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Confirmed causal effect of obesity on asthma and new insights on potential underlying shared genetic mechanisms

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Asthma is a highly heterogeneous chronic respiratory disease characterised by symptoms of wheeze, cough and breathlessness. In the US, 250,000 new asthma cases per year are related to obesity and characterized by severity of symptoms, poor prognosis, poor asthma control and resistance to current treatments and this applies to both children and adults (1). Most of the observational and experimental evidence in the literature points towards obesity modifying asthma risk in children and adults. Results from Mendelian Randomization (MR) studies have provided causal evidence for obesity increasing the risk of asthma while little evidence has been found to support the opposite effect (2). However, the shared biological mechanisms remain unclear and the heterogeneity of asthma and the obese-asthma phenotypes adds complexity and inconsistency in the results.

It is well recognised that there are different asthma phenotypes, and different obese-asthma phenotypes are starting to emerge (1, 3). In this issue of the *Journal*, Zhu et al. (4) explored the shared genetic associations between obesity and obesity-related metabolic traits and early vs. later-onset asthma in adults. Early onset asthma (often characterised as atopic) and late onset asthma (non-atopic, more often in females) are recognised as distinct asthma phenotypes that differ clinically and genetically (5). The authors have also explored the shared genetics between obesity traits and atopic vs. non-atopic asthma, and results were consistent with previous reports showing stronger associations for non-atopic compared to atopic asthma.

Zhu et al. reported, for the first time, positive genome-wide genetic correlations between BMI and later-onset asthma (0.25, $p=9.8\times10^{-22}$), non-atopic asthma (0.24, $p=5.8\times10^{-17}$), and atopic asthma (0.08, p=0.002), implying that higher BMI Single Nucleotide Polymorphisms (SNPs) correlated with higher asthma risk SNPs. Little evidence of shared genetic correlation between BMI and early-onset asthma was reported. Furthermore, they were able to confirm causal effects of BMI on later-onset (OR=1.21, $p=6.3\times10^{-7}$), atopic (OR=1.20, $p=8.4\times10^{-6}$) and non-atopic (OR=1.10, p=0.04) asthma and identified 32 independent shared loci between these traits (via cross-trait GWAS and functional analyses) including the *HLA* region (key role in immune system), *ERBB3* (regulation of bronchial epithelial repair and remodelling) and *SMAD3* (regulation of inflammatory response).

Two genes (*ACOXL* in chromosome 2 and *MYL6* in chromosome 12) were differentially expressed in mouse lung tissues when comparing obese db/db or high-fat-diet fed mice to controls. The *ACOXL* gene encodes an important enzyme involved in fatty acid beta-oxidation using acyl-CoA oxidase. The differential expression of *ACOXL* gene shown by Zhu et al. (4) supports a role of fatty acid oxidation caused by obesity in the inflammatory state of asthma. The *MYL6* gene encodes a motor protein (that converts chemical energy into mechanical work) expressed in smooth and non-muscle tissues. This gene, shown by Zhu et al. (4) to be differentially expressed, is involved in airway smooth muscle contractile function, a contributing factor in the excessive airway narrowing in asthma. These two

genes open potential new mechanisms underlying obesity and asthma identified by shared-genetic analyses and further confirmed by experimental mouse models (Figure 1).

The study by Zhu et al. has several limitations. While different traits were used to define obesity, these were all BMI based. BMI does not distinguish between fat mass and lean mass nor capture information on the location of body fat. Assessing body composition is needed to investigate the development and progression of obese patients throughout life as these components might better reflect differing physiology and metabolic health (6), and this, in turn, might be relevant in obese asthma patients.

They found more evidence for positive genetic correlation between obesity and later-onset asthma compared to early-onset asthma using a cut-off of 16 years. However, it is possible that early-onset asthma before 16 years was under-reported in this adult population (age range at recruitment 40-69 years) due to recall bias. Similarly, atopic asthma is more common during childhood, therefore the number of self-reported (early onset) atopic-asthma cases might also be under-reported.

The role of gender remains unclear. Many studies have reported differing obesity-asthma associations by sex, with the obese patient more often characterized by being female, with less atopy and late onset asthma. Zhu et al. found evidence of a higher genetic correlation between later-onset asthma and BMI (adjusted waist-to-hip ratio) in males compared to females, but not for other BMI traits.

The role of glucose metabolism was not discussed despite reporting significant genetic correlations of later-onset and non-atopic asthma with type-2 diabetes, fasting glucose and fasting insulin and reporting the same region in chromosome 11 as a shared genetic region associated with fasting glucose and both later-onset and non-atopic asthma in this adult population. These findings are in agreement with studies reporting that airway inflammation is not the only mechanism driving the association between obesity and asthma and the reason why some obese-asthma patients do not respond to anti-inflammatory drugs. Metabolic changes induced by altered glucose metabolism (insulin resistance) could mediate inflammatory Th2-independent mechanisms in obese patients with asthma (7). Zhu et al. results suggest that these mechanisms are particular to late onset non-atopic asthma.

The strength of this study relies on performing the largest genome wide association study (GWAS) (N>450,000) of sub-phenotypes of asthma, providing summary results that will be used in future MR and genetic analyses. Their results have strengthened the evidence supporting a causal link between obesity and asthma and the identified shared loci support the involvement of inflammation (Th2 and non Th2-dependent), airway repair & remodelling and the immune system as having key roles in the shared aetiologies between both traits. The question now for future research is whether there are any other factors, besides shared genetics, with a causal role.

Recently, Peters et al. (1) have reviewed the many metabolic and immune function-related factors that contribute to the obese-asthma syndrome: changes in lung function associated with higher leptin, decreased adiponectin levels and adipose tissue inflammation, increased airway oxidative-stress in obese adults with late onset asthma, innate immune responses (Th17 pathways and innate lymphoid cells) implicated in both obesity and asthma, CD4 cells skewed by obesity associated with worse asthma severity and control and insulin resistance associated with asthma and poor lung function. Other factors proposed to mediate the obesity-asthma relationship include environmental exposures (smoking, air pollution), diet (vitamin D, high-fat), physical activity and, the microbiome. For instance, changes in the diet (low fiber diet, antibiotic use) alters the gut microbiota and this, in

turn, might affect the development of allergic airway disease (1). A small study by Rastogi et al. (8) described differential epigenome-wide DNA methylation patterns in children according to their obesity and asthma status. The impact of indoor and outdoor pollution might also be of interest in the obese asthma population (9).

Obesity is associated with increased asthma risk and comorbidity. The large number and variety of inflammatory and non-inflammatory processes that co-occur in the obese asthma population and the fact that most asthma treatments only target a single pathway could explain the poor response to treatment observed in these patients. Zhu et al. (4) have highlighted that the obese-asthma syndrome is complex and multifactorial and the underlying biological mechanisms might differ between children and adults and males and females, reinforcing the idea of precision medicine and the need to identify and develop treatments that are effective for particular groups of patients (10). Future studies characterising obesity beyond BMI and involving new areas of research such as epigenetics and the microbiome might suggest distinct novel pathways.

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Figure 1 Potential new mechanisms underlying obesity and asthma identified in shared-genetic and experimental analyses by Zhu et al.