Two genetic analyses to elucidate causality between body mass index and personality

Two genetic analyses to elucidate causality between body mass index and personality

Running head: Causality between BMI and personality

Kadri Arumäe, MA[1]; Daniel Briley, PhD[2]; Lucía Colodro-Conde, PhD[3]; Erik Lykke Mortensen, MSc[4]; Kerry Jang, PhD[5]; Juko Ando, PhD[6]; Christian Kandler, PhD[7]; Thorkild I. A. Sørensen, MD, Dr Med Sci[4]; Alain Dagher, MD, PhD[8]; René Mõttus, PhD[9,1]; Uku Vainik, PhD[1,8]*

1: University of Tartu

2: University of Illinois

3: QIMR Berghofer Medical Research Institute Brisbane

4: University of Copenhagen

5: University of British Columbia

6: Keio University

7: University of Bremen

8: Montreal Neurological Institute, McGill University

9: University of Edinburgh

* Corresponding author at: Institute of Psychology, Faculty of Social Sciences, University of Tartu, Näituse 2, 50409, Tartu, Estonia; uku.vainik@gmail.com; +372 737 5912

The authors declare no competing financial interests.

Abstract

Background/Objectives: Many personality traits correlate with BMI, but the existence and direction of causal links between them are unclear. If personality influences BMI, knowing this causal direction could inform weight management strategies. Knowing that BMI instead influences personality would contribute to a better understanding of the mechanisms of personality development and the possible psychological effects of weight change. We tested the existence and direction of causal links between BMI and personality.

Subjects/Methods: We employed two genetically informed methods. In Mendelian randomization, allele scores were calculated to summarize genetic propensity for the personality traits Neuroticism, Worry, and Depressive Affect and used to predict BMI in an independent sample (*N*=3 541). Similarly, an allele score for BMI was used to predict eating-specific and domain-general phenotypic personality scores (PPSs; aggregate scores of personality traits weighted by BMI). In a Direction of Causation analysis, twin data from five countries (*N*=5 424) were used to assess the fit of four alternative models: PPSs influencing BMI, BMI influencing PPSs, reciprocal causation, and no causation.

Results: In Mendelian randomization, the allele score for BMI predicted domain-general (β=0.05; 95% CI 0.02, 0.08; *P*=.003) and eating-specific PPS (β=0.06; 95% CI 0.03, 0.09; *P*<.001). The allele score for Worry also predicted BMI (β=-0.05; 95% CI -0.08, -0.02; *P*<.001), while those for Neuroticism and Depressive Affect did not (*P*≥.459). In Direction of Causation, BMI similarly predicted domain-general (β=0.21; 95% CI 0.18, 0.24; *P*<.001) and eating-specific personality traits (β=0.19; 95% CI 0.16, 0.22; *P*<.001), suggesting causality from BMI to personality traits. In exploratory analyses, links between BMI and domain-general personality

traits appeared reciprocal for higher-weight individuals (BMI>~25).

Conclusions: Although both genetic analyses suggested an influence of BMI on personality traits, it is not yet known if weight management interventions could influence personality. Personality traits may influence BMI in turn, but effects in this direction appeared weaker.

Introduction

Excess adiposity, commonly proxied by body mass index (BMI), is a global health concern associated with increased economic[1] and disease burden[2]. BMI, like many other health outcomes, has been robustly linked to personality traits[3]—individuals' behavioral, affective, and cognitive patterns. Still, it is unclear whether BMI and personality are causally associated. Even longitudinal analyses say little about their causal links as personality and BMI are both relatively stable and could be influenced by common processes[4]. If personality traits influence weight, understanding this could provide input for behavioral treatment of obesity[5]. If BMI is instead found to influence personality, this could help delineate some of the otherwise elusive mechanisms of personality development.

Understanding the causal impact of personality on body weight could also have wider implications. Personality traits are associated with a range of outcomes like mental and physical health, life events, occupational success, and longevity[6–8]. For example, personality interventions have been proposed to improve human welfare[9], although it is still to be shown that personality traits are causal to life outcomes, including obesity. The direction of causation for body weight may generalize to other outcomes.

Much of the research regarding the links between personality and obesity has operationalized personality with five broad domains: Neuroticism, Extraversion, Openness to Experience, Agreeableness, and Conscientiousness. Studies have consistently reported a negative correlation between BMI and Conscientiousness, whereas associations with the other domains are less consistent[3,10]. Each broad trait is also comprised of subtraits, facets, which can be further split into narrower traits, nuances[11]. As with many other health-related outcomes[12], subtraits

within the same domain often vary markedly in their associations with BMI, sometimes even in direction[13]. Representing personality trait–BMI associations with the domains may thus unduly attenuate or otherwise obscure them. While BMI–personality correlations are small, the numerous nuance-level associations can be aggregated into phenotypic personality scores (PPSs). We constructed such PPSs by weighting personality questionnaire items by their correlations with BMI (obtained from independent samples) and summing them. The PPSs, bespoke personality-based propensity scores for high BMI, provide greater statistical power to detect modestly sized associations[13].

Beyond cross-sectional links, longitudinal studies have demonstrated that personality traits predict future BMI[14,15] and BMI predicts future personality traits[16]. However, longitudinal studies have sometimes failed to predict results of randomized controlled trials because they are unable to eliminate confounding factors like alcohol abuse, socioeconomic status, or co-morbid diseases[4]. These factors could potentially influence both personality and obesity. Change in various personality traits has also been observed following bariatric surgery[17], but it is uncertain whether these results could generalize to weight change that follows more traditional, non-surgical attempts or interventions. Altogether, causal links between personality and BMI remain unknown.

When randomized controlled trials are difficult or impossible to conduct, genetic methods can provide an alternative way to test causal models[18]. Importantly, although any one method may be fallible, converging results from different statistical approaches can increase confidence in results[19]. First, we used Mendelian randomization, a statistical technique where patterns of correlations between genetic propensities for phenotypes and the phenotypic outcomes

themselves are used to assess potential causal links (see Briley et al (2018)[20] for a brief and Haycock et al (2016)[21] for an in-depth overview). So far, genetic propensity for BMI has been found to track psychological distress[22], lower subjective well-being[23], and ADHD[24] in Mendelian randomization studies. Because personality and BMI are both influenced by a high number of genetic variants[25–27], we summarized the genetic propensities for high BMI and, when possible, personality traits, in allele scores–aggregate scores of a person's genetic predisposition for the traits in question.

Second, we applied a structural equation model analysis called Direction of Causation (DoC) on twin data. There, phenotypic variance in BMI and personality traits was parsed into genetic and environmental variance components and the most plausible causal model based on patterns of correlation between these components was chosen. The DoC analysis relies on the assumption that if an outcome is causally explained by a phenotype, then the phenotype's variance components should be proportionally represented in the outcome[28] (see Briley et al (2018)[20] for a brief summary). We compared four models: 1) correlated (no causal links—a common cause for BMI and PPS), 2) reciprocal causation between PPS and BMI, 3) PPS influencing BMI, and 4) BMI influencing PPS. As personality influencing physical health is the commonly assumed causal direction[5], we labeled personality influencing BMI the forward model; BMI influencing personality was accordingly termed the reverse model.

Materials and Methods

Participants

Mendelian randomization. Mendelian randomization was based on a subsample drawn from the Estonian Biobank[29], a volunteer-based sample of Estonian residents recruited by medical

personnel from among individuals visiting general practitioners and hospitals throughout the country. After giving informed consent, participants donated blood for DNA testing and underwent a standardized health examination. The data used in the current study were collected between 2002 and 2014. Analysis included individuals that had DNA, demographic, and personality data available (*N*=3 541). Mean age of participants was 46.74 (*SD*=16.97, range 18–91) years, 2 112 (59.64%) were female. 1 174 (33.15%) participants were overweight and an additional 719 (20.30%) obese; mean BMI was 26.18 kg/m^2 (*SD*=4.97). Although men were somewhat underrepresented, the proportions of weight groups were comparable to the Estonian adult population[30]. Exclusions and sample sizes by cohort are detailed in Supplementary Tables 1–2; sample sizes reported in the main text are after exclusions. The study was approved by Estonian Committee on Bioethics and Human Research.

Direction of Causation. The dataset for DoC analysis comprised cross-sectional twin samples from five countries: Australia, Canada, Denmark, Germany, and Japan. To obtain the data, we approached several cohorts known to have the information on both the NEO PI–R/3 and BMI and solicited access to the five datasets. Current analyses included only complete twin pairs (*N*=5 424). Across the full DoC sample, participants' mean age was 29.91 years (*SD*=12.29), mean BMI was 22.62 kg/m^2 (*SD*=3.85) and 3 531 (65.10%) were female; the full sample's and the subsamples' characteristics are expanded upon in Supplementary Table 2. Each study was approved by the local ethics committee. Informed consent was obtained from all participants.

Materials

Phenotypic personality. In all samples, personality was assessed with NEO PI–R[31] or NEO PI–3[32], comprehensive personality questionnaires measuring the five broad personality domains and

their 30 facets with a total of 240 questions. Answers were provided on five-point Likert scales. To maximize prediction, the items were aggregated in composite PPSs, detailed in the Statistical analyses section.

Phenotypic BMI. BMI (kg/m^2) was calculated as weight in kilograms divided by height in meters squared. Height and weight were self-reported in the Japanese, as well as in part of the Australian and German samples, and measured objectively in others.

Personality and BMI allele scores. Allele scores were calculated for BMI and, where possible, personality traits, to be used in Mendelian randomization. As an aggregate score of genetic effects on a phenotypic trait, an allele score reflects an individual's genetic propensity for the trait. Calculation of the allele scores is detailed in the Statistical analyses section.

Statistical analyses

Phenotypic personality scores. For each participant in the Mendelian randomization and DoC analyses, three types of PPSs were calculated: an all-encompassing PPS_{ALL}, an eating-specific PPS_{EAT}, and a domain-general PPS_{GEN}. Namely, PPS_{ALL} was calculated from all 240 personality questions. To disentangle the links of eating-related personality from domain-general personality, we additionally created an eating-specific PPS_{EAT} from two personality items (N5.4 "Overeats favorite foods" and N5.6 "Eats excessively") reflecting Uncontrolled Eating—a trait robustly correlated with BMI[33]. We also created a domain-general PPS_{GEN} excluding these two items. This enabled us to clarify whether personality–BMI links were solely driven by the two eating-specific questions. To create the PPSs, the NEO PI items included in the scores were weighted by their empirical association with BMI (calculated in independent samples) and subsequently summed. A regression-based procedure, the least absolute shrinkage and selection operator[34], was

used to calculate the weights. As a way of dealing with multicollinearity, this procedure sets the weights for some predictors to zero, effectively eliminating their contributions; the number of items remaining in the PPSs after weighting can be seen in **Table 1**. The weighting procedure is described in the Supplement; details on the weights and samples used to create them can be found in Supplementary Tables 3–6.

Prior to use in main analyses, the PPSs were validated in terms of predictive performance by regressing them on BMI—the target phenotype. The relative independence of PPS_{GEN} and PPS_{EAT} was further assessed by regressing the former on the latter. PPS validation was done on a combined sample of the Estonian Biobank and the twin samples (total N=9 151).

Allele scores. Allele scores of BMI and personality traits were calculated for each individual in the Estonian Biobank from independent samples. The allele scores included single nucleotide polymorphisms (SNPs) that correlated with their target phenotype at a genome-wide significance level ($P<5\times10^{-8}$) in UK Biobank data. To exclude the SNPs from each allele score that correlated more strongly with the outcome than with the intended phenotype, we applied a Steiger filtering procedure (detailed in the Supplement). Each trait-increasing SNP's effect on the target phenotype was multiplied by the count of the allele present in the individual. The SNPs included in each allele score are listed in Supplementary Tables 9–12. Weights were calculated from an automatic genome-wide association study (GWAS) using UK Biobank data[35], N=461 460. Of personality traits, we were able to obtain allele scores for Neuroticism (N=390 278), as well as for two narrower traits within the Neuroticism domain: Worry (N=348 219) and Depressive Affect (N=357 957)[27]. Although the Neuroticism, Worry, and Depressive Affect allele scores were weighted with Eysenck's Personality Questionnaire–Revised[36] data, they were used to

predict the largely overlapping NEO PI Neuroticism domain[37] and its facets N1 Anxiety and N3 Depression, respectively, in the Estonian Biobank. Prior to the Mendelian randomization analyses, phenotypic BMI and personality traits were regressed on their allele scores (weighted in the UK Biobank) to confirm sufficient predictive power in Estonian Biobank.

We also attempted to create allele scores for other broad personality factors based on available GWAS data[38]. Possibly due to low sample size (N≈60 000), these allele scores were underpowered and therefore not included in further analyses. Creation of allele scores is described in more detail in the Supplement.

Mendelian randomization. In the Mendelian randomization analysis the allele scores were used to predict relevant phenotypes in the Estonian Biobank cohort: the PPSs were regressed on BMI's allele score, and phenotypic BMI on the allele scores of Neuroticism, Worry, and Depressive Affect, controlling for age, age^2, sex, and 10 principal components of ancestry.

Although Mendelian randomization is often conducted using single genetic variants, combining the effects of many SNPs in allele scores was necessary to reach sufficient statistical power. To minimize potential confounders and pleiotropic effects arising from the use of many SNPs[18], only GWAS-significant ($P<5\times10^{-8}$) variants were included in the allele scores. Further details regarding the power considerations of Mendelian randomization can be found in the Supplement.

While Mendelian randomization analyses are less susceptible to confounding than common observational studies[39], the method requires the consideration of three central assumptions[39]: (a) that the genetic instrument (here: allele score) is associated with its corresponding phenotype, (b) that the genetic instrument and the outcome do not share common

causes, and (c) that the genetic instrument is associated with the outcome only through the intermediate phenotype (i.e, the genetic instrument does not have a direct effect on the outcome). Assumption (a) was assessed by calculating regression coefficients, partial F, and R^2 statistics between allele scores and their corresponding phenotypes (see **Table 1**). Because no testing procedure can definitively rule out common causes, assumption (b) cannot be fully assessed. However, common causes between genetic variants and outcomes can arise due to ancestry effects, which were controlled for by including 10 principal components of ancestry in the models.

As a rule, assumption (c) is the most problematic in Mendelian randomization studies as pleiotropic effects are not easy to rule out. Knowledge of the biological processes through which the genetic variants are related to the phenotypes would be required[39]; however, such knowledge is currently unavailable and, in case of allele scores comprising large numbers of genetic variants, the information is particularly unlikely to be available. Still, a procedure known as MR-Egger regression can estimate pleiotropic effects, and was applied to statistically significant associations (detailed in the Supplement). Applying Steiger filtering and using a stringent *P*-value in SNP selection ($P<5\times10^{-8}$) additionally decrease the likelihood of pleiotropic effects[18]. Yet another way to ensure robustness of the findings is to compare them to the results of complementary methods[19]. In the current study, this was done with DoC analyses.

Direction of Causation. With DoC models, quasi-causal effects can be tested on cross-sectional phenotypic twin data[28]. Variance in the phenotypes of interest (BMI and the PPSs) in the combined twin sample was partitioned into additive genetic (A), common-to-siblings environmental (C), and unique-to-individual environmental (E) components based on the

average genetic similarity between monozygotic and dizygotic twin pairs. This method assumes that a causal trait would leave a trace on the outcome trait. Namely, the variance components of the purported causal variable should be proportionally represented in the outcome: for instance, if the causal variable has a large C component, then the C component should be accordingly present in the outcome[20]. The best-fitting causal model is chosen by comparing the observed covariance structure to those implied by different causal models. When certain assumptions are met (discussed in the Supplement), the best-fitting model implies causal associations between the traits at the phenotypic level.

For each PPS, we compared four models: 1) correlated (a common cause for BMI and PPS), 2) reciprocal causation, 3) forward causation (PPS influencing BMI), and 4) reverse causation (BMI influencing PPS). All analyses were run in Mplus[40], controlling for age, age^2, cohort, and sex.

Fit of the DoC models was assessed using Root Mean Square Error of Approximation (RMSEA) and the Comparative Fit Index (CFI) with RMSEA<.05 and CFI>.95 suggesting good fit[41,42]. The fit of hierarchically nested models was compared using the χ^2 test: the reciprocal model was tested against the correlated model, and the unidirectional forward and reverse models against the reciprocal and correlated models. Where χ^2 *P*-values did not differ, the more parsimonious model was preferred. Comparison of the two non-nested unidirectional models was based on Akaike information criterion (AIC) with $\Delta AIC \geq 4$ signifying meaningfully different models[43].

DoC analyses also require certain considerations to be met[28,44]. The considerations and the tests conducted to assess them are described in the Supplement; results of the tests are reported in

Supplementary Table 7 along with power calculations in Supplementary Table 8. We found the considerations to be met. Importantly, the proportions of heritability were required to be and indeed found to be different for BMI (74%) and PPS (42%).

Test-retest reliabilities were incorporated in the models to avoid biases arising from reliability differences. Test-retest reliability was established for PPS_{ALL} from 263 assessments over 7–10 days (.89[45]), and for BMI from 170 assessments over 7 days (.95[46]).

To clarify whether the same causal model fit the data across all BMI levels, we ran follow-up DoC analyses with a) underweight (BMI<18.5) participants excluded, *N*=4 898, and b) overweight (BMI≥25) participants excluded, *N*=4 163. As only borderline significant differences were found between alternative models in some cases, we additionally applied a local structural equation modeling (LOSEM) approach[47] to provide an additional way to compare model fit at different BMI levels. Detailed descriptions of the follow-up analyses can be found in the Supplement.

BMI was log-transformed in all analyses. The analytic process is outlined in **Figure 1**.

Code availability

Code for the analyses is available at https://osf.io/meqxn/.

Results

Predictive performance of allele scores and phenotypic personality scores

As specified in **Table 1**, the allele scores for BMI, Neuroticism and Worry significantly predicted their target phenotype, suggesting their suitability for use as indicators of genetic propensity for the traits. The allele score for Depressive Affect, however, fell short of statistical significance in predicting its target phenotype, suggesting that it may not be able to capture

effects on related outcomes.

Further, we found that each PPS captured additional variation in BMI after accounting for age, age^2, cohort, and sex, supporting their applicability as BMI-specific personality scores. Results of these regressions are detailed in **Table 1** along with allele score validation. Although significant, the association between the domain-general PPS_{GEN} and the two-item PPS_{EAT} was modest (β=0.06; *SE*=0.01; *P*<.001; R^2=0.003; 95% CI 0.001, 0.006) compared to the PPSs' associations with BMI, suggesting that the PPSs were largely able to isolate eating-specific from domain-general personality effects.

Mendelian randomization

Results of Mendelian randomization are shown in **Table 2**. We found a negative effect of the allele score of Worry on phenotypic BMI, while the allele scores of Neuroticism and Depressive Affect had no detectable effect; in the latter case, however, the lack of effect may be explained by the allele score's low predictive power. In the reverse direction, BMI's allele score was able to predict all three PPSs, suggesting an effect of BMI-related genetic variation on eating-specific as well as domain-general personality traits. We found no evidence for pleiotropic effects in any of the significant associations (see the Supplement for results). Altogether, this suggests that BMI may influence eating-specific as well as domain-general personality traits, whereas certain personality traits like Worry may also influence BMI.

Direction of Causation

Table 3 details fit indices and model comparison results for each PPS. Coefficients are specified in **Table 4** for the best-fitting models and in Supplementary Table 13 for the remaining models. For the eating-specific PPS_{EAT}, the reverse model fit best, and for the all-encompassing

$PPS_{ALL,}$ the reverse model was close in fit to the more complex reciprocal model and was preferred as the more parsimonious model. The reciprocal model fit best for the domain-general PPS_{GEN}. Interestingly, in this model, the forward direction (PPS_{GEN} influencing BMI) had a negative coefficient and the reverse direction (BMI influencing PPS_{GEN}) a positive coefficient, suggesting a negative feedback loop between BMI and PPS_{GEN}. Remarkably, the forward model had the worst fit across all three PPSs as it significantly differed from the correlated and reciprocal models in terms of χ^2 (**Table 3**). Thus, while BMI appeared to influence eating-related as well as domain-general personality traits, domain-general personality may have additionally had a comparatively smaller influence on BMI.

In the follow-up DoC analysis with underweight participants excluded, the reciprocal model fit best for PPS_{GEN} whereas the reverse model fit best for PPS_{EAT} and PPS_{ALL}. With overweight participants excluded, on the other hand, the difference between the reverse and reciprocal models was borderline significant for PPS_{EAT} (P=.037) while the reverse model was superior for PPS_{GEN} and PPS_{ALL} (see Supplementary Tables 14–15 for BMI subgroup analyses). The LOSEM analyses suggested influences of BMI on PPS_{EAT} across all BMI levels, and a switch from BMI unidirectionally influencing PPS_{GEN} to reciprocal influences between them at BMI≈25 (Supplementary Figure 1). Altogether, these follow-up analyses suggest influences of BMI on the PPSs with additional reciprocal influences at higher BMI levels for domain-general personality.

Results of the main analyses are summarized in **Figure 2**.

Discussion

Two genetic analyses indicated a potential influence of BMI on personality traits. Genetic

propensity for BMI predicted eating-related and domain-general PPSs—aggregates of BMI-related personality traits. In contrast, although genetic propensity for Worry predicted lower BMI, no such effect was detected for the broader Neuroticism domain. Analyses on twin data corroborated the effect of BMI on personality traits in all models. A reciprocal effect emerged for domain-general personality, particularly in higher-weight individuals. Namely, BMI had a positive effect on aggregate personality traits, whereas personality traits had a slightly decreasing effect on BMI in return. This suggests a compensatory effect of relevant personality traits on BMI. Notably, the reciprocal model fit best for people with BMI≈25 and higher. As this number roughly corresponds to the lower bound of overweight, there may be something unique to excess weight that triggers effects of personality on BMI. Yet, effect sizes from DoC suggest that even in higher-weight individuals, the influence of BMI on personality may dominate over the opposite effect.

BMI influencing eating-specific personality is consistent with higher BMI leading to a higher overall energy requirement[48], thereby affecting eating behaviors like Uncontrolled Eating[49]. It is unclear whether this effect is purely driven by the energy need of increased fat-free mass or also cognitions about weight status which are likely driven by fat mass. In a broader sense, the personality profile of obesity could be considered a collection of behavioral symptoms accompanying obesity. For instance, people with overweight and obesity tend to score higher than normal-weight individuals on facets of Neuroticism and lower on facets of Conscientiousness[13]—the two personality domains in which people most often wish to change[50]. Although additional analyses are necessary to clarify if weight change can influence personality traits, if this is the case, maintaining or achieving a healthy BMI may influence traits favorably.

While evidence for BMI influencing the PPSs emerged across both genetic methods employed, the results regarding Neuroticism-related traits should be interpreted more cautiously. Although similar negative relations between aspects of Neuroticism and BMI have been reported previously[27,51,52], positive correlations have been found elsewhere[13,53]. Although the allele score for Depressive Affect was underpowered and may have potentially missed a link with BMI, the fact that the allele score for Worry, but not Neuroticism, negatively predicted BMI, suggests that a focus on narrower personality traits is warranted. Still, given the contradictory findings regarding Worry and similar traits in extant literature, making conclusions regarding their possible effects on body weight would be premature. Future studies could consider potential moderators to clarify the nature of their links.

Current findings also have broader implications for personality development. Although some[54] have been skeptical toward the possibility of identifying specific drivers of personality development and such effects have indeed remained elusive[55], our analyses suggest that body weight may be among the contributors to personality development. Despite the substantial genetic contribution to overweight[56], lifestyle changes—regulation of food environments[57] or physical activity[58], for instance—can to some extent override genetic propensity for high BMI. This may, in turn, affect personality, possibly through biological mechanisms or the social environment. As personality traits are linked with various mental health disorders[6] including eating disorders[59], the potential for personality change may play a role in their development or treatment. Even beyond clinical populations, most people would like to change their personality and success in doing so is associated with increased well-being[50,60]. Although effects may be small, having a healthy BMI could contribute to such goals.

While strengths of the current work include the use of different statistical approaches and multiple samples, our analyses were not without limitations. First, due to the unavailability of well-powered GWASs, we were unable test the effects of single personality traits outside the Neuroticism domain on BMI. Similarly, while using PPSs provided the necessary statistical power, this approach simultaneously limited our ability to distinguish specific traits and hindered our ability to evaluate the magnitude of effects. The results are informative about the direction of the effects of BMI and personality traits on each other, but not their magnitude; the logarithmic transformation applied to BMI should additionally be considered when interpreting the effects. Further, results of the genetic analyses do not necessarily imply that weight loss interventions lead to personality change as they may target other aspects of variance in BMI than the variance in BMI that relates to personality. Although some of the assumptions the current analyses relied upon were untestable, the convergence of results across two approaches strengthens our conclusions.

To conclude, in a novel application of two types of genetically informative analyses, BMI was found to be a potential contributor to personality differences. These findings counter common assumptions about the direction of causal effects, highlighting ways in which BMI may be relevant in mental health and well-being. While personality traits may additionally influence BMI, especially in higher-weight individuals, their combined effects appear weaker. If weight management interventions are to consider personality, knowledge of narrow traits' role in body weight is required; for instance, domain-level Neuroticism may be too broad a focus, but its facet Worry may turn out to be relevant. Although current results may not generalize to weight loss interventions, if BMI does influence personality, achieving a healthy weight may also manifest

favorably in psychological traits. This remains to be clarified in future research.

Acknowledgements

UV has been funded by Estonian Research Council grant MOBTP94.

Supplementary information is available at International Journal of Obesity's website and at https://osf.io/preprints/nutrixiv/q8ehr/

Competing interests

The authors declare no competing financial interests.

References

1 Tremmel M, Gerdtham U-G, Nilsson PM, Saha S. Economic burden of obesity: A systematic literature review. *Environ Res Public Health* 2017; **14**: 435.

2 The GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med* 2017; **377**: 13–27.

3 Jokela M, Hintsanen M, Hakulinen C, Batty GD, Nabi H, Singh-Manoux A *et al.* Association of personality with the development and persistence of obesity: A meta-analysis based on individual-participant data. *Obes Rev* 2013; **14**: 315–323.

4 Davey Smith G, Holmes MV, Davies NM, Ebrahim S. Mendel's laws, Mendelian randomization and causal inference in observational data: Substantive and nomenclatural issues. *Eur J Epidemiol* 2020; **35**: 99–111.

5 Friedman HS. Neuroticism and health as individuals age. *Personality Disorders: Theory, Research, and Treatment* 2019; **10**: 25–32.

6 Widiger TA. Personality and psychopathology. *World Psychiatry* 2011; **10**: 103–106.

7 Roberts BW, Kuncel NR, Shiner R, Caspi A, Goldberg LR. The power of personality: The comparative validity of personality traits, socioeconomic status, and cognitive ability for predicting important life outcomes. *Perspect Psychol Sci* 2007; **2**: 313–345.

8 Murray AL, Booth T. Personality and physical health. *Curr Opin Psychol* 2015; **5**: 50–55.

9 Bleidorn W, Hill PL, Back MD, Denissen JJA, Hennecke M, Hopwood CJ *et al.* The policy relevance of personality traits. *Am Psychol* 2019; **74**: 1056–1067.

10 Gerlach G, Herpertz S, Loeber S. Personality traits and obesity: A systematic review. *Obes Rev* 2015; **16**: 32–63.

11 McCrae RR. A more nuanced view of reliability: Specificity in the trait hierarchy. *Pers Soc Psychol Rev* 2015; **19**: 97–112.

12 Mõttus R. Towards more rigorous personality trait-outcome research. *Eur J Pers* 2016; **30**: 292–303.

13 Vainik U, Dagher A, Realo A, Colodro-Conde L, Mortensen EL, Jang K *et al.* Personality-obesity associations are driven by narrow traits: A meta-analysis. *Obes Rev* 2019; **20**: 1121–1131.

14 Armon G, Melamed S, Shirom A, Shapira I, Berliner S. Personality traits and body weight measures: Concurrent and across-time associations. *Eur J Pers* 2013; **27**: 398–408.

15 Hampson SE, Edmonds GW, Goldberg LR, Dubanoski JP, Hillier TA. A life-span behavioral mechanism relating childhood conscientiousness to adult clinical health. *Health Psychol* 2015; **34**: 887–895.

16 Lahti M, Räikkönen K, Lemola S, Lahti J, Heinonen K, Kajantie E *et al.* Trajectories of physical growth and personality dimensions of the Five-Factor Model. *J Pers Soc Psychol* 2013; **105**: 154–169.

17 Bordignon S, Aparício MJG, Bertoletti J, Trentini CM. Personality characteristics and bariatric surgery outcomes: A systematic review. *Trends Psychiatry Psychother* 2017; **39**: 124–134.

18 Pingault J-B, O'Reilly PF, Schoeler T, Ploubidis GB, Rijsdijk F, Dudbridge F. Using genetic data to strengthen causal inference in observational research. *Nat Rev Genet* 2018; **19**: 566–580.

19 Lawlor DA, Tilling K, Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol*

427 2017;: dyw314.
428 20 Briley DA, Livengood J, Derringer J. Behaviour genetic frameworks of causal reasoning for
429 personality psychology. *Eur J Pers* 2018; **32**: 202–220.
430 21 Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, Davey Smith G. Best (but oft-
431 forgotten) practices: The design, analysis, and interpretation of Mendelian randomization studies.
432 *Am J Clin Nutr* 2016; **103**: 965–978.
433 22 Lawlor DA, Harbord RM, Tybjaerg-Hansen A, Palmer TM, Zacho J, Benn M *et al.* Using
434 genetic loci to understand the relationship between adiposity and psychological distress: A
435 Mendelian Randomization study in the Copenhagen General Population Study of 53,221 adults.
436 *J Intern Med* 2011; **269**: 525–537.
437 23 Wootton RE, Lawn RB, Millard LAC, Davies NM, Taylor AE, Munafò MR *et al.* Evaluation
438 of the causal effects between subjective wellbeing and cardiometabolic health: Mendelian
439 randomisation study. *BMJ* 2018; **362**. doi:10.1136/bmj.k3788.
440 24 Martins-Silva T, Vaz J dos S, Hutz MH, Salatino-Oliveira A, Genro JP, Hartwig FP *et al.*
441 Assessing causality in the association between attention-deficit/hyperactivity disorder and
442 obesity: A Mendelian randomization study. *Int J Obes* 2019; **43**: 2500–2508.
443 25 Chabris CF, Lee JJ, Benjamin DJ, Beauchamp JP, Glaeser EL, Borst G *et al.* Why it is hard to
444 find genes associated with social science traits: Theoretical and empirical considerations. *Am J*
445 *Public Health* 2013; **103**: S152–S166.
446 26 Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR *et al.* Genetic studies of body
447 mass index yield new insights for obesity biology. *Nature* 2015; **518**: 197–206.
448 27 Nagel M, Watanabe K, Stringer S, Posthuma D, van der Sluis S. Item-level analyses reveal

449 genetic heterogeneity in neuroticism. *Nat Commun* 2018; **9**: 905.
450 28 Heath AC, Kessler RC, Neale MC, Hewitt JK, Eaves LJ, Kendler KS. Testing hypotheses
451 about direction of causation using cross-sectional family data. *Behav Genet* 1993; **23**: 29–50.
452 29 Leitsalu L, Haller T, Esko T, Tammesoo M-L, Alavere H, Snieder H *et al.* Cohort profile:
453 Estonian Biobank of the Estonian Genome Center, University of Tartu. *Int J Epidemiol* 2015; **44**:
454 1137–1147.
455 30 Reile R, Tekkel M, Veideman T. Eesti täiskasvanud rahvastiku tervisekäitumise uuring 2018
456 [Health Behaviour among Estonian Adult Population 2018]. National Institute for Health
457 Development, 2019.
458 31 Costa PT, McCrae RR. *Revised NEO personality inventory (NEO PI-R) and NEO five-factor*
459 *inventory (NEO-FFI): Professional manual*. Psychological Assessment Resources, Inc: Odessa,
460 FL, 1992.
461 32 McCrae RR, Costa PT Jr., Martin TA. The NEO-PI-3: A more readable revised NEO
462 Personality Inventory. *J Pers Assess* 2005; **84**: 261–270.
463 33 Vainik U, Neseliler S, Konstabel K, Fellows LK, Dagher A. Eating traits questionnaires as a
464 continuum of a single concept. Uncontrolled eating. *Appetite* 2015; **90**: 229–239.
465 34 Yarkoni T, Westfall J. Choosing prediction over explanation in psychology: Lessons from
466 machine learning. *Perspect Psychol Sci* 2017; **12**: 1100–1122.
467 35 Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D *et al.* The MR-Base
468 platform supports systematic causal inference across the human phenome. *eLife* 2018; **7**: e34408.
469 36 Eysenck SBG, Eysenck HJ, Barrett P. A revised version of the psychoticism scale. *Pers Indiv*
470 *Dif* 1985; **6**: 21–29.

37 Draycott SG, Kline P. The Big Three or the Big Five - the EPQ-R vs the NEO-PI: A research note, replication and elaboration. *Pers Indiv Dif* 1995; **18**: 801–804.

38 Lo M-T, Hinds DA, Tung JY, Franz C, Fan C-C, Wang Y *et al.* Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nat Genet* 2017; **49**: 152–156.

39 Davies NM, Holmes MV, Smith GD. Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. *BMJ* 2018; **362**. doi:10.1136/bmj.k601.

40 Muthén MK, Muthén B. *Mplus. The comprehensive modelling program for applied researchers: User's guide*. 2016.

41 Hu L-t, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Struct Equ Modeling* 1999; **6**: 1–55.

42 MacCallum RC, Browne MW, Sugawara HM. Power analysis and determination of sample size for covariance structure modeling. *Psychol Methods* 1996; **1**: 130–149.

43 Burnham KP, Anderson DR. Multimodel inference: Understanding AIC and BIC in model selection. *Sociol Method Res* 2004; **33**: 261–304.

44 Rasmussen SHR, Ludeke S, Hjelmborg JVB. A major limitation of the direction of causation model: Non-shared environmental confounding. *Twin Res Hum Genet* 2019; **22**: 14–26.

45 Henry S, Mõttus R. Traits versus adaptations: Examining item-level characteristics of the five-factor model of personality. 2018.https://osf.io/3cebh/ (accessed 9 Feb2020).

46 Leatherdale ST, Laxer RE. Reliability and validity of the weight status and dietary intake measures in the COMPASS questionnaire: Are the self-reported measures of body mass index (BMI) and Canada's food guide servings robust? *Int J Behav Nutr Phys Act* 2013; **10**: 42.

47 Briley DA, Harden KP, Bates TC, Tucker-Drob EM. Nonparametric estimates of gene environment interaction using local structural equation modeling. *Behav Genet* 2015; **45**: 581–596.

48 Blundell JE, Gibbons C, Beaulieu K, Casanova N, Duarte C, Finlayson G *et al.* The drive to eat in homo sapiens: Energy expenditure drives energy intake. *Physiol Behav* 2020; **219**: 112846.

49 Vainik U, García-García I, Dagher A. Uncontrolled eating: A unifying heritable trait linked with obesity, overeating, personality and the brain. *European Journal of Neuroscience* 2019; **50**: 2430–2445.

50 Hudson NW, Roberts BW. Goals to change personality traits: Concurrent links between personality traits, daily behavior, and goals to change oneself. *J Res Pers* 2014; **53**: 68–83.

51 Millard LAC, Davies NM, Tilling K, Gaunt TR, Davey Smith G. Searching for the causal effects of body mass index in over 300 000 participants in UK Biobank, using Mendelian randomization. *PLOS Genetics* 2019; **15**: e1007951.

52 Weiss A, Deary IJ. A new look at neuroticism: Should we worry so much about worrying? *Curr Dir Psychol Sci* 2020; **29**: 92–101.

53 Emery RL, Levine MD. Questionnaire and behavioral task measures of impulsivity are differentially associated with body mass index: A comprehensive meta-analysis. *Psychol Bull* 2017; **143**: 868–902.

54 Turkheimer E, Pettersson E, Horn EE. A phenotypic null hypothesis for the genetics of personality. *Annu Rev Psychol* 2014; **65**: 515–540.

55 Denissen JJA, Luhmann M, Chung JM, Bleidorn W. Transactions between life events and personality traits across the adult lifespan. *J Pers Soc Psychol* 2019; **116**: 612–633.

56 Silventoinen K, Jelenkovic A, Sund R, Yokoyama Y, Hur YM, Cozen W *et al*. Differences in genetic and environmental variation in adult BMI by sex, age, time period, and region: An individual-based pooled analysis of 40 twin cohorts. *Am J Clin Nutr* 2017; **106**: 457–66.

57 Schrempft S, Jaarsveld CHM van, Fisher A, Herle M, Smith AD, Fildes A *et al.* Variation in the heritability of child body mass index by obesogenic home environment. *JAMA Pediatr* 2018; **172**: 1153–1160.

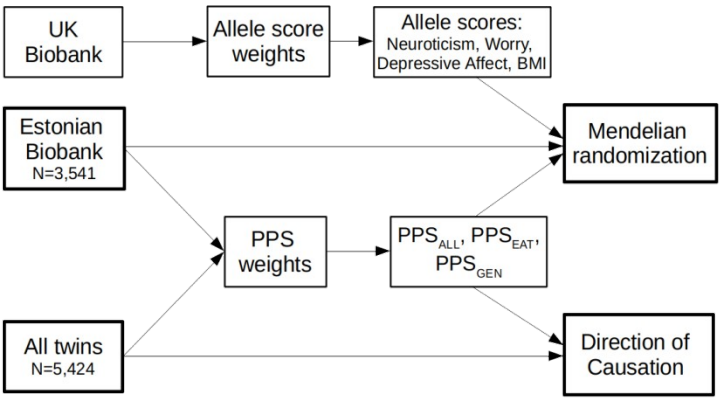
58 Horn EE, Turkheimer E, Strachan E, Duncan GE. Behavioral and environmental modification of the genetic influence on body mass index: A twin study. *Behav Genet* 2015; **45**: 409–426.

59 Levallius J, Clinton D, Bäckström M, Norring C. Who do you think you are? - Personality in eating disordered patients. *J Eat Disord* 2015; **3**: 3.

60 Hudson NW, Fraley RC. Changing for the better? Longitudinal associations between volitional personality change and psychological well-being. *Pers Soc Psychol Bull* 2016; **42**: 603–615.

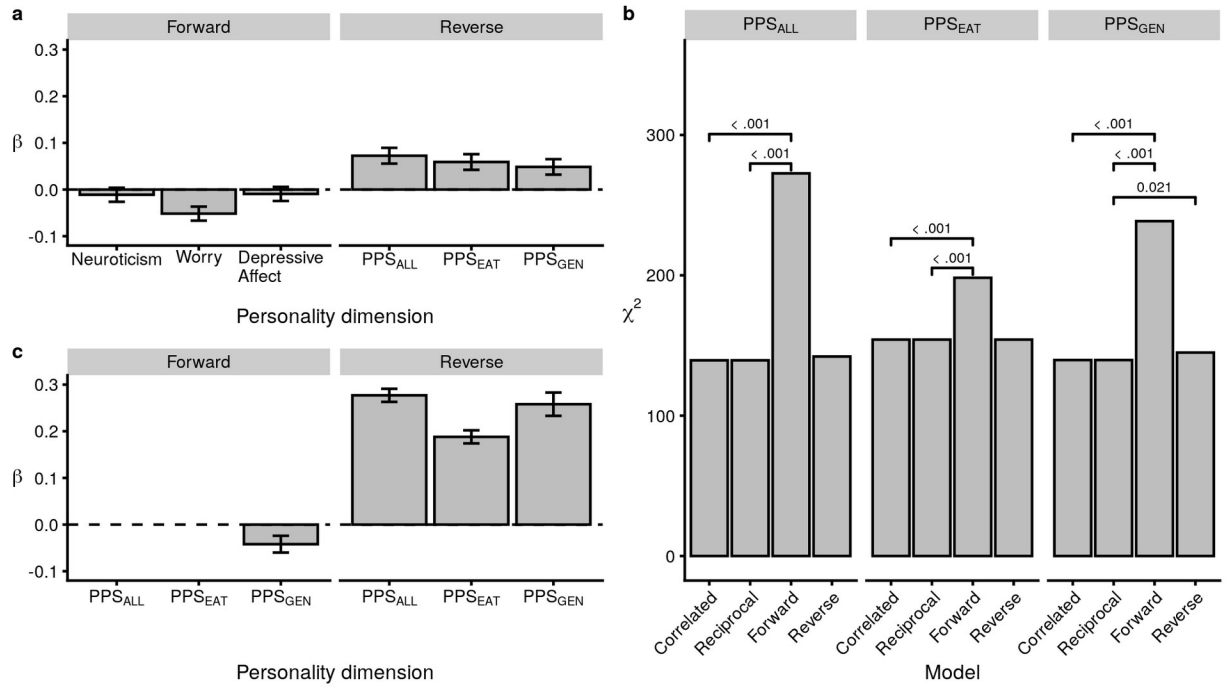
Figures

Figure 1. The analytic process.



Note. PPS=phenotypic personality score. PPS_{ALL} was calculated from all 240 personality items, PPS_{EAT} includes two eating-specific items and PPS_{GEN} was calculated from the remaining 238 items.

Figure 2. A graphical summary of the main findings.



Note. Panel **a** shows standardized Mendelian randomization coefficients. The forward direction represents effects of Neuroticism-related allele scores on phenotypic BMI; the reverse direction represents effects of BMI allele score on the PPSs. Panel **b** illustrates model comparison in Direction of Causation analyses. The figure specifies only *P*-values of key comparisons; the remaining significance values are indicated in **Table 3**. Correlated model=no causal effects between BMI and personality; reciprocal model=bidirectional causation between BMI and personality; forward model=personality influences BMI; reverse model=BMI influences personality. Panel **c** shows the effects between BMI and personality in Direction of Causation analyses. The best-fitting models suggest that BMI unidirectionally influences PPS_{ALL} and PPS_{EAT}, but influences between BMI and PPS_{GEN} are bidirectional. The forward direction indicates the effect of personality on BMI; the reverse direction indicates the effects of BMI on

personality.

PPS=phenotypic personality score. PPS_{ALL} was calculated from all 240 personality items, PPS_{EAT} includes two eating-specific items and PPS_{GEN} was calculated from the remaining 238 items.

Error bars in panels **a** and **c** represent standard errors.

Table 1. Validation of allele scores and phenotypic personality scores

Validated score	Phenotype	Items[a]	β [95% CI]	*SE*	*t*	*P*	R^2 [95% CI]	χ^2/partial F^b
Allele score								
BMI	BMI	957	0.21 [0.18, 0.23]	0.01	14.02	<.001	0.042 [0.031, 0.054]	196.44
Neuroticism	Neuroticism	109	0.07 [0.03, 0.10]	0.02	3.99	<.001	0.004 [0.001, 0.009]	15.88
Worry	N1: Anxiety	59	0.05 [0.01, 0.08]	0.02	2.79	0.005	0.002 [0.000, 0.006]	7.80
Depressive Affect	N3: Depression	61	0.03 [-0.01, 0.06]	0.02	1.52	0.129	0.001 [0.000, 0.004]	2.31
Phenotypic personality score								
PPS_{ALL}	BMI	115–156	0.18 [0.17, 0.20]	0.01	23.94	< .001	0.047 [0.039, 0.056]	551.05
PPS_{GEN}	BMI	113–154	0.12 [0.10, 0.13]	0.01	14.84	< .001	0.018 [0.013, 0.024]	217.03
PPS_{EAT}	BMI	2	0.15 [0.13, 0.17]	0.01	19.43	< .001	0.031 [0.025, 0.039]	367.22

Note. PPS=phenotypic personality score. The betas represent the change in the phenotype given a one-unit increase in the allele score or PPS, controlling for age, age^2, sex, and, for allele scores, 10 principal components of ancestry. The units of the PPSs are not interpretable in a straightforward manner as the scores were constructed by weighting personality item scores by their associations with BMI. Incremental R^2s for PPSs were calculated accounting for age, age^2, sex, and, for allele scores, 10 principal components of ancestry. Confidence intervals were estimated using bootstrapping (1 000 iterations). Allele score weights were derived from UK Biobank data[35]. *N*=9 151 for PPSs, *N*=3 541 for allele scores.

[a] Number of personality items included in PPSs or number of SNPs included in allele scores. PPS_{ALL} was calculated from an initial set of all 240 personality items, PPS_{EAT} includes two eating-specific items and PPS_{GEN} was calculated from the remaining 238 items. The table indicates the numbers of predictors with nonzero weights included in PPS_{ALL} and PPS_{EAT} after applying the least absolute shrinkage and

selection operator. Separate weights were calculated for each training subsample; ranges reflect the number of items included in the PPSs in different subsamples.

[b] Partial *F* is reported for allele scores; χ^2 is reported for the PPSs as the linear models also included a random intercept for family structure of the twin data.

564 **Table 2.** Prediction of phenotypes in Mendelian randomization

Allele score	Phenotype	β [95% CI]	*SE*	*t*	*P*	R^2 [95% CI]	Partial *F*
Neuroticism	BMI	-0.01 [-0.04, 0.02]	0.02	-0.74	0.459	0.000 [0.000, 0.002]	0.55
Worry	BMI	-0.05 [-0.08, -0.02]	0.02	-3.43	<.001	0.003 [0.001, 0.006]	11.79
Depressive Affect	BMI	-0.01 [-0.04, 0.02]	0.02	-0.62	0.533	0.001 [0.000, 0.002]	0.39
BMI	PPS_{ALL}	0.07 [0.04, 0.11]	0.02	4.29	<.001	0.005 [0.002, 0.011]	18.38
BMI	PPS_{EAT}	0.06 [0.03, 0.09]	0.02	3.52	<.001	0.003 [0.001, 0.008]	12.36
BMI	PPS_{GEN}	0.05 [0.02, 0.08]	0.02	2.93	0.003	0.002 [0.000, 0.006]	8.60

565 *Note.* PPS=phenotypic personality score. PPS_{ALL} was calculated from all 240 personality items, PPS_{EAT} includes two eating-specific items
566 and PPS_{GEN} was calculated from the remaining 238 items. The betas represent the change in the outcome phenotype given a one-unit increase
567 in the allele score, controlling for age, age^2, sex, and 10 principal components of ancestry. The betas are informative about the directions of
568 the effects and their size in comparison to other effects measured in the same units, but do not directly translate to the magnitude of the effect
569 of changes in phenotypic personality traits on BMI or vice versa. Incremental R^2s for PPSs were calculated accounting for age, age^2, sex,
570 and 10 principal components of ancestry. *N*=3 541.

571 **Table 3.** Comparison of models in Direction of Causation analyses

Model	χ^2	*df*	Compared to Correlated	Compared to Reciprocal	AIC	CFI	RMSEA
PPS_{ALL}							
Correlated	139.44	71	-	-	28 302.13	0.97	0.03
Reciprocal	139.44	72	> .999	-	28 300.13	0.97	0.03
Forward	272.61	73	< .001	< .001	28 431.30	0.92	0.06
Reverse	142.11	73	.263	.102	28 300.80	0.97	0.03
PPS_{EAT}							
Correlated	154.19	71	-	-	28 407.68	0.97	0.04
Reciprocal	154.19	72	> .999	-	28 405.68	0.97	0.04
Forward	198.23	73	< .001	< .001	28 447.72	0.95	0.04
Reverse	154.19	73	> .999	.975	28 403.68	0.97	0.04
PPS_{GEN}							
Correlated	139.65	71	-	-	28 443.97	0.97	0.03
Reciprocal	139.65	72	> .999	-	28 441.97	0.97	0.03
Forward	238.60	73	< .001	< .001	28 538.92	0.93	0.05

Reverse	144.97	73	.070	.021	28 445.30	0.97	0.03

Note. PPS=phenotypic personality score, correlated model=no causal effects between BMI and personality, reciprocal model=bidirectional causation between BMI and personality, forward model=personality influences BMI, reverse model=BMI influences personality, AIC=Akaike Information Criterion, CFI=Comparative Fit Index, RMSEA=Root Mean Square Error of Approximation. PPS_{ALL} was calculated from all 240 personality items, PPS_{EAT} includes two eating-specific items and PPS_{GEN} was calculated from the remaining 238 items.

Table 4. Estimates of the best-fitting Direction of Causation models for each phenotypic personality score

Phenotypic personality score	Model[a]	β [95% CI]	*P*
PPS_{ALL}	Reverse	0.28 [0.25, 0.30]	<.001
PPS_{EAT}	Reverse	0.19 [0.16, 0.22]	<.001
PPS_{GEN}	Reverse	0.21 [0.18, 0.24]	<.001
PPS_{GEN}	Reciprocal: PPS_{GEN} influencing BMI	-0.04 [-0.08, -0.01]	.022
	Reciprocal: BMI influencing PPS_{GEN}	0.26 [0.21, 0.31]	<.001

Note. Reverse model=BMI influences personality, reciprocal model=bidirectional causation between BMI and personality. PPS_{ALL} was calculated from all 240 personality items, PPS_{EAT} includes two eating-specific items and PPS_{GEN} was calculated from the remaining 238 items.

[a]Two models—reverse and reciprocal—are presented for PPS_{GEN} due to their borderline significant difference in fit (P=0.021). Coefficients for both directions of the reciprocal model are presented.