia, L., Abbas, A., Strain, T., Schuch, F. B., Golubic, R., … Woodcock, J. (2022). Association between physical activity and risk of depression: A systematic review and meta-analysis. *JAMA Psychiatry*, **79**(6), 550–559. doi:10.1001/jamapsychiatry.2022.0609

Popkin, B. M., Adair, L. S., & Ng, S. W. (2012). Global nutrition transition and the pandemic of obesity in developing countries. *Nutrition Reviews*, **70**(1), 3–21. doi:10.1111/j.1753-4887.2011.00456.x

R Core Team. (2023). R: A language and environment for statistical computing. https://www.R-project.org/

Rebar, A. L., Stanton, R., Geard, D., Short, C., Duncan, M. J., & Vandelanotte, C. (2015). A meta-meta-analysis of the effect of physical activity on depression and anxiety in non-clinical adult populations. *Health Psychology Review*, **9**(3), 366–378. doi:10.1080/17437199.2015.1022901

Rees, J. M. B., Wood, A. M., & Burgess, S. (2017). Extending the MR-Egger method for multivariable Mendelian randomization to correct for both measured and unmeasured pleiotropy. *Statistics in Medicine*, **36**(29), 4705–4718. doi:10.1002/sim.7492

Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of depression on physical activity. *General Hospital Psychiatry*, **31**(4), 306–315. doi:10.1016/j.genhosppsych.2009.04.002

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, **48**, 1–36. doi:10.18637/jss.v048.i02

Saghafian, F., Malmir, H., Saneei, P., Milajerdi, A., Larijani, B., & Esmaillzadeh, A. (2018). Fruit and vegetable consumption and risk of depression: accumulative evidence from an updated systematic review and meta-analysis of epidemiological studies. *British Journal of Nutrition*, **119**(10), 1087–1101. doi:10.1017/s0007114518000697

Sanderson, E., Davey Smith, G., Windmeijer, F., & Bowden, J. (2018). An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. *International Journal of Epidemiology*, **48**(3), 713–727. doi:10.1093/ije/dyy262

Sanderson, E., Spiller, W., & Bowden, J. (2021). Testing and correcting for weak and pleiotropic instruments in two-sample multivariable Mendelian randomization. *Statistics in Medicine*, **40**(25), 5434–5452. doi:10.1002/sim.9133

Schuch, F. B., Stubbs, B., Meyer, J., Heissel, A., Zech, P., Vancampfort, D., … Hiles, S. A. (2019). Physical activity protects from incident anxiety: A meta-analysis of prospective cohort studies. *Depress Anxiety*, **36**(9), 846–858. doi:10.1002/da.22915

Schuch, F. B., Vancampfort, D., Firth, J., Rosenbaum, S., Ward, P. B., Silva, E. S., … Stubbs, B. (2018). Physical activity and incident depression: A meta-analysis of prospective cohort studies. *American Journal of Psychiatry*, **175**(7), 631–648. doi:10.1176/appi.ajp.2018.17111194

Shadish, W. R., Cook, T. D., & Campbell, D. T. (2002). *Experimental and quasi-experimental designs for generalized causal inference*. Houghton Mifflin Boston, MA.

Singh, M., Verhulst, B., Vinh, P., Zhou, Y. D., Castro-de-Araujo, L. F. S., Hottenga, J. J., … Neale, M. C. (2024). Using instrumental variables to measure causation over time in cross-lagged panel models. *Multivariate Behavioral Research*, **59**(2), 342–370. doi:10.1080/00273171.2023.2283634

Skrivankova, V. W., Richmond, R. C., Woolf, B. A., Davies, N. M., Swanson, S. A., VanderWeele, T. J., … Langenberg, C. (2021). Strengthening the reporting of observational studies in epidemiology using mendelian randomisation (STROBE-MR): Explanation and elaboration. *BMJ*, **375**. doi:10.1136/bmj.n2233

Spiga, F., Gibson, M., Dawson, S., Tilling, K., Davey Smith, G., Munafò, M. R., & Higgins, J. P. T. (2023). Tools for assessing quality and risk of bias in Mendelian randomization studies: A systematic review. *International Journal of Epidemiology*, **52**(1), 227–249. doi:10.1093/ije/dyac149

Strain, T., Flaxman, S., Guthold, R., Semenova, E., Cowan, M., Riley, L. M., … Stevens, G. A. (2024). National, regional, and global trends in insufficient physical activity among adults from 2000 to 2022: A pooled analysis of 507 population-based surveys with 5· 7 million participants. *The Lancet Global Health*, **12**(8), e1232–e1243. doi:10.1016/S2214-109X(24)00150-5

Treur, J. L., Lukas, E., Sallis, H. M., & Wootton, R. E. (2024). A guide for planning triangulation studies to investigate complex causal questions in behavioural and psychiatric research. *Epidemiology and Psychiatric Sciences*, **33**, e61. doi:10.1017/S2045796024000623

Tuck, N. J., Farrow, C., & Thomas, J. M. (2019). Assessing the effects of vegetable consumption on the psychological health of healthy adults: A systematic review of prospective research. *The American Journal of Clinical Nutrition*, **110**(1), 196–211. doi:10.1093/ajcn/nqz080

Van de Velde, S., Levecque, K., & Bracke, P. (2009). Measurement equivalence of the CES-D 8 in the general population in Belgium: A gender perspective. *Archives of Public Health*, **67**, 1–15. doi:10.1186/0778-7367-67-1-15

van den Broek, N., Larsen, J. K., Verhagen, M., Burk, W. J., & Vink, J. M. (2020). Is adolescents' food intake associated with exposure to the food intake of their mothers and best friends? *Nutrients*, **12**(3). doi:10.3390/nu12030786

van den Broek, N., Maran, P. L., Beckers, D., Burk, W. J., Verhagen, M., Vink, J. M., & Larsen, J. K. (2024). Examining the bidirectional associations between adolescents' physical activity and depressive symptoms before and during the COVID-19 pandemic. *Mental Health and Physical Activity*, **27**, 100618. doi:10.1016/j.mhpa.2024.100618

van Hooijdonk, K. J. M., Simons, S. S. H., van Noorden, T. H. J., Geurts, S. A. E., & Vink, J. M. (2023). Prevalence and clustering of health behaviours and the association with socio-demographics and mental well-being in Dutch university students. *Preventive Medicine Reports*, **35**, 102307. doi:10.1016/j.pmedr.2023.102307

Verbanck, M., Chen, C. Y., Neale, B., & Do, R. (2018). Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics*, **50**(5), 693–698. doi:10.1038/s41588-018-0099-7

Vitaro, F., Brendgen, M., & Arseneault, L. (2009). The discordant MZ-twin method: One step closer to the holy grail of causality. *International Journal of Behavioral Development*, **33**(4), 376–382. doi:10.1177/0165025409340805

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *The Lancet*, **370**(9596), 1453–1457. doi:10.1016/S0140-6736(07)61602-X

Wang, Q., Ou, Z., Chen, J., Li, L., Chen, Y., & Ye, D. (2024). Association between vegetable intake and major depressive disorder: results from National Health and Nutrition Examination Survey 2005-2018 and bidirectional two-sample Mendelian randomisation. *Public Health Nutrition*, **27**(1), e220. doi:10.1017/s1368980024001691

Wang, Y., Zhao, R., Wang, B., Zhao, C., Zhu, B., & Tian, X. (2022). The dose-response associations of sugar-sweetened beverage intake with the Risk of stroke, depression, cancer, and cause-specific mortality: A systematic review and meta-analysis of prospective studies. *Nutrients*, **14**(4). doi:10.3390/nu14040777

Wanjau, M. N., Möller, H., Haigh, F., Milat, A., Hayek, R., Lucas, P., & Veerman, J. L. (2023). Physical activity and depression and anxiety disorders: A systematic review of reviews and assessment of causality. *AJPM Focus*, **2**(2), 100074. doi:10.1016/j.focus.2023.100074

Warburton, D. E., Nicol, C. W., & Bredin, S. S. (2006). Health benefits of physical activity: The evidence. *CMAJ*, **174**(6), 801–809. doi:10.1503/cmaj.051351

World Health Organization. (2022). World mental health report: Transforming mental health for all. https://iris.who.int/bitstream/handle/10665/356119/9789240049338-eng.pdf?sequence=1

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., … Sullivan, P. F. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, **50**(5), 668–681. doi:10.1038/s41588-018-0090-3

Yan, Z., Xu, Y., Li, K., & Liu, L. (2023). Increased fruit intake is associated with reduced risk of depression: Evidence from cross-sectional and Mendelian randomization analyses. *Frontiers in Public Health*, **11**, 1276326. doi:10.3389/fpubh.2023.1276326

Zhao, Q., Wang, J., Hemani, G., Bowden, J., & Small, D. S. (2018). Statistical inference in two-sample summary-data Mendelian randomization using robust adjusted profile score. *Annals of Statistics*. doi:10.1214/19-AOS1866