

Original Article

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

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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 activity¹ 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,

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¹Insufficient 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; Pasma 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; Pasma 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 from 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

Triangulation Framework

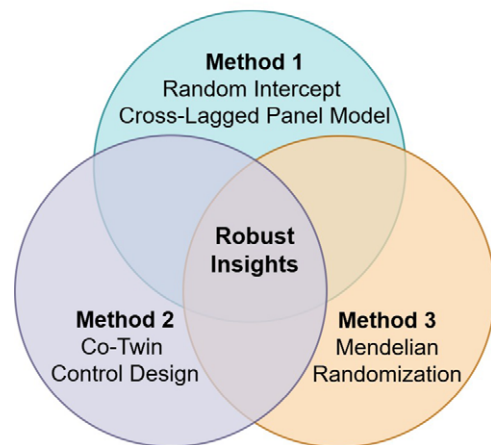


Figure 1. Concept of triangulation.

Note. Illustration of how our three complementary methods help to strengthen causal inference.

²In 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).

³In 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).

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 extent 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

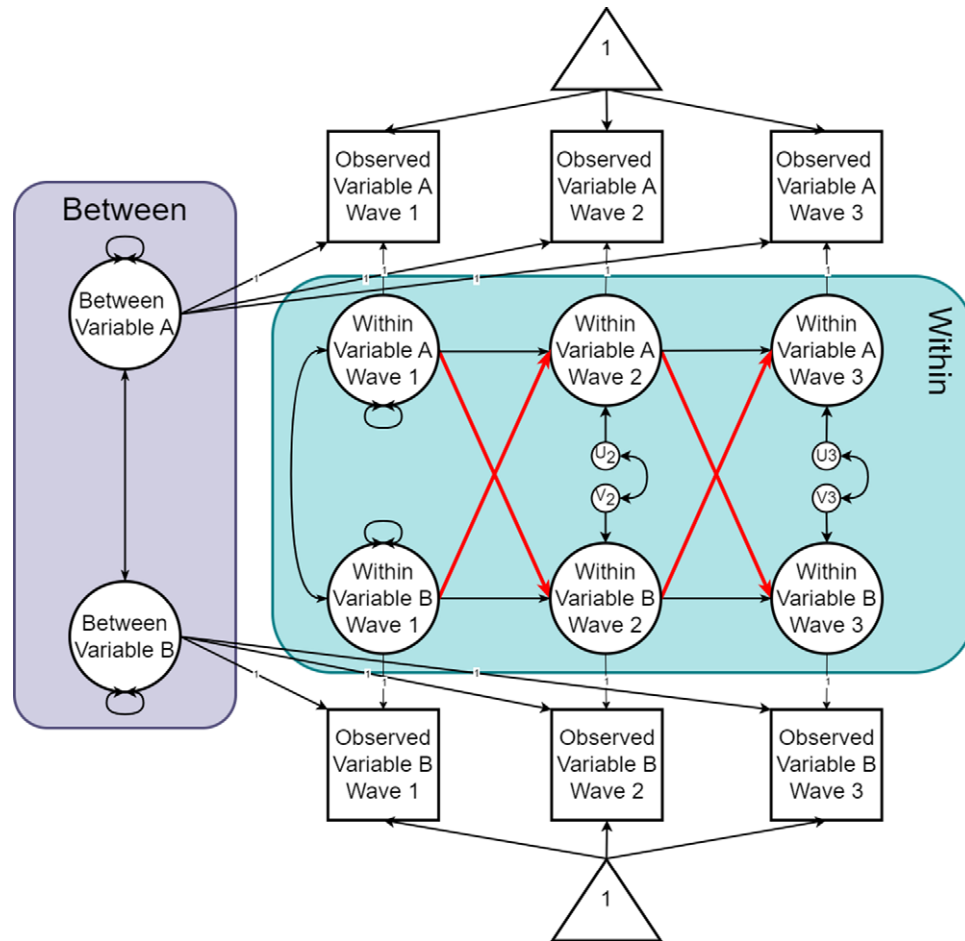


Figure 2. Example of a random intercept cross-lagged panel model (RI-CLPM) assessing the bidirectional pathways between variable A and variable B, including between-person and within-person components at three survey waves.

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

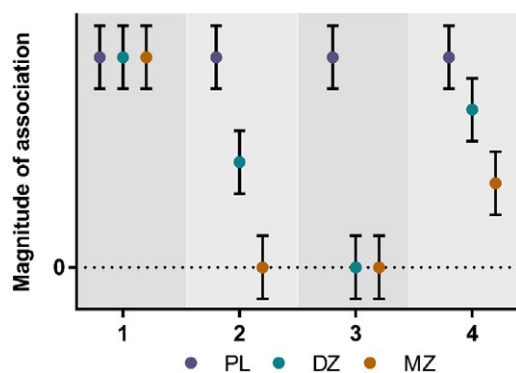


Figure 3. Hypothetical outcome scenarios of a co-twin control design (CTCD).

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 discordant⁴ 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.

⁴Discordance 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/m²), 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.

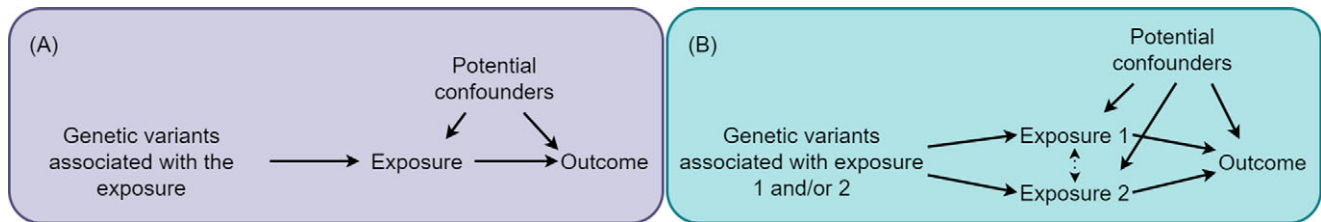


Figure 4. Directed acyclic graphs for (A) Univariable mendelian randomization and (B) Multivariable mendelian randomization.

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 segregation⁵ and independent assortment⁶ (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), depression⁷ (Howard *et al.*, 2019),

and anxiety⁸ (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-Egger⁹ (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,

⁵Mendel'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).

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

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

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

⁹MVMR-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.

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: univariable mendelian randomization ^c	
	<i>b</i> W1 → W2	SE	<i>b</i> W2 → W3	SE	Group	<i>b</i>	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 where 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.

^aOnly the cross-lagged within-person effects have been presented. Full results can be found in [Supplementary Tables ST12–ST29](#).

^bOnly 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.

^cOnly 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

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 where 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)).

Table 3. Results within-person cross-lagged effects

Pathways	Unadjusted models								Adjusted models							
	W1 → W2				W2 → W3				W1 → W2				W2 → W3			
	<i>b</i>	<i>SE</i>	β	<i>p</i>	<i>b</i>	<i>SE</i>	β	<i>p</i>	<i>b</i>	<i>SE</i>	β	<i>p</i>	<i>b</i>	<i>SE</i>	β	<i>p</i>
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.

^aAdjusted models were corrected for physical activity.

^bAdjusted models were corrected for all diet measures and these cross-lagged effects have been presented in [Supplementary Tables S22–S29](#).

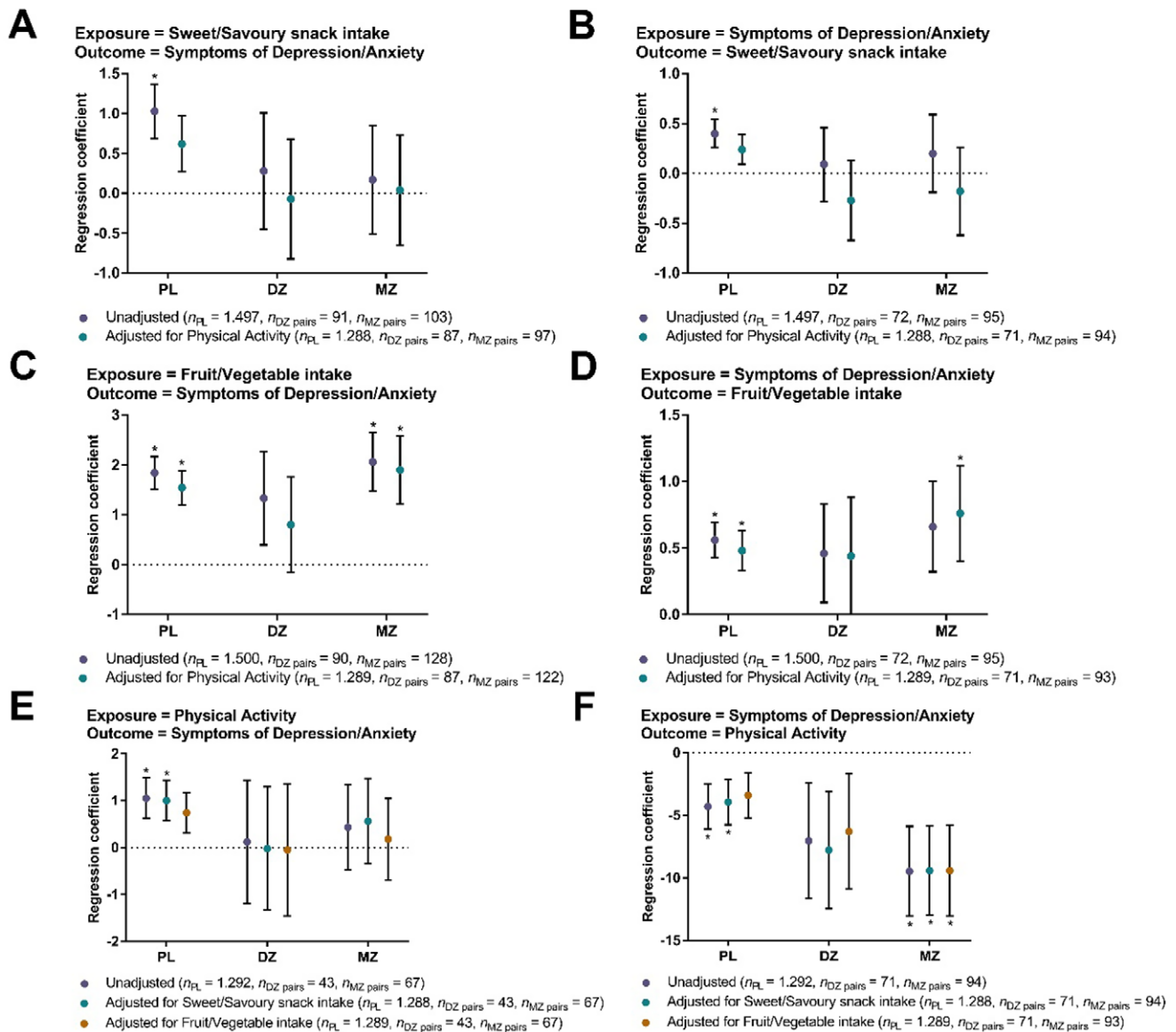


Figure 5. Results mixed-effects models - patterns in regression coefficients at population-level (PL), within dizygotic (DZ) same-sex twins and within monozygotic (MZ) twins. Asterisks represent associations between exposure and outcome per subgroup where $p < .05$.

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

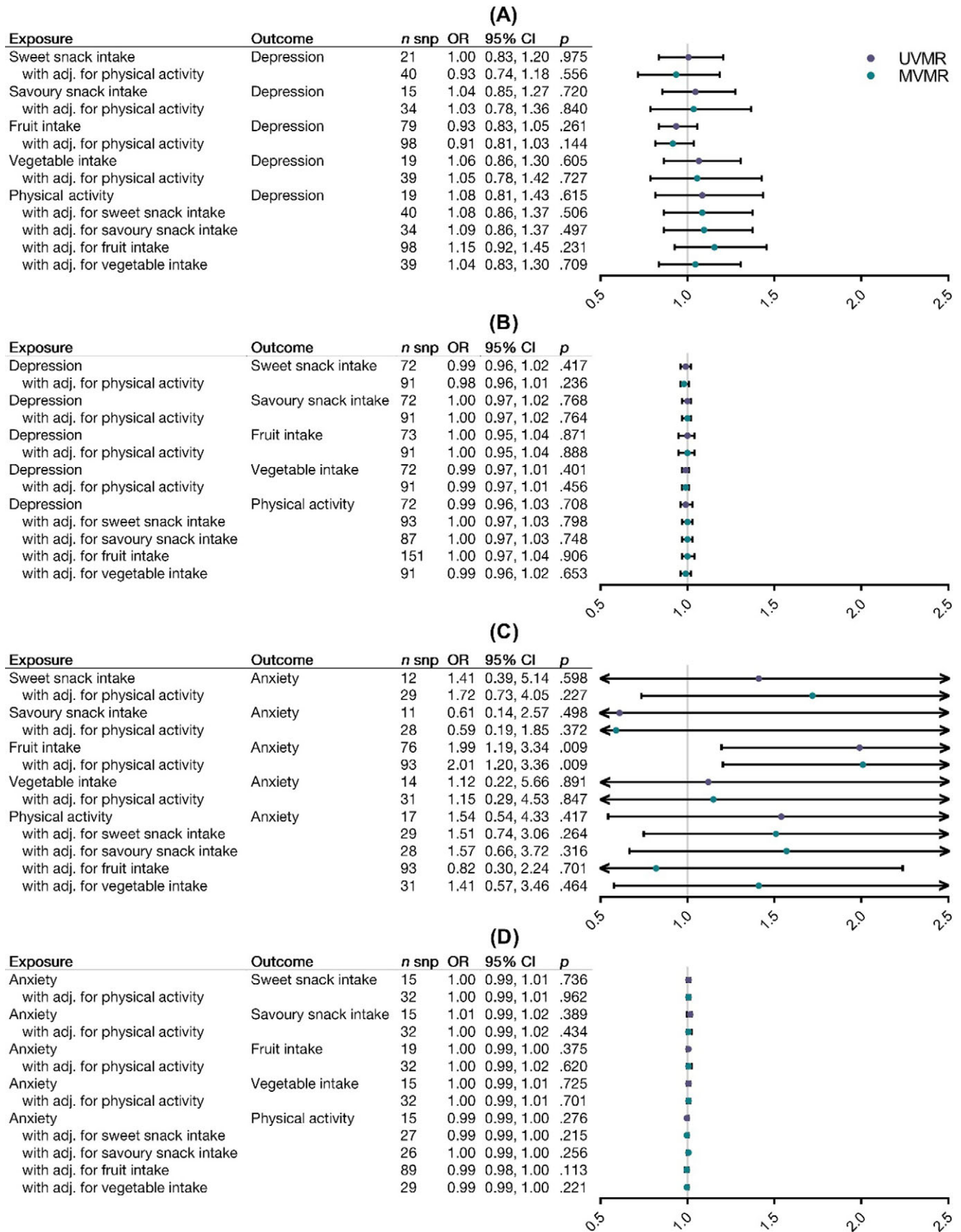


Figure 6. Results of the univariable and multivariable mendelian randomization.

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.

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 pleiotropy¹⁰) 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 bias¹¹, measurement errors and selection bias¹² could not fully be ruled out (Hammerton

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

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

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

& Munafo, 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 & Munafo, 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.

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