Variation in body-mass index but not waist-hip ratio influences risk for multiple sclerosis

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DISCLOSURES

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BACKGROUND

- **Obesity** is an established risk factor for **multiple sclerosis (MS),** but the causal mechanisms behind this relationship are unclear [1,2].

- The most widely-used measure of obesity in large-scale medical studies is **body-mass index (BMI),** but **this measure fails to take into account variation in distribution of adiposity due to age [3].**

- Additionally, observational studies that investigate obesity and MS risk are frequently prone to issues of **confounding, reverse causality, and measurement error.**

OBJECTIVE

- Investigate the causal impact of **two measures of obesity** on MS risk using **Mendelian randomization,** a framework for causal analysis **robust to the effects of confounding and reverse causality.**

1) Gianfrancesco & Barcellos, 2016, *J Neurol Neuromedicine;* 2) Munger et al. 2013, *Mult Scler;* 3) Rothman 2008, *Int J Obes*

Study Design

- Mendelian randomization (MR) is a genetic **instrumental variable analysis,** a robust approach for causal inference (**Fig. 1**).

- In MR, the instrument is created from genetic variants (Z) associated with the exposure (A), but **only associated with the outcome (Y) through the exposure-outcome pathway (Z→A →Y) [4].**

Fig 1. Instrumental Variable Analysis

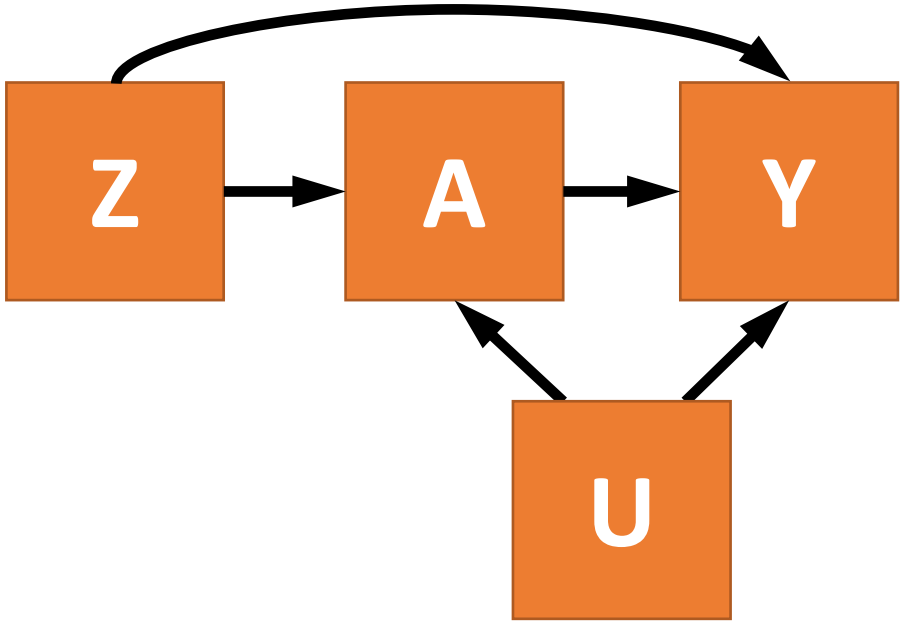


Fig 1. An instrument (Z) is created as a proxy for the exposure (A) when it cannot be reliably measured due to confounding factors (U). The outcome (Y) is then regressed on Z rather than A.

- Genetic variants for the instrument are selected from **genome-wide association (GWA) results for the exposure,** and the effects for the **same variants** are observed in **GWA results for the outcome [4,5].**

4) Haycock et al. 2016, *Am J Clin Neurol;* 5) von Hinke et al. 2016, *J Health Econ*

METHODS

- **Instrument Selection**
  - Genome-wide association studies (GWAS) were selected for white, non-Hispanic populations to identify variants associated with BMI and WHR:
    - **Yengo et al. 2018 [6]:** N(BMI) = 681,275
    - **Pulit et al. 2019 [7]:** N(WHR) = 694,649
  - **Palindromic variants** were **removed from the instrument** prior to analysis
  - Variants were **pruned for LD** at a threshold of r^2 >0.05 within 10kb windows

- **Outcome Dataset**
  - GWAS results for MS risk were taken from the most recent analysis from the International Multiple Sclerosis Genetics Consortium
    - **Patsopoulos et al. 2019 [8]:** N = 14,802 MS Cases; 26,703 Controls

6) Yengo et al. 2018, *Human Mol Gen*; 7) Pulit et al. 2019, *Human Mol Gen; 8)* Patsopoulos et al. 2019, *Science*

METHODS: 2-SAMPLE MENDELIAN RANDOMIZATION

- **Inverse-variance weighted (IVW) Analysis [9]**
  - For each variant (Z) in the instrument, the **effect estimates** and **standard errors** of the variant associated with the outcome are collected in both the exposure (X) and outcome (Y) datasets and combined into **Wald Ratios.**

$$\beta_{Wald} = \frac{\hat{\beta}_{Y|Z}}{\hat{\beta}_{X|Z}} \qquad \sigma_{Wald} = \frac{\sigma_{Y|Z}}{\beta_{X|Z}}$$

  - The Wald Ratios and their standard errors are then combined a single measure of association through **inverse-weighted meta-analysis.**

$$\bar{\beta} = \frac{\sum_{i=1}^{n} w_i \beta_i}{\sum_{i=1}^{n} w_i} \qquad Var(\bar{\beta}) = \frac{1}{\sum_{i=1}^{n} w_i} = \frac{1}{\sum_{i=1}^{n} \frac{1}{\sigma_i^2}}$$

- **MR-Egger Analysis [9]**
  - MR-Egger Analysis was also conducted to **account for potential horizontal pleiotropy between the exposure and outcome** by allowing for the incorporation of an intercept term in the calculation of the meta-analyzed effect estimate

9) Hemani et al. 2017, *eLife*; https://github.com/MRCIEU/TwoSampleMR

RESULTS – BMI AND MS RISK

- **683 variants** were identified for use in the instrument for BMI after LD pruning, removal of palindromic SNPs, and availability in the MS Risk dataset.

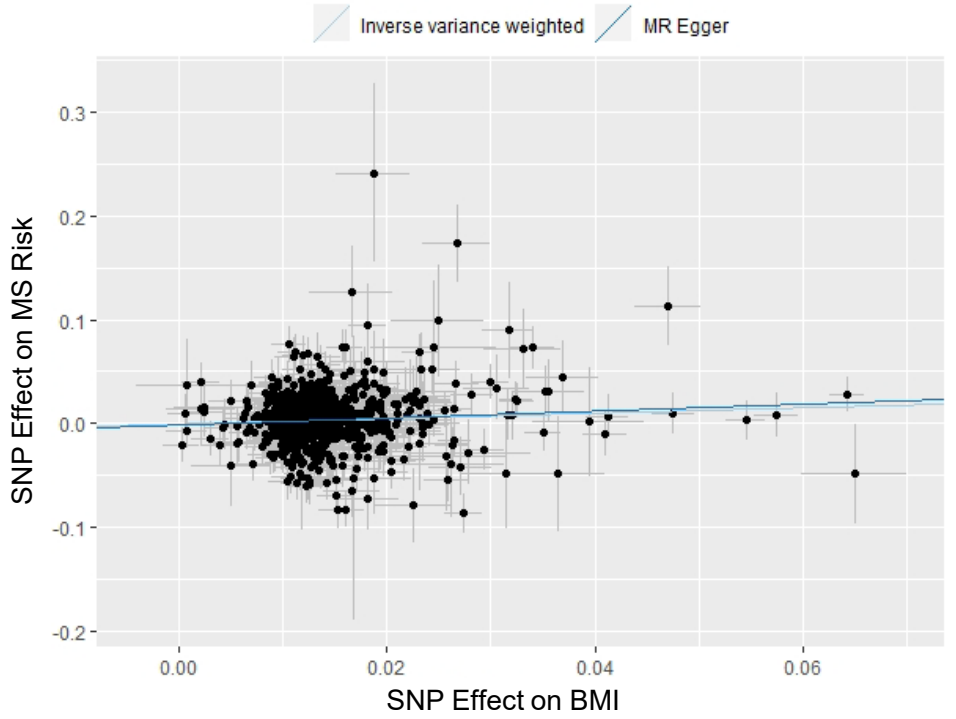
- There was a **significant association between BMI and MS Risk** in both the IVW analysis and the Egger analysis, indicating an effect independent of horizontal pleiotropy (**Table 1**).

- **Figure 2** shows the relationship between BMI and MS Risk effect estimates by individual variant in the instrument. Both MR analyses reveal **positive associations between increasing BMI and MS risk.**

Table 1. MR Results for the effects of Body-mass Index on MS Risk

Method	Beta	SE	p
IVW Analysis	0.25	0.06	***<0.001***
MR-Egger Analysis	0.34	0.16	***0.030***

Figure 2. Scatterplot of effect estimates of Body-mass Index on MS Risk



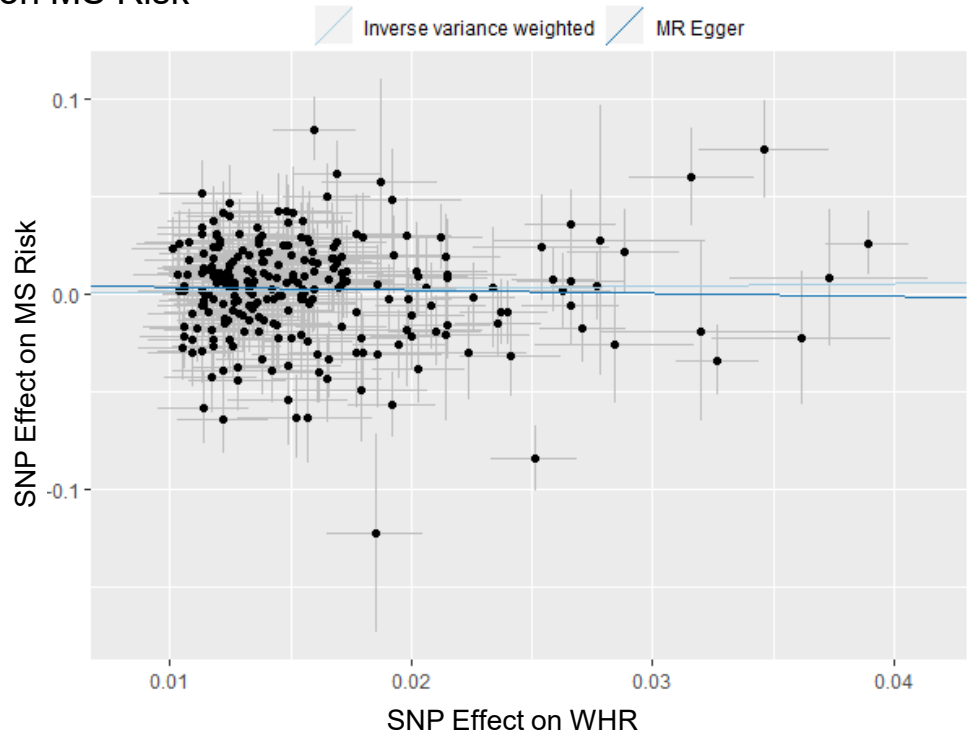
RESULTS – WHR AND MS RISK

- **254 variants** were identified for use in the WHR instrument after the removal of palindromic SNPs, LD pruning, and availability in the MS Risk dataset
- There was **no observed association between WHR and MS Risk,** even after adjustment for horizontal pleiotropy (**Table 2**).
- **Figure 3** further demonstrates the lack of relationship between WHR and MS risk.

Table 2. MR Results for the effects of Waist-Hip Ratio on MS Risk

Method	Beta	SE	p
IVW Analysis	0.03	0.13	0.82
MR-Egger Analysis	-0.49	0.40	0.223

Figure 3. Scatterplot of effect estimates of Waist-Hip Ratio on MS Risk



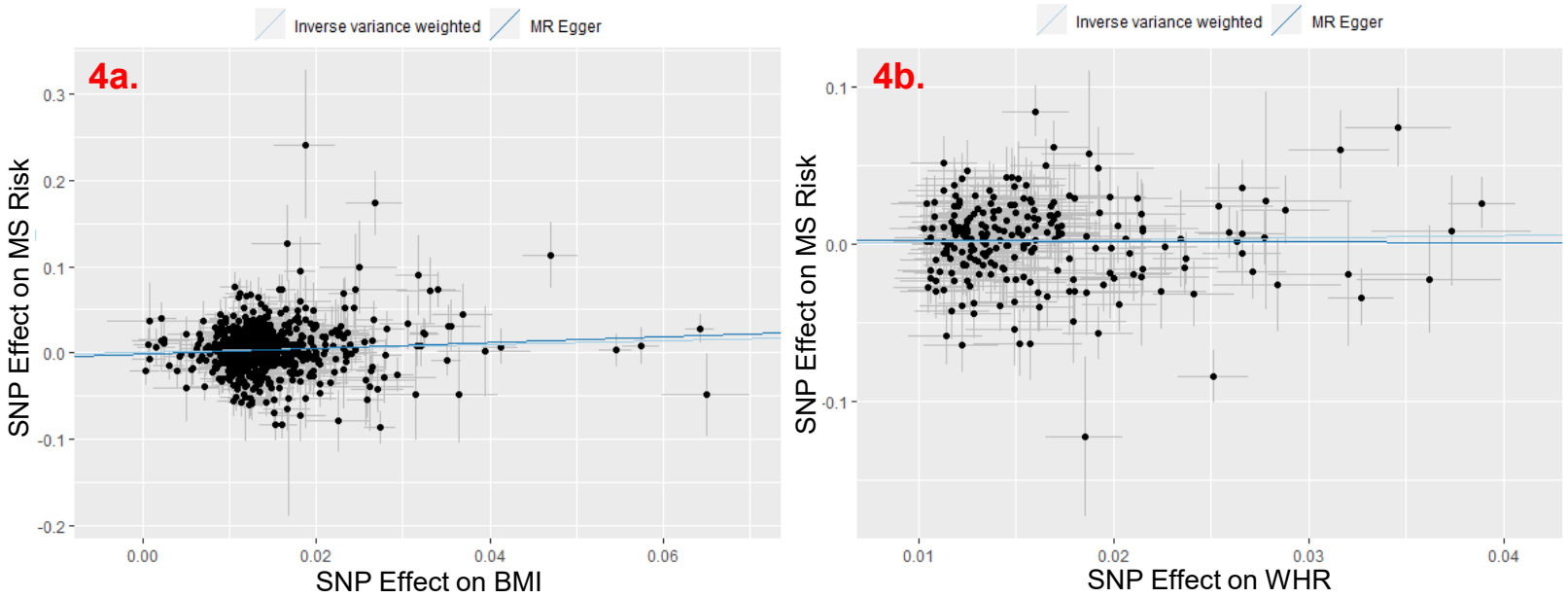
Results – Investigation of BMI and WHR Subsets

- There was an overlap of ~30 variants associated with both BMI and WHR.
  - **915 variants** uniquely associated with BMI
  - **290 variants** uniquely associated with WHR
- 2-sample Mendelian randomization was conducted for each instrument of unique variants.
- **663 variants** were retained in the BMI analysis. **232 variants** were retained in the WHR analysis.
- BMI remained significantly associated with MS risk, while WHR was not (**Table 3**). **Figure 4** shows similar results.

Table 3. MR Results for the effects of Waist-Hip Ratio on MS Risk

Exposure	Method	Beta	SE	p
BMI-Unique SNPs	IVW Analysis	0.24	0.06	***<0.001***
	MR-Egger Analysis	0.33	0.16	***0.048***
WHR-Unique SNPs	IVW Analysis	0.01	0.14	0.95
	MR-Egger Analysis	-0.40	0.42	0.35

Figure 4. Scatterplot for the effects of SNPs uniquely associated with BMI (**Fig. 4a**) and MS risk, and SNPs uniquely associated with WHR (**Fig. 4b**) and MS risk.



CONCLUSIONS

- Our results for BMI are supported by other similar Mendelian randomization studies for obesity and MS risk; **we are the first to investigate WHR and MS risk in this manner.**

- While BMI and WHR are both measures of obesity and share a small fraction of risk loci, it appears that the genetic drivers of the obesity-MS Risk relationship are mediated by BMI over WHR.

- Our results do not support a relationship between WHR and MS risk; this suggests that **the biological mechanisms related to overall body mass are more closely tied to developing MS than the mechanisms related to waist-hip ratio.**