

Mendelian randomisation supports causal link between obesity and asthma

Diana A van der Plaats 

Over the last few decades the prevalence of both obesity and asthma has increased substantially in many parts of the world. A clear link between obesity and asthma incidence and severity has been shown in both children and adults in observational studies.^{1 2} The biological mechanisms underlying this relationship are not fully understood. Hypotheses to explain the association include mechanisms related to one or more factors, including systemic inflammation, endocrine factors, oxidative stress, decreased lung volumes and comorbidities (type 2 diabetes, obstructive sleep apnoea and gastro-oesophageal reflux disease).^{3–6} The systemic inflammation pathway has gained particular traction, as both obese subjects and asthmatics have high inflammatory burdens. In addition, obese patients with asthma present with a different type of airway inflammation, tending to be more neutrophilic than eosinophilic.³ Controversy exists over whether obesity has a different effect on asthma in males and females, as studies in children show mixed results while some studies in adults suggest stronger effects in females.^{4 5} Furthermore, there has been a concern that the body mass index (BMI)–asthma association is due to reverse causation; that is, that people with asthma become obese due to the impact of asthma on their ability to remain active or perhaps even due to medications. Overall, findings by observational studies are susceptible to bias (confounding) and cannot elucidate the directionality of the relationship between obesity and asthma.

The Mendelian randomisation (MR) approach is increasingly used to assess causal relationships and can be regarded as a ‘natural’ randomised controlled trial. MR uses genetic variants (single nucleotide polymorphisms; SNP), which were randomly assigned at conception, as proxies (‘instrumental variables’) for an exposure of interest.⁷ Indirect evidence of a causal effect of the exposure on the outcome is provided when the SNPs that are known to modify the exposure (eg,

BMI) also modify the outcome of interest (eg, asthma). MR is less prone to classical confounding as one’s genetic make-up does not change throughout life and therefore is not influenced by any lifestyle factors such as poor diet or low physical activity. It is also not affected by reverse causation as genetic variation is present before any outcome. However, the approach can be problematic if the genetic proxies used are associated with the exposure of interest, and with other traits that affect the outcome via other independent biological pathways. This phenomenon is called horizontal pleiotropy and efforts have been made to develop MR methods which are more robust to pleiotropy (eg, median/mode MR, MR-Egger, MR-PRESSO, MR-RAPS).⁷ A limitation is the statistical power of MR studies to detect causal effects, which may lead to non-significant findings. Power depends strongly on the amount of variance explained in the exposure by the included genetic variants and on the sample size.⁷ As usually only a very small proportion of the variance is explained by genetics, large sample sizes (tens of thousands) are typically required.

In their *Thorax* study, Sun *et al*⁸ used MR to assess the causal effect of BMI on asthma in 56 105 adults. Seventy-three SNPs were included in the MR analysis which explained 2% overall of the variance in BMI. They confirmed the causal association between increased BMI and a higher risk of asthma (OR per 1 SD (4.1 kg/m²) 1.36 (1.10–1.68)) in both adult men and women, with no evidence for a sex difference. The association appeared to be stronger for non-atopic asthma (OR per 1 SD 1.42 (1.09–1.85)) compared with atopic asthma (OR per 1 SD 1.25 (0.89–1.77)), but no formal interaction was tested. Furthermore, no difference in effect was observed between controlled (OR per 1 SD 1.43 (0.78–2.61)) and partly controlled active asthma (OR per 1 SD 1.44 (0.99–2.10)). The authors also assessed if the waist-to-hip ratio, a maker of central adiposity, was associated with asthma by using 47 SNPs (explaining only 0.3% of the variance), but no effect was found. They also addressed whether there is evidence for the opposite effect, that is, the causal effect of asthma on BMI, but

found no evidence for this hypothesis when using seven SNPs previously associated with asthma (explaining 0.4%). These last two findings may reflect lack of power as only a small proportion of the variance was explained by the genetic variants chosen. Overall, the study by Sun *et al*⁸ provides evidence that increased BMI might play a role in causing (non-atopic) asthma.

This evidence builds on five similar previous MR studies (three in adults and two in children),^{9–13} of which four reported a significant effect of increased BMI on a higher risk of asthma.^{9 11–13} The fifth study reported a non-significant effect in the same direction (OR per unit BMI 1.08 (0.98–1.19)), and found an effect of BMI on a higher risk of wheezing (without asthma).¹⁰ The two MR studies in children^{11 12} both reported a stronger effect on non-atopic asthma; and one study suggested a stronger effect in boys¹² whereas the other study did not find a statistically significant difference between sexes.¹¹ These five previous MR studies, however, did not assess the effect of BMI on asthma symptom control, nor the effect of waist-to-hip ratio on asthma as in the current.⁸ Two MR studies, one study in adults and one in children,^{12 13} have also addressed the question of whether or not the opposite relationship is true, but both found no evidence to support the hypothesis that asthma is causally related to higher BMI.

There is now strong evidence from MR studies indicating that there is a causal relationship between high BMI (or obesity) and asthma. Whether sex differences exist remains an open question as only one study in children found a stronger effect in boys. In MR, sex differences can be assessed in two ways, depending on the underlying hypothesis. Either different genes are associated with BMI in each sex, or obesity caused by the same genes has a different effect on the outcome in men and women. The first hypothesis, having different genes, is unlikely to be the case for BMI as only 2 of the 96 SNPs associated with adult BMI showed evidence of heterogeneity between sexes.¹⁴ Genetic effects on BMI could also differ between infancy, childhood and adulthood, possibly explaining the positive finding in boys only and not in adults. Interestingly, two independent studies reported simultaneously the identification of a novel locus (leptin receptor) that was specifically associated with BMI during infancy only.^{15 16} Moreover, all three MR studies^{8 12 13} which addressed whether asthma has an effect on BMI

National Heart and Lung Institute, Imperial College London, London, UK

Correspondence to Dr Diana A van der Plaats, National Heart and Lung Institute, Imperial College London, London SW3 6LR, UK; d.van-der-plaats@imperial.ac.uk

found no significant effect, making the hypothesis that asthmatics become obese due to being less physically active less likely. However, these studies included SNPs that explained only a small proportion of the variance in asthma which likely decreased the statistical power to detect causal associations. In addition, and maybe even more importantly, these studies did not differentiate between childhood-onset and adult-onset asthma genetic variants. A recent genome-wide association study determined that based on genetics childhood-onset and adult-onset asthma are similar but not identical with a genetic correlation between the two types of asthma of 0.67.¹⁷ This opens the possibility for future MR studies to specifically assess if the timing of obesity or asthma onset is of importance.

Future (MR) studies should also focus on identifying the mechanisms underlying the BMI–asthma relationship. The most likely mechanism appears to be related to systemic inflammation. Only two MR studies have assessed this relationship and suggest that indeed inflammation is a consequence rather than a cause of obesity by showing that greater adiposity is associated with higher C-reactive protein levels.^{18 19} Future MR studies could be designed to assess the effect of obesity on other inflammatory markers such as leptin and adiponectin, and subsequently, the effect of these markers on asthma. Genetic variants are available for these inflammatory markers^{20 21} and a recent extension of MR called ‘multivariable MR’ would permit one to simultaneously assess the effect of multiple (correlated) traits on an outcome.²²

In summary, these data add to the evidence on the relationship between obesity and asthma, suggesting the existence of a causal relationship. This suggests steps should be implemented to reduce obesity in both children and adults. In addition to the many other health benefits that come from having a healthy weight, reducing obesity could prevent new asthma cases. Even though the current study did not find an effect of BMI on asthma symptom control possibly due to low power, reducing obesity in asthmatics could also be beneficial as observational studies have shown that obese asthmatics experience more frequent asthma exacerbations, have a

reduced response to inhaled corticosteroid medication and a lower quality of life.²³ However, further longitudinal studies on the effects of weight loss on asthma and MR studies on the underlying mechanisms are warranted in both adults and children to better understand the relationship between obesity and asthma.

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ORCID iD
Diana A van der Plaats <http://orcid.org/0000-0002-0361-357X>

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