



The Effect of BMI and Type 2 Diabetes on Socioeconomic Status: A Two-Sample Multivariable Mendelian Randomization Study

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OBJECTIVE

To assess the independent causal effect of BMI and type 2 diabetes (T2D) on socioeconomic outcomes by applying two-sample Mendelian randomization (MR) analysis.

RESEARCH DESIGN AND METHODS

We performed univariable and multivariable two-sample MR to jointly assess the effect BMI and T2D on socioeconomic outcomes. We used overlapping genome-wide significant single nucleotide polymorphisms for BMI and T2D as instrumental variables. Their causal impact on household income and regional deprivation was assessed using summary-level data from the UK Biobank.

RESULTS

In the univariable analysis, higher BMI was related to lower income (marginal effect of 1-SD increase in BMI [$\beta = -0.092$; 95% CI -0.138 ; -0.047]) and higher deprivation ($\beta = 0.051$; 95% CI 0.022 ; 0.079). In the multivariable MR, the effect of BMI controlling for diabetes was slightly lower for income and deprivation. Diabetes was not associated with these outcomes.

CONCLUSIONS

High BMI, but not diabetes, shows a causal link with socioeconomic outcomes.

Previous evidence indicates that high BMI and type 2 diabetes (T2D) are associated with poorer labor market prospects, lower productivity, and higher absenteeism (1–6). These disadvantages may accumulate over time and affect income and living circumstances, leading to a selection of individuals in more regionally deprived areas.

However, identifying the causal effect of BMI or diabetes on socioeconomic outcomes is challenging, mainly due to intrinsic problems of unmeasured confounding and reverse causation (1–3). Earlier approaches focused on the use of instrumental variable (IV) methods, exploiting the disease status of biological parents as IV (1–3). Recent studies have used genetic characteristics in one-sample Mendelian randomization (MR) approaches and showed an effect of BMI on socioeconomic status (4–6), while no effect of diabetes could be revealed (5).

This study aims at estimating the causal effect of BMI and T2D on household income and regional deprivation using a multivariable two-sample MR approach. This approach allows considering the shared genetic components of BMI and diabetes (7) to jointly estimate their causal effects on these socioeconomic outcomes (8).

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RESEARCH DESIGN AND METHODS

MR

The principle of MR roots in Mendel's laws of inheritance (i.e., the individual genotype is largely independent of external factors and therefore independent of potential confounders). In MR techniques, significant single nucleotide polymorphisms (SNPs) that are associated with the exposure are exploited as exogenous genetic variation in the form of IVs (8,9).

Genome-wide association studies (GWAS) have shown significant independent associations between several SNPs and BMI or T2D (10,11) but also the presence of distinct signals influencing both conditions (7). While the relevance assumption and exclusion criteria are satisfied for our data (see Supplementary Material 1), this overlap could lead to horizontal pleiotropy that violates the exchangeability assumption (i.e., the same SNP independently influences multiple phenotypes) and could result in biased estimates (9). Horizontal pleiotropy can be overcome by using multivariable MR methods (i.e., by considering the overlapping instruments directly in the estimation) (8).

Data

For the associations between SNPs and socioeconomic outcomes, we used publicly available summary-level data from a GWAS of UK Biobank data (12,13), including 464,708 individuals of European ancestry. Our outcomes were household income, defined as the average total household income before tax, and regional deprivation, defined using the Townsend deprivation index (14) (Supplementary Material 1).

Regarding the exposures, we used summary-level data on the associations between SNPs and BMI or T2D from published meta-analyses of GWAS (10,11), excluding UK Biobank participants, because independency of data of the SNP-exposure and SNP-outcome association is a key prerequisite for the validity of the two-sample MR approach (9) (Supplementary Materials 1 and 2).

Statistical Analysis

First, we performed a univariable MR analysis, testing the single effects of BMI and diabetes on the outcomes (8). Second, we estimated two-sample multivariable MR analysis of the effects of BMI and diabetes on the outcomes, using

the set of overlapping SNPs as instruments (10,11).

We estimated the effects using the inverse-variance weighted (IVW) method (9). Furthermore, we tested their robustness against other estimation methods, including median-based, MR Egger, and MR-robust adjusted profile score (RAPS) methods (Supplementary Materials 1 and 3). Moreover, we tested the sensitivity of the results by excluding other potentially pleiotropic SNPs (Supplementary Material 4).

In both the univariable and the multivariable analyses, we tested the effects of two exposures on two outcomes. We therefore assumed a conservative Bonferroni-corrected P value for statistical significance of $0.05/4 = 0.0125$.

RESULTS

In total, we included 69 SNPs for BMI and 42 SNPs for T2D, which overlapped at two distinct loci: FTO and TCF7L2 (Supplementary Table 2).

Results of the univariable MR analysis indicated that a higher BMI was associated with a lower household income ($\beta = -0.092$; 95% CI -0.138 ; -0.047) and with a higher regional deprivation ($\beta = 0.051$; 95% CI 0.022 ; 0.079) (Table 1). Diabetes did not have any effect on the socioeconomic outcomes considered.

All analyses, except for BMI on income, presented low to middle levels of heterogeneity ($I^2 = 0$ –57%), indicating good validity of the instruments. The difference between MR Egger and IVW estimates and a significant MR Egger intercept indicated the presence of horizontal pleiotropy, highlighting the need for multivariable MR analysis. The resulting effects from the multivariable MR analysis (Table 1) revealed that the direct effect of BMI controlling for diabetes was lower than in the univariable setting but still significant for both household income ($\beta = -0.089$; 95% CI -0.13 ; -0.048) and regional deprivation ($\beta = 0.049$; 95% CI 0.023 ; 0.075). Again, no effect of diabetes on socioeconomic outcomes could be observed.

The results from the MR Egger regression were almost identical to the estimates resulting from the IVW regression, indicating that the multivariable approach successfully accounted for the bias resulting from horizontal pleiotropy in the univariable setting.

All results were robust to the use of alternative estimation methods

(Supplementary Material 3) and to the exclusion of other potentially pleiotropic SNPs (Supplementary Material 4).

CONCLUSIONS

In this study, we estimated the independent effects of BMI and T2D on household income and regional deprivation using a novel multivariable MR technique (8). Our results indicate negative effects of BMI but no effect of diabetes.

These findings strengthen the evidence of the deleterious role of BMI on income and regional deprivation reported in previous observational and one-sample MR studies (1,4–6). The potential underlying mechanisms include a lower ability to work, higher absenteeism, higher probability of musculoskeletal injuries, and higher discrimination, which may lead to poorer career prospects, decreasing labor market participation, and lower income (1). A lower income could in turn affect living standards, leading individuals to self-select into more deprived areas with more affordable housing and food options.

Similar to a previous one-sample MR study (5), our results did not show any significant effect of T2D on household income or regional deprivation. In contrast, other studies that did not use a multivariate two-sample MR approach showed a negative effect of diabetes on socioeconomic outcomes (2,3). This result should be object of further studies, aiming at establishing whether this null effect can be replicated or whether it is mainly due to methodological shortcomings in our study.

In fact, this study has some methodological limitations. First, despite the fact that genetic characteristics are independent of possible confounders, high BMI or diabetes genetic risk of parents might be an unmeasured confounder, causing a "dynastic bias" (15). Second, although the relevance assumption of our IVs is satisfied, the explanatory power of the set of SNPs used in the analysis for both the exposures and the outcomes is limited (10,11). Finally, because the UK Biobank population is a selected one (13), our results might suffer from selection bias.

In conclusion, the current study provides evidence of a negative causal effect of higher BMI on income and regional deprivation, controlling for diabetes. In contrast, T2D does not have an effect on these two socioeconomic outcomes. Further studies should investigate this

Table 1—MR results for the effect of BMI AND diabetes on household income and regional deprivation

| Method | Household income (SD) | | | | | | Deprivation (SD) | | | | | |
|------------------|-----------------------|----------------|--------|--------|-----------|----------|------------------|---------------|--------|--------|-----------|----------|
| | β | 95% CI | pval | Q pval | I^2 (%) | Int pval | β | 95% CI | pval | Q pval | I^2 (%) | Int pval |
| Univariable MR | | | | | | | | | | | | |
| BMI | | | | | | | | | | | | |
| IVW | -0.092 | -0.138; -0.047 | <0.001 | <0.001 | 71 | | 0.051 | 0.022; 0.079 | 0.001 | <0.001 | 57 | |
| MR Egger | -0.045 | -0.11; 0.019 | 0.080 | <0.001 | 71 | 0.359 | 0.013 | -0.036; 0.057 | 0.282 | <0.001 | 55 | 0.045 |
| T2D | | | | | | | | | | | | |
| IVW | -0.002 | -0.005; 0.008 | 0.793 | <0.001 | 50 | | 0.002 | -0.005; 0.008 | 0.634 | 0.524 | 0 | |
| MR Egger | -0.005 | -0.014; 0.02 | 0.312 | <0.001 | 49 | 0.702 | 0.003 | -0.012; 0.019 | 0.346 | 0.516 | 0 | 0.375 |
| Multivariable MR | | | | | | | | | | | | |
| BMI | | | | | | | | | | | | |
| IVW | -0.089 | -0.13; -0.048 | <0.001 | | | | 0.049 | 0.023; 0.075 | <0.001 | | | |
| MR Egger | -0.089 | -0.131; -0.048 | <0.001 | | | | 0.049 | 0.023; 0.076 | <0.001 | | | |
| T2D | | | | | | | | | | | | |
| IVW | -0.001 | -0.016; 0.013 | 0.854 | | | | 0.0004 | -0.009; 0.01 | 0.940 | | | |
| MR Egger | -0.001 | -0.016; 0.013 | 0.866 | | | | 0.0003 | -0.009; 0.01 | 0.958 | | | |

The estimates for BMI indicate the change in the outcomes for a 1-SD increase in the genetically predicted level of BMI. The estimates for T2D can be interpreted as the change in outcomes in response to a 1-unit increase in the log_e odds of genetic risk of diabetes. All changes in outcome are expressed in SD units. β , marginal effect; Int pval, intercept P value; pval, P value; Q pval, P value of the Cochran Q statistic.

result, using new generations of GWAS with a higher explanatory power and including a more representative population. Furthermore, applied research may help to improve the understanding for the underlying mechanisms and to create targeted strategies to break the negative connection between BMI and socioeconomic outcomes.

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