

DR MARYAM ASGARI (Orcid ID : 0000-0003-1582-3475)

CATHERINA PAN (Orcid ID : 0000-0002-4403-8508)

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## **Relationship Between Body Mass Index and Atopic Dermatitis: Critical Appraisal of a Mendelian Randomization Approach in Exploring Causality**

*Dear Editor:* Atopic dermatitis (AD) is a common, chronic inflammatory skin disease with a complex etiology including genetic and environmental risk factors.<sup>1</sup> Obesity has been associated with increased AD risk and severity,<sup>2</sup> but a causal relationship has not been established. In the *Journal of Allergy and Clinical Immunology*, Budu-Aggrey *et al.*<sup>3</sup> assessed the causality between elevated body mass index (BMI) and AD using a Mendelian randomization (MR) approach<sup>1</sup>. The authors demonstrated a small but significant association between genetically predicted BMI and AD, inferring a causal effect of higher BMI in increasing AD risk (~2% for each 1 kg/m<sup>2</sup> increase in BMI), suggesting that obesity may be a modifiable risk factor AD development.

The authors explored the strength of the association between BMI and AD by performing a meta-analysis of 33 observational studies and found that the odds ratio (OR) of AD was 1.02 for each 1 kg/m<sup>2</sup> increase in BMI (p=0.07 for patients with BMI 25-30, and p=3.3 x 10<sup>-4</sup> for patients with BMI >30). However, as observational studies only demonstrate correlations and are limited by confounders and reverse causation, the authors used MR for further inference on causality.

MR is a powerful analytic tool that can infer causal relationships between variables via genetic variants as proxies for exposures and outcomes. However, these inferences depend on three assumptions: i) that genetic variants associate with the risk factor of interest; ii) that they share no common cause with the outcome; iii) and that they do not affect the outcome except through the risk

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factor of interest (i.e. no horizontal pleiotropy). Horizontal pleiotropy occurs when genetic variants affect the outcome through factors other than the one examined. While these assumptions cannot be validated empirically, the authors' design choices, multiple sensitivity analyses and cautious reasoning provide some confidence that causal inference is supported.<sup>5</sup>

The authors used one- and two-sample MR including individual and summative data from the UK Biobank and HUNT databases. Genetic variants associated with BMI and AD were derived from large genome-wide association studies and combined into genetic risk scores (GRS). The relationship between BMI GRS and other factors associated with BMI (**Figure 1A**) were assessed for potential confounders. Although some associations between BMI GRS and alcohol intake and education attainment were found, they were insufficient in magnitude to account for the causal relationship between BMI and AD. The authors also accounted to population stratification, a concept that addresses difference in allele frequencies between cases and controls due to disparate systematic ancestries (**Figure 1B**). To address the last assumption, the authors used sensitivity analyses and found no evidence for horizontal pleiotropy (**Figure 1C**). They also assessed for reverse causation and found no effect of genetic risk for AD leading to increased BMI, though there was some heterogeneity in the results suggesting there may be a subset of AD SNPs that may affect BMI. Further analyses such as MR pleiotropy residual sum and outlier are needed to detect and correct for horizontal pleiotropic outliers.<sup>6</sup>

One limitation of the study is that its conclusions are based on subject of primarily European ancestry, which may not be generalizable to non-European populations. While AD is common among individuals of European descent, epidemiological and genetic studies have demonstrated longer duration of AD among Hispanics and non-Hispanics Blacks, as well as different genetic variants between European and African-Americans.<sup>7</sup> Further work is needed to identify SNPs associated with AD and obesity in non-white individuals to demonstrate that a similar causality exists in racially and ethnically diverse populations. As a testament to the validity of this study's findings, a recent publication by Yew *et al.* using MR analyses yielded similar conclusions.<sup>8</sup>

Given that AD often arises in childhood, the authors examined the causality of BMI on AD onset using SNPs associated with childhood obesity and reported a similar causal effect. While the implications on BMI causality on AD risk are intriguing, examining the clinical impact of an intervention on BMI as a means of reducing AD risk would need to be assessed with a clinical trial as this study's findings do not necessarily inform the clinical impact of a weight loss intervention in childhood on the onset of AD in later life.

In conclusion, Budu Aggrey *et al.* employed robust epidemiological methods on large datasets to demonstrate that obesity may be a modifiable risk factor in the development of AD.

C.X. Pan,<sup>1\*</sup> Y.-H. Jee,<sup>2\*</sup> K.J. Moore,<sup>3</sup> P. Kraft<sup>2</sup> and M.M. Asgari<sup>3,4</sup>

<sup>1</sup> Harvard Medical School Boston, MA, USA 02115

<sup>2</sup> Departments of Epidemiology and Biostatistics, Harvard T.H. Chan School of Public Health, Boston MA, USA

<sup>3</sup> Massachusetts General Hospital, Department of Dermatology, Boston, MA, USA.

<sup>4</sup> Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA.

\*Denotes co-first authorship

**Correspondence:** Maryam M. Asgari, MD, MPH

**Email:** PORES@mgh.harvard.edu

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