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Examining Causal Effects of Body Mass Index on Back Pain: A Mendelian Randomization Study

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Abstract

Purpose: Measures of body fat accumulation are associated with back pain, but a causal association is unclear. We hypothesized that body mass index (BMI) would have causal effects on back pain and chronic back pain. To test the hypothesis, we conducted a two-sample Mendelian randomization (MR) study to assess the causal effect of BMI on the outcomes of 1) back pain and 2) chronic back pain (duration > 3 months).

Methods: We identified genetic instrumental variables for BMI (n=60 variants) from a meta-analysis of genome-wide association studies (GWAS) conducted by the Genetic Investigation of ANthropometric Traits consortium in individuals of European ancestry (n=322,154). We conducted GWAS of back pain and chronic back pain (n=453,860) in a non-overlapping sample of individuals of European ancestry. We used inverse-variance weighted (IVW) meta-analysis as the primary method to estimate causal effects.

Results: The IVW analysis showed evidence supporting a causal association of BMI on back pain, with a 1-standard deviation (4.65 kg/m^2) increase in BMI conferring 1.15 times the odds of back pain (95% confidence interval [CI]: 1.06–1.25, p=0.001); effects were directionally consistent in secondary analysis and sensitivity analyses. The IVW analysis supported a causal association of BMI on chronic back pain (OR 1.20 per 1 SD deviation increase in BMI [95% CI 1.09–1.32; p=0.0002), and effects were directionally consistent in secondary analysis and sensitivity analyses.

Conclusion: In this first MR study of BMI and back pain, we found a significant causal effect of BMI on both back pain and chronic back pain.

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Keywords

Low back pain; epidemiology; prognosis; risk factor; obesity

INTRODUCTION

Back pain is the leading cause of years lived with disability worldwide.[1] Decreasing the burden of back-related disability on the population level might be achieved by targeting common modifiable risk factors for this prevalent and often debilitating symptom. However, the success of back pain prevention strategies based on risk factor modification depend entirely on whether or not the targeted risk factors of interest are truly causes of back pain.[2]

Many health conditions are found more commonly in those with back pain than in those without, yet few of these factors have strong evidence for causal relations with back pain. Even when a risk factor temporally precedes and predicts an outcome, the question remains of whether the risk factor is simply a surrogate for another condition that is the true underlying cause. The moderate heritability of back pain (40%)[3,4] is a reminder that shared genetic effects acting both upon back pain and putative back pain risk factors (pleiotropy) are a plausible explanation for many of the associations with back pain seen in conventional observational studies. Consistent with this, twin studies have shown that many associations between back pain and putative risk factors do not persist once genetics are controlled for. If pleiotropy explains why a risk factor predicts future back pain, then modifying that risk factor in the general population will have no effect on the downstream societal burden of back pain.

Overweight and obesity are defined by the World Health Organization (WHO) as “abnormal or excessive fat accumulation that may impair health”,[5] and are commonly thought of as causes of back pain. Body mass index (BMI), or a person’s weight in kilograms divided by the square of his/her height in meters (kg/m^2), is the most widely used population-level measure of overweight and obesity.[5] However the association of BMI and other measures of obesity with future back pain may be largely explained by pleiotropy, and a causal connection has been questioned based on findings from longitudinal twin studies, which show no association once genetic factors have been accounted for.[2,6]

Mendelian randomization (MR) is a method that uses specific genetic variants in order to evaluate whether an observed risk factor-outcome association is consistent with a causal effect.[7] The method capitalizes on the random allocation of genetic variants during gamete formation, which results in a random distribution of variants in a population.[8] Each genetic variant may or may not affect a risk factor of interest. Because these genetic variants are typically independent of potentially confounding environmental exposures, differences in an outcome between those with and without a variant can be attributed to differences in the risk factor under study.[8] If a risk factor (such as BMI) causes an outcome (such as back pain), then a genetic variant with an effect on that risk factor is expected to influence the downstream outcome to a proportional degree, provided no other pathway exists by which the variant influences the outcome (a phenomenon known as “horizontal pleiotropy”). In such a situation, a genetic variant associated with a risk factor can serve as a proxy, or an

"instrumental variable", for estimating the causal effects of a risk factor on an outcome, and multiple genetic variants can be used simultaneously as instruments to increase the statistical power for estimating causal effects.[7] A two-sample MR study uses summary statistics from different non-overlapping genome-wide association study (GWAS) samples for the estimation of causal effects.

We conducted a two-sample MR to assess the causal association of BMI on the outcomes of 1) back pain, and 2) chronic back pain (duration > 3 months). We hypothesized that BMI would have causal effects on back pain and chronic back pain.

METHODS

This study used both individual-level and publicly available summary-level GWAS data. Research ethics approvals included the UK Biobank Research Ethics Committee (#11/NW/0382) and the VA Puget Sound Health Care System (RDIS 0010, MIRB 00903).

Data Sources and Instrument Selection

Body Mass Index—We selected BMI as the exposure of interest, rather than obesity or overweight categories, because body fat accumulation reflects a continuum that may not be fully captured by the thresholds used for epidemiologic purposes, and BMI is the most commonly used measure of body fat accumulation in population studies.[5] We identified genetic instruments for BMI from a meta-analysis of GWAS of BMI conducted by the Genetic Investigation of ANthropometric Traits (GIANT) consortium in individuals of European ancestry (n=322,154).[9] This GWAS examined the phenotype of BMI as determined from measured or self-reported weight and height, and identified 77 genetic variants, or single-nucleotide polymorphisms (SNPs), with an additive SNP-based heritability of 2.7%. In this GWAS, a 1-standard deviation change in BMI equaled 4.65 kg/m^2.[10] Since a SNP with a p-value exceeding genome-wide significance corresponds to an F statistic > 30,[11] each SNP instrument had substantial strength. We extracted summary statistics from http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. We excluded SNPs not present in 1000 Genomes phase 3 version 5 reference data. SNPs were clumped and pruned for independence in PLINK v1.9 by retaining only 1 SNP within a 10000kb window among SNPs correlated at $r^2>0.001$. Last, we excluded SNPs with minor allele frequencies (MAF) < 0.05 and SNPs with effect vs. other allele mismatches for BMI and outcome.

Back Pain and Chronic Back Pain Outcomes—We conducted GWAS of back pain and chronic back pain (n=453,860) in a non-overlapping sample of individuals of European ancestry using imputed genotypes from the UK biobank (version 3) in PLINK v2.0. We used logistic regression to evaluate additive genetic effects of the SNPs on each back pain outcome as a binary trait adjusting for age, sex, genotyping array, and 10 genetic principal components, using filters and exclusions as described previously.[12] Participants were asked the question "In the last month have you experienced any of the following that interfered with your usual activities?". Back pain cases (n= 120,842) were defined as those who reported back pain, and controls (n= 333,018) as those who did not report back pain; those who declined to answer the question or reported pain all over their body were excluded from

the analysis. A subsequent question asked “Have you had back pain for more than 3 months?”. Chronic back pain cases (n= 78,935) were defined as those who reported having had back pain for more than 3 months, and controls (n= 360,896) as those who reported having no back pain or denied having had back pain for more 3 months. GWAS results were processed using the MR-Base R package and harmonized with the set of SNP instruments; those instruments not present in the back pain/chronic back pain GWAS were excluded from subsequent analysis.

Statistical Analysis—To estimate the causal effect of BMI on each outcome (back pain or chronic back pain), we examined the association of each genetic instrument (SNP) with each exposure, and the association of each SNP with each outcome. We then combined these estimates using inverse-variance weighted (IVW) meta-analysis.[13] The IVW estimate was the primary MR effect estimate, reported as odds ratios (ORs) and 95% confidence intervals (95% CIs), with a p-value threshold of 0.05. Because IVW estimates may be biased in the presence of horizontal pleiotropy (a key MR assumption), we also estimated causal effects using two other methods which are robust to horizontal pleiotropy: the weighted median estimator and MR Egger regression methods.[14-16] Both these methods are statistically inefficient compared to the IVW method, but MR Egger particularly so.[14,15] Heterogeneity of MR estimates may indicate problems affecting the analyses, such as horizontal pleiotropy, or factors unrelated to pleiotropy, [14] and may be more likely when the outcome is binary. [14,17] We examined heterogeneity of causal estimates using the Cochran’s Q test, the MR-Egger intercept test for directional horizontal pleiotropy, forest plots, funnel plots and leave-1-SNP-out analyses.

We also examined associations between the genetic instruments and covariates relevant to back pain, using large publicly available GWAS (sample sizes between n=110,452 and n=766,345; Electronic Supplementary Content, Table S1). Covariates were grouped into two categories corresponding to distinct purposes. The first category included 5 covariates representing likely consequences of obesity (systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol, type 2 diabetes, and physical activity), or causes of obesity (physical activity). For this category, we expected associations with the genetic instruments due to mediation (or “vertical pleiotropy”), which does not violate MR assumptions. The second category included 8 covariates representing potential confounders of the BMI-back pain relationship (education, major depressive disorder, alcohol consumption, employment, subjective well-being, depressive symptoms, sleep duration, and smoking). For this category, instrument-covariate associations may reflect horizontal pleiotropy. A Bonferroni-corrected threshold of $p < 6.4 \times 10^{-5}$ (0.05/60 SNP instruments x 13 covariates) was applied. Although the practice of pruning potentially pleiotropic variants is controversial due to the potential for imparting bias rather than removing it,[7] we conducted a sensitivity analysis excluding SNP instruments associated potential confounders, and also excluding SNPs identified as outliers by the MR-PRESSO (Pleiotropy Residual Sum and Outlier) residual sum and outlier test.[18] Statistical precision in the sensitivity analyses was expected to be decreased compared to the primary analysis, due to using fewer genetic instruments.

RESULTS

Of 77 SNPs, 60 met inclusion criteria and were used as genetic instrumental variables. The IVW analysis results supported a causal association of BMI on back pain, with a 1-SD unit (4.65 kg/m^2) increase in BMI conferring 1.15 times the odds of back pain (95% CI 1.06–1.25, p=0.001); effects were directionally consistent with the weighted median and MR Egger methods, though not statistically significant (Table 1). The Cochran's *Q* test indicated heterogeneity of causal estimates (p<0.0001), as did forest and funnel plots, but other assessments did not indicate heterogeneity (Electronic supplementary material, Table S2, Figures S1-S3). Examination of instrument-covariate associations revealed 16 SNPs significantly associated with covariates and expected to lie along the causal pathway connecting obesity and back pain, with most associations seen for systolic blood pressure (9 SNPs) and HDL cholesterol (5 SNPs) (Electronic supplementary material, Table S1). Significant associations were also found for 16 SNPs thought to be potential confounders, with the most associations seen for educational attainment (10 SNPs) and alcohol intake (8 SNPs). In sensitivity analyses excluding the 16 SNP instruments that were potential confounders and 7 significant outliers identified by MR-PRESSO (leaving 37 instruments), there was no indication of heterogeneity (Electronic supplementary material, Table S1, Figures S4-S6). Sensitivity analyses showed similar direction and magnitude effects as the main analyses (Table 1).

The IVW analysis also supported a causal association of BMI on chronic back pain (OR 1.20 per 1 SD deviation increase in BMI [95% 1.09–1.32; p=0.0002) and effects with other methods were directionally consistent (Table 1). The Cochran's *Q* test indicated heterogeneity (p<0.0001), as did forest and funnel plots (Electronic supplementary material, Table S2, Figures S7-S9). In sensitivity analyses excluding the 16 SNP instruments that were potential confounders and 6 significant outliers identified by MR-PRESSO (Electronic supplementary material, Figures S10-S12), the direction and magnitude of effects were generally similar to the main analyses (Table 1).

DISCUSSION

Measures of obesity are often considered risk factors for the development of back pain, yet it has been unclear whether a higher BMI actually *causes* back pain. The current study used MR to address this uncertainty. We found evidence supporting causal associations of BMI on back pain (OR=1.15 per SD of BMI) and chronic back pain (OR=1.20 per SD of BMI).

A recent meta-analysis of cohort studies by Zhang et. al compared the incidence of back pain in those with WHO-defined overweight (BMI 25.0–29.9) vs. normal weight (BMI 18.5–24.9), in which between-category BMI differences would be expected to average between 5 and 6 kg/m^2.[19] Zhang et. al. estimated an OR of 1.15 (95% CI 1.08–1.21) of incident back pain for overweight vs. normal weight individuals,[19] a magnitude of effect that is closely comparable with the current study's MR estimate of BMI on back pain (OR=1.15 per 4.65 kg/m^2 of BMI). This similarity between observational and MR estimates indicates that the association between BMI and back pain from conventional observational studies is likely *not* explained by shared genetic factors predisposing to both conditions. This

inference contrasts with findings from longitudinal twin studies in which associations between BMI and future back pain become non-significant once accounting for genetic factors.[20,21] However, the different conclusions reached are well-explained by the small numbers of monozygotic twins informing the co-twin control estimates (between 60 and 156 participants),[20,21] and the current analysis of data from 776,014 participants had substantially greater power to detect an effect of BMI.

Randomized trials of intensive weight loss interventions in knee osteoarthritis (OA) have significant yet modest effect sizes on pain (Cohen's $d = 0.33$) and disability (Cohen's $d = 0.42$).[22] Our MR estimate of BMI on back pain (OR =1.15) is considerably smaller than that from a recent MR study examining the causal associations of BMI on knee OA[23] (OR 1.76 [95% 1.56–1.99]; $p=1.5 \times 10^{-31}$), which used the same exposure and outcome datasets as the current study. This is perhaps unsurprising given the heterogeneity of conditions which underlie the symptom of back pain, in contrast to the more specific phenotype of knee OA. However, it suggests that treatments based on intensive BMI reduction alone may have quite small effects on limiting back pain and disability in large groups of people. Multifaceted lifestyle interventions addressing several modifiable risk factors simultaneously, including BMI, may have greater potential for achieving larger effects on back pain. A trial of one such lifestyle intervention is currently underway.[24] Given that our MR estimates pertain to risk conferred by *lifelong* differences in BMI, it is also possible that protective effects stemming from interventions to reduce BMI (or maintain low BMI) may require such interventions to take place in childhood or adolescence, and might not yield results if applied to older adults.

To our knowledge, this is the first MR study of the effects of BMI on back pain. The validity of conclusions drawn from MR depend on several assumptions, of which the absence of meaningful horizontal pleiotropy is central. Our analyses of SNP instrument-covariate associations indicated possible pathways reflecting horizontal pleiotropy. Nevertheless, methods robust to horizontal pleiotropy (weighted median and MR Egger) yielded results that were directionally consistent with IVW analyses and of generally comparable magnitude. In addition, sensitivity analyses excluding instruments associated with potential confounders yielded results that comparable to the main analyses, albeit with reduced statistical power due to fewer SNP instruments. A possible limitation of our study was that the back pain questions used did not allow specification of the precise location where back pain was occurring (e.g. low back vs. midback). Given the high agreement between general back pain and low back pain questions,[3] and since midback pain without concurrent low back pain is less common,[25] we expect that our findings regarding causal effects of BMI pertain also to low back pain. Future MR studies should examine low back pain specifically, as well as lumbar spine endophenotypes such as lumbar disc herniation.

CONCLUSIONS

In summary, we conducted the first MR study of the effects of obesity on back pain. Our findings support causal effects of BMI on both back pain and chronic back pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Mendelian randomization estimates for the causal effect of BMI on back pain

Method	# of SNPs	Beta	SE	OR (95% CI)	p-value
Primary analyses					
Outcome: back pain					
IVW (primary)	60	0.141	0.044	1.15 (1.06-1.25)	0.001
Weighted median	60	0.056	0.043	1.06 (0.97-1.15)	0.19
MR Egger	60	0.140	0.129	1.15 (0.89-1.48)	0.28
Outcome: chronic back pain					
IVW (primary)	60	0.183	0.049	1.20 (1.09-1.32)	0.0002
Weighted median	60	0.137	0.048	1.15 (1.04-1.26)	0.004
MR Egger	60	0.140	0.129	1.19 (0.90-1.58)	0.23
Sensitivity analyses[a]					
Outcome: back pain					
IVW	37	0.083	0.040	1.09 (1.00-1.18)	0.04
Weighted median	37	0.045	0.056	1.05 (0.94-1.17)	0.42
MR Egger	37	0.262	0.121	1.30 (1.03-1.64)	0.04
Outcome: chronic back pain					
IVW	38	0.063	0.043	1.06 (1.09-1.32)	0.15
Weighted median	38	0.132	0.061	1.14 (1.01-1.29)	0.03
MR Egger	38	0.140	0.129	1.18 (0.91-1.54)	0.22

SNP=single-nucleotide polymorphism, SE=standard error, OR=odds ratio, CI=confidence interval

[a] after excluding SNP instruments associated with possible confounders, and outliers