



# Weighing Evidence from Mendelian Randomization—Early-Life Obesity as a Causal Factor in Multiple Sclerosis?

## Citation

Ascherio, Alberto, and Cassandra L. Munger. 2016. "Weighing Evidence from Mendelian Randomization—Early-Life Obesity as a Causal Factor in Multiple Sclerosis?" *PLoS Medicine* 13 (6): e1002054. doi:10.1371/journal.pmed.1002054. <http://dx.doi.org/10.1371/journal.pmed.1002054>.

## Published version

<https://doi.org/10.1371/journal.pmed.1002054>

## Link

<http://nrs.harvard.edu/urn-3:HUL.InstRepos:27822311>

## Terms of use

This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material (LAA), as set forth at

<https://harvardwiki.atlassian.net/wiki/external/NGY5NDE4ZjgzNTc5NDQzMGIzZWZhMGFIOWI2M2EwYTg>

## Accessibility

<https://accessibility.huit.harvard.edu/digital-accessibility-policy>

## Share Your Story

The Harvard community has made this article openly available. Please share how this access benefits you. [Submit a story](#)

PERSPECTIVE

# Weighing Evidence from Mendelian Randomization—Early-Life Obesity as a Causal Factor in Multiple Sclerosis?

Alberto Ascherio\*, Cassandra L. Munger

Harvard T. H. Chan School of Public Health, Harvard University, Boston, Massachusetts, United States of America

\* [aascheri@hsph.harvard.edu](mailto:aascheri@hsph.harvard.edu)



CrossMark  
click for updates

 OPEN ACCESS

**Citation:** Ascherio A, Munger KL (2016) Weighing Evidence from Mendelian Randomization—Early-Life Obesity as a Causal Factor in Multiple Sclerosis? *PLoS Med* 13(6): e1002054. doi:10.1371/journal.pmed.1002054

**Published:** June 28, 2016

**Copyright:** © 2016 Ascherio, Munger. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** Work is funded by NIH/NINDS grant R01NS073633 (PI: AA) <http://www.ninds.nih.gov/>. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

**Abbreviations:** BMI, body mass index; GWAS, genome wide association studies; MR, mendelian randomization; MS, multiple sclerosis; SNP, single nucleotide polymorphism.

**Provenance:** Commissioned; not externally peer reviewed.

Could prevention or correction of obesity in early life contribute to reduction of multiple sclerosis (MS) risk? Several observational studies have found that individuals who are obese in early life have about a 2-fold increased risk of MS [1–5], including two prospective studies: in a cohort of United States women, those with a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> at age 18 had a greater than twofold risk of developing MS than lean women [1]; and in Denmark, individuals with childhood BMI  $\geq 95$ th percentile were 70% more likely to develop MS than those with childhood BMI  $< 85$ th percentile [2]. While such prospective study designs eliminate or minimize bias from several sources, confounding by unknown factors cannot be excluded as an explanation for the findings.

In this issue of *PLoS Medicine*, J. Brent Richards and colleagues use a mendelian randomization (MR) approach to address the question of causality between obesity and MS risk [6]. MR has been touted as a study design that further minimizes bias, as genetic variations are expected to be randomly inherited and thus not subject to confounding. Conceptually, the MR approach is straightforward—consider a variation in a hypothetical gene G that directly affects a characteristic A (e.g., body mass index), such that carriers of the variant G' allele have higher levels of A than noncarriers. If A causes disease B (e.g., MS), but not otherwise, we would expect carriers of G' to have a higher risk of disease B.

Richards and colleagues used summary statistics from two separate genome-wide association studies (GWAS), one comprising over 340,000 individuals (with no information on MS) to identify genetic predictors of BMI (GIANT [7]), and one comprising over 14,000 MS cases and 24,000 controls (IMSGC [8,9]; with no information on BMI) to identify whether the genetic predictors of BMI were associated with MS risk. They identified 70 single nucleotide polymorphisms (SNPs) that were predictors of BMI and available in the IMSGC. MR analysis found that one standard deviation increase in genetically determined BMI was associated with a statistically significant 41% increased risk of MS (OR = 1.41, 95% CI: 1.20–1.66,  $p = 2.72 \times 10^{-5}$ ). The authors interpreted this result as providing evidence that obesity is a causal factor in MS. There are, however, a few important limitations of this study to consider.

One underlying critical assumption of MR studies is that of no pleiotropic effects. Specifically, in this MR study, that would mean that the 70 SNPs can affect the risk of MS only through their effects on BMI, i.e., none of the genes has pleiotropic effects. However, the absence of pleiotropic effects can only be assessed indirectly [10]; this assessment was done by examining whether the 70 SNPs relate to MS risk in a manner consistent with their effects on BMI (i.e., whether the effect of each of the 70 SNPs on MS risk is proportional to its effect on BMI, a

method known as MR-Egger regression), and by using a weighted median estimator [10]. While these are useful approaches, neither is unbiased when there are pleiotropic effects that are correlated with the effect on BMI, which could happen, for example, if the identified SNPs affect preference for an obesogenic diet, and that this diet, rather than obesity, is causally related to MS.

Second, the genetic determinants of BMI in GIANT were derived from adult populations, including many individuals who were past the age of MS incidence, whereas we know from epidemiological studies that only obesity in early life appears to be etiologically relevant for MS. This discrepancy is important, because genetic effects on BMI are likely to be age-dependent, as recently demonstrated [11–13]. This is not surprising, because the prevalence of obesity and median BMI increase dramatically with age [12], and the effect of a genetic variant on BMI can be present early in life or may become manifest decades later, either as a consequence of aging itself or because of interactions with environmental exposures [11]. Thus, the estimate of the magnitude of the effect of genetically increased BMI on MS risk found by Richards and colleagues is likely to be biased; the direction of the bias is difficult to predict, because there is insufficient information on the age-dependency of the 70 SNPs that contribute to the effect estimate. Further, it is a general limitation of MR studies that little information can be obtained on dose–response. The genetic effect usually explains only a modest proportion of the overall variance of the characteristic of interest (e.g., in GIANT, 97 loci explain only 2.7% of the total BMI variance [7]) and predict small variations in disease risk. Meaningful relative risks have to be estimated by extrapolating the data and assuming a linear dose–response relation, which may not be appropriate.

MR studies are increasing in popularity in part because of the increasing public availability of results from GWAS such as those used by Richards and colleagues, and are sometimes presented by themselves as proof of causality for associations reported in observational studies. We agree that MR studies are an important complement to observational investigations based on directly observed exposure–disease associations, but caution should be used in interpreting the results. Many underlying assumptions cannot be tested and are rarely fully satisfied, particularly in the case of weak instruments (i.e., an instrument that is a poor predictor of the exposure of interest) and complex exposure variables such as BMI that are determined by complex gene–environment interactions [14]. Further, important public health questions such as dose–response and relevant age at exposure cannot be directly addressed. A judgment of causality should therefore be based on the totality of evidence, including the traditional criteria of Bradford Hill [15] and the results of well-conducted MR studies.

In the case of obesity and MS risk, the results of Richards and colleagues' MR study, when interpreted in the context of temporality, strength, consistency, and plausibility demonstrated in previous observational investigations, suggest that obesity in early life is indeed causally related to MS risk and provide a further rationale for obesity prevention.

## Author Contributions

Wrote the first draft of the manuscript: AA. Contributed to the writing of the manuscript: AA KLM. Agree with the manuscript's results and conclusions: AA KLM. All authors have read, and confirm that they meet, ICMJE criteria for authorship.

## References

1. Munger KL, Chitnis T, Ascherio A. (2009) Body size and risk of MS in two cohorts of US women. *Neurology* 73: 1543–1550. doi: [10.1212/WNL.0b013e3181c0d6e0](https://doi.org/10.1212/WNL.0b013e3181c0d6e0) PMID: [19901245](https://pubmed.ncbi.nlm.nih.gov/19901245/)

2. Munger KL, Bentzen J, Laursen B, Stenager E, Koch-Henriksen N, et al. (2013) Childhood body mass index and multiple sclerosis risk: a long-term cohort study. *Mult Scler* 19: 1323–1329. doi: [10.1177/1352458513483889](https://doi.org/10.1177/1352458513483889) PMID: [23549432](https://pubmed.ncbi.nlm.nih.gov/23549432/)
3. Hedstrom AK, Olsson T, Alfredsson L. (2012) High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. *Mult Scler* 18: 1334–1336. doi: [10.1177/1352458512436596](https://doi.org/10.1177/1352458512436596) PMID: [22328681](https://pubmed.ncbi.nlm.nih.gov/22328681/)
4. Wesnes K, Riise T, Casetta I, Drulovic J, Granieri E, et al. (2015) Body size and the risk of multiple sclerosis in Norway and Italy: The EnvIMS study. *Mult Scler* 21: 388–395. doi: [10.1177/1352458514546785](https://doi.org/10.1177/1352458514546785) PMID: [25182290](https://pubmed.ncbi.nlm.nih.gov/25182290/)
5. Gianfrancesco MA, Acuna B, Shen L, Briggs FB, Quach H, et al. (2014) Obesity during childhood and adolescence increases susceptibility to multiple sclerosis after accounting for established genetic and environmental risk factors. *Obes Res Clin Pract* 8: e435–447. doi: [10.1016/j.orcp.2014.01.002](https://doi.org/10.1016/j.orcp.2014.01.002) PMID: [25263833](https://pubmed.ncbi.nlm.nih.gov/25263833/)
6. Mokry LE, Ross S, Timpson NJ, Sawcer S, Davey Smith G, Richards BJ. Obesity and multiple sclerosis: a medelian randomization study. *PLoS Med* 2016.
7. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, et al. (2015) Genetic studies of body mass index yield new insights for obesity biology. *Nature* 518: 197–206. doi: [10.1038/nature14177](https://doi.org/10.1038/nature14177) PMID: [25673413](https://pubmed.ncbi.nlm.nih.gov/25673413/)
8. Beecham AH, Patsopoulos NA, Xifara DK, Davis MF, Kempainen A, et al. (2013) Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat Genet* 45: 1353–1360. doi: [10.1038/ng.2770](https://doi.org/10.1038/ng.2770) PMID: [24076602](https://pubmed.ncbi.nlm.nih.gov/24076602/)
9. International Multiple Sclerosis Genetics Consortium, Wellcome Trust Case Control Consortium, Sawcer S, Hellenthal G, Pirinen M, et al. (2011) Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. *Nature* 476: 214–219. doi: [10.1038/nature10251](https://doi.org/10.1038/nature10251) PMID: [21833088](https://pubmed.ncbi.nlm.nih.gov/21833088/)
10. Haycock PC, Burgess S, Wade KH, Bowden J, Relton C, et al. (2016) Best (but oft-forgotten) practices: the design, analysis, and interpretation of Mendelian randomization studies. *Am J Clin Nutr*.
11. Winkler TW, Justice AE, Graff M, Barata L, Feitosa MF, et al. (2015) The Influence of Age and Sex on Genetic Associations with Adult Body Size and Shape: A Large-Scale Genome-Wide Interaction Study. *PLoS Genet* 11: e1005378. doi: [10.1371/journal.pgen.1005378](https://doi.org/10.1371/journal.pgen.1005378) PMID: [26426971](https://pubmed.ncbi.nlm.nih.gov/26426971/)
12. Hardy R, Wills AK, Wong A, Elks CE, Wareham NJ, et al. (2010) Life course variations in the associations between FTO and MC4R gene variants and body size. *Hum Mol Genet* 19: 545–552. doi: [10.1093/hmg/ddp504](https://doi.org/10.1093/hmg/ddp504) PMID: [19880856](https://pubmed.ncbi.nlm.nih.gov/19880856/)
13. Elks CE, Loos RJ, Hardy R, Wills AK, Wong A, et al. (2012) Adult obesity susceptibility variants are associated with greater childhood weight gain and a faster tempo of growth: the 1946 British Birth Cohort Study. *Am J Clin Nutr* 95: 1150–1156. doi: [10.3945/ajcn.111.027870](https://doi.org/10.3945/ajcn.111.027870) PMID: [22456663](https://pubmed.ncbi.nlm.nih.gov/22456663/)
14. Glymour MM, Tchetgen Tchetgen EJ, Robins JM. (2012) Credible Mendelian randomization studies: approaches for evaluating the instrumental variable assumptions. *Am J Epidemiol* 175: 332–339. doi: [10.1093/aje/kwr323](https://doi.org/10.1093/aje/kwr323) PMID: [22247045](https://pubmed.ncbi.nlm.nih.gov/22247045/)
15. Hill AB. (1965) The Environment and Disease: Association or Causation? *Proc R Soc Med* 58: 295–300. PMID: [14283879](https://pubmed.ncbi.nlm.nih.gov/14283879/)