

Causal associations between body mass index and mental health: a Mendelian randomisation study

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ABSTRACT

Background Body mass index (BMI) is correlated negatively with subjective well-being and positively with depressive symptoms. Whether these associations reflect causal effects is unclear.

Methods We examined bidirectional, causal effects between BMI and mental health with Mendelian randomisation using summary-level data from published genome-wide association studies (BMI: $n=339\,224$; subjective well-being: $n=204\,966$; depressive symptoms: $n=161\,460$). Genetic variants robustly related to the exposure variable acted as instrumental variable to estimate causal effects. We combined estimates of individual genetic variants with inverse-variance weighted meta-analysis, weighted median regression and MR-Egger regression.

Results There was evidence for a causal, increasing effect of BMI on depressive symptoms and suggestive evidence for a decreasing effect of BMI on subjective well-being. We found no evidence for causality in the other direction.

Conclusion This study provides support for a higher BMI causing poorer mental health. Further research should corroborate these findings and explore mechanisms underlying this potential causality.

INTRODUCTION

Obesity and poor mental health are two of the most pressing public health problems.^{1,2} Previous studies suggested that body mass index (BMI) and mental health are correlated—increased adiposity is related to lower subjective well-being³ and more depressive symptoms.⁴ It is unclear, however, whether these associations are (partly) due to causal effects and if so, in which direction. Longitudinal studies support associations in both directions,⁵ suggesting that there are reciprocal causal effects and/or overlapping third variables (environmental and/or genetic risk factors).

Mendelian randomisation (MR) uses genetic variants related to a hypothesised cause (the exposure) as instruments to estimate the causal effect of this exposure on an outcome.⁶ Given the random nature of transmission of genes from parents to offspring, genetic variants are unlikely to be affected by confounders. Additionally, since genetic variation is fixed at conception, associations between genetic variants and outcomes cannot be attributed to reverse causality. MR relies on three assumptions: (1) the genetic instrument is predictive of the exposure, (2) the genetic instrument is independent of confounders and (3) there is no horizontal

pleiotropy (the genetic instrument does not affect the outcome, other than through its possible causal effect on the exposure). *Two-sample MR* takes a genetic instrument from a genome-wide association (GWA) study on the exposure variable and identifies the same instrument in a separate GWA study on the outcome variable. By using summary-level data of large scale, published GWA studies, this approach hugely increases statistical power.⁷

Previous *one-sample MR* studies exploring BMI and mental health yielded inconsistent results,^{8–11} potentially due to lack of power because of small sample sizes ($n=1731–4145$). With *two-sample MR*, Hartwig *et al*¹² showed weak, but consistent evidence of a causal effect of BMI on major depressive disorder (MDD), but not on bipolar disorder and schizophrenia. Recently, Wray *et al*¹³ performed the largest GWA meta-analysis of MDD and, with two-sample MR, found strong evidence for a causal increasing effect of BMI on MDD, but no indication of a causal effect in the other direction. For the first time, we perform bidirectional, two-sample MR to examine causal effects between BMI and less severe mental health problems, (lower) subjective well-being and depressive symptoms. These outcomes are much more prevalent in the general population than MDD and identifying potential causal links is therefore of high public health relevance. Knowledge of such causal links may enable us to intervene before full-blown disorders are present.

METHODS

Analyses were conducted with *MR-Base* in R statistical software.¹⁴ Causal effects were tested from BMI (summary statistics Genetic Investigation of ANthropometric Traits (GIANT) consortium; $n=339\,224$ ¹⁵) to subjective well-being (summary statistics Social Science Genetic Association Consortium (SSGAC); $n=204\,966$ (after the 23andMe sample was excluded¹⁶) and depressive symptoms (summary statistics from SSGAC consortium; $n=161\,460$ ¹⁶) and vice versa. Subjective well-being was measured by a combination of validated survey questions on life satisfaction and/or positive effect and depressive symptoms was a Diagnostic and Statistical Manual of Mental Disorders (DSM) oriented or International Classification of Diseases (ICD) oriented symptom count measure.¹⁶

Two sets of analyses were performed: one where only genetic variants (single nucleotide polymorphisms (SNPs)) exceeding the threshold for genome-wide significance ($p<5e-08$) in the exposure GWA study were included as instruments and one with



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Table 1 Causal effect estimates of BMI on SWB and DEP

Exposure	Outcome	P value threshold genetic instrument	N SNPs	IVW			Weighted median			MR-Egger		
				Beta	SE	P values	Beta	SE	P values	Beta	SE	P values
BMI	SWB	<5e-08	78	-0.05	0.02	0.025	-0.05	0.02	0.025	-0.13	0.05	0.011*
BMI	SWB	<1e-05	179	-0.03	0.01	0.046	-0.04	0.02	0.020	-0.10	0.04	0.004*
BMI	DEP	<5e-08	78	0.05	0.02	0.012*	0.08	0.03	0.003*	0.07	0.05	0.148
BMI	DEP	<1e-05	180	0.04	0.02	0.006*	0.07	0.02	0.004*	0.07	0.04	0.061

Nominal significant associations are in bold and associations surviving correction for multiple testing (alpha level of 0.0125 (0.05/4)) are denoted with an asterisk. BMI, body mass index; DEP, depressive symptoms; IVW, inverse variance weighted; MR, Mendelian randomization; SNP, single nucleotide polymorphism; SWB, subjective well-being.

genetic variants exceeding a less stringent threshold ($p < 1e-05$). Before analysis, SNPs were clumped ($r^2 < 0.001$).¹⁴ If a SNP was not present in the outcome GWA study, a proxy was identified (a SNP in high linkage disequilibrium, $r^2 \geq 0.80$).¹⁴ To provide an indication of instrument strength, we calculated the F-statistic for each SNP, $F > 10$ indicating a sufficiently strong instrument.

When a genetic instrument consisted of one SNP, the causal effect was estimated using the Wald ratio (*gene-outcome association/gene-exposure association*).⁶ For multiple SNPs, inverse-variance weighted (IVW) linear regression was applied, summing the ratio estimates of all variants in a weighted average formula.¹⁷ For genetic instruments with sufficient SNPs (≥ 10), we applied two sensitivity analyses which are more robust to horizontal pleiotropy and can indicate the validity of the IVW results. First, the weighted median approach, which can provide a consistent estimate of a causal effect even when up to 50% of the weight comes from invalid instruments.¹⁸ Second, MR-Egger regression, which adapts Egger's test for small study bias in meta-analyses to genetic instruments with multiple genetic variants. The MR-Egger intercept indicates whether there is horizontal pleiotropy.¹⁷

To further examine the robustness of our findings, we performed leave-one-out analysis, repeating IVW after excluding each of the SNPs, one at a time. Cochran's (Q) statistic was calculated to provide an indication of heterogeneity between the estimates of the individual SNPs.

Since we tested four different causal associations, we assumed a multiple testing alpha level of 0.0125 (0.05/4).

RESULTS

The main MR results are shown in [table 1](#) and Forest plots of the results per individual SNP is shown in the online Supplementary figure 1. For all analyses, instrument strength was sufficient ($F > 10$, online Supplementary table 1). We found suggestive evidence for a causal effect of BMI on subjective well-being, such that a higher BMI was associated with lowered well-being ([table 1](#); IVW analyses beta = -0.05, $p = 0.025$ and beta = -0.03, $p = 0.046$ for genetic instruments with p value threshold $5e-08$ and $1e-05$, respectively). Negative effects of similar magnitude were found with both sensitivity analyses. While MR-Egger

intercepts provided suggestive evidence for pleiotropy (online Supplementary table 2), the beta's (which are corrected for this potential pleiotropy) survived correction for multiple testing. Leave-one-out analysis indicated that the effect was largely driven by three influential SNPs (*rs1421085*, *rs943005* and *rs13021737*; online Supplementary table 2) and there was significant heterogeneity as indicated by Q (online Supplementary table 3).

There was evidence for a causal effect of BMI on depressive symptoms (IVW analyses beta = 0.05, $p = 0.012$ and beta = 0.04, $p = 0.006$, respectively). This positive effect, indicating that higher BMI increases depressive symptoms, was consistent in effect size and direction across both sensitivity analyses, but with weaker statistical evidence for MR-Egger. Since MR-Egger intercepts indicated no pleiotropy, it is likely that this analysis was simply underpowered.

There was no evidence for a causal effect in the opposite direction, from subjective well-being and depressive symptoms to BMI ([table 2](#)).

DISCUSSION

Bidirectional, two-sample MR analyses suggest that a higher BMI causally decreases subjective well-being and increases depressive symptoms. There was no evidence for causality in the other direction. Our findings are in line with two recent two-sample MR studies reporting evidence for a higher BMI causally increasing the risk of MDD^{12 13} (but not in the other direction¹³), and two smaller one-sample MR studies reporting causal effects of BMI on common mental disorders in men (but not in women)⁸ and on depressive symptoms.⁹ Two other one-sample MR studies did not find evidence for a causal effect of BMI on depression diagnosis/symptoms.^{10 11} These mixed findings may be explained by heterogeneity in the outcome variables, a lack of power in the smaller studies or violations of the MR assumptions. Our findings are strengthened by the two-sample MR approach, which is well powered to identify causal effects and allows sensitivity analyses to examine pleiotropy.

The current data do not provide insight into causal mechanisms underlying the BMI-mental health link. Weight-related problems, such as physical illness and/or weight stigmatisation, may

Table 2 Causal effect estimates of SWB and DEP on BMI

Exposure	Outcome	P value threshold genetic instrument	N SNPs	IVW*			Weighted median			MR-Egger		
				Beta	SE	P values	Beta	SE	P values	Beta	SE	P values
SWB	BMI	<5e-08	3	0.26	0.21	0.220	-	-	-	-	-	-
SWB	BMI	<1e-05	27	-0.02	0.06	0.761	-0.04	0.07	0.527	0.23	0.20	0.269
DEP	BMI	<5e-08	1	0.11	0.17	0.526	-	-	-	-	-	-
DEP	BMI	<1e-05	30	0.10	0.08	0.185	-0.01	0.07	0.914	-0.19	0.32	0.568

*Wald ratio is reported if only one genetic variant is used.

BMI, body mass index; DEP, depressive symptoms; IVW, inverse variance weighted; MR, Mendelian randomisation; SNP, single nucleotide polymorphism; SWB, subjective well-being.

negatively affect mental health.¹⁹ Also, a higher BMI could lead to inflammation and a dysregulated hypothalamic–pituitary–adrenal (HPA) axis, inducing the development of depressive symptoms.²⁰ The exact causal mechanism between BMI and mental health are likely more complex and need further investigation.²⁰

While two-sample MR greatly improves power over one-sample MR, our genetic instruments still only account for a small part of the variance of the exposure variables. The lack of evidence for a causal influence of mental health on BMI may be due to lower power of the instrumental variables (all SNPs under the p value threshold of 5×10^{-8} explained 0.03% and 0.06% of the variance for subjective well-being and depressive symptoms,¹⁶ respectively, compared with 2.7% for BMI¹⁵). There was some sample overlap between the GWA studies that we used, which may have caused bias in the direction of the observational association. Replicating our approach when even larger GWA studies become available is warranted. Another limitation is that we were unable to address non-linear effects. The association between BMI and mental health may be inverse u-shaped, with both very low and very high levels of BMI leading to impaired mental health.³ Finally, there may be sex-specific differences in weight stigma consequences and obesity.

To our knowledge, this is the first two-sample MR study to bidirectionally assess causal associations between BMI and mental health, other than MDD. Our findings support the idea that a higher BMI causally leads to poorer mental health. Future research needs to corroborate our findings and explore mechanisms underlying this causal link.

What is already known on this subject

- ▶ Observationally, a higher body mass index (BMI) is associated with poorer mental health.
- ▶ Recent Mendelian randomisation (MR) studies—using genetic variants as instrumental variables—suggested that a higher BMI causally increases the risk of major depressive disorder (MDD).
- ▶ It is, however, unclear whether there are similar causal effects of BMI on less severe mental health problems and whether such causal effects can also be found in the other direction (from mental health to BMI).

What this study adds

- ▶ We significantly add to the current literature by reporting evidence from two-sample MR analyses, suggesting that BMI causally decreases subjective well-being and increases depressive symptoms.
- ▶ As these less severe mental health problems are much more prevalent than MDD, our findings are of high public health relevance.
- ▶ No evidence was found for causality in the other direction, suggesting that the association that exists between BMI and mental health is not due to poor mental health leading to a higher BMI.

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Contributors JLT, KJHV and JMV were responsible for the study concept and the design of the study. NvdB, JLT and KJHV performed the data analyses, under

supervision of JMV. NvdB and JLT drafted the manuscript. JKL, MV, KJHV and JMV provided critical revision of the manuscript for important intellectual content. All authors contributed to the interpretation of data and approved the final version for publication.

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Competing interests None declared.

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