

Relationship among genetic variants, obesity traits and asthma in the Taiwan Biobank

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ABSTRACT

Background and objective Obesity and asthma impose a heavy health and economic burden on millions of people around the world. The complex interaction between genetic traits and phenotypes caused the mechanism between obesity and asthma is still vague. This study investigates the relationship among obesity-related polygenic risk score (PRS), obesity phenotypes and the risk of having asthma.

Methods This is a matched case–control study, with 4 controls (8288 non-asthmatic) for each case (2072 asthmatic). Data were obtained from the 2008–2015 Taiwan Biobank Database and linked to the 2000–2016 National Health Insurance Research Database. All participants were ≥30 years old with no history of cancer and had a complete questionnaire, as well as physical examination, genome-wide single nucleotide polymorphisms and clinical diagnosis data. Environmental exposure, PM_{2.5}, was also considered. Multivariate adjusted ORs and 95% CIs were calculated using conditional logistic regression stratified by age and sex. Mediation analysis was also assessed, using a generalised linear model.

Results We found that the obese phenotype was associated with significantly increased odds of asthma by approximately 26%. Four obesity-related PRS, including body mass index (OR=1.07 (1.01–1.13)), waist circumference (OR=1.10 (1.04–1.17)), central obesity as defined by waist-to-height ratio (OR=1.09 (1.03–1.15)) and general–central obesity (OR=1.06 (1.00–1.12)), were associated with increased odds of asthma. Additional independent risk factors for asthma included lower educational level, family history of asthma, certain chronic diseases and increased PM_{2.5} exposure. Obesity-related PRS is an indirect risk factor for asthma, the link being fully mediated by the trait of obesity.

Conclusions Obese phenotypes and obesity-related PRS are independent risk factors for having asthma in adults in the Taiwan Biobank. Overall, genetic risk for obesity increases the risk of asthma by affecting the obese phenotype.

INTRODUCTION

Asthma and obesity impose a heavy health and economic burden on billions of people around the world.^{1–3} In recent decades, a considerable body of epidemiological studies have shown that obesity is associated with a

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous epidemiological studies have shown that obesity is associated with a higher risk of asthma and poor asthma control.

WHAT THIS STUDY ADDS

⇒ This study used the integrated cohort database with phenotypes, genetic and morbidity data to elucidate the relationship among obesity-related polygenic risk score, obesity traits and asthma risk.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may lead to practical advice for reducing the risk of asthma in individuals with a higher genetic susceptibility for obesity.

higher risk of asthma and poor asthma control, and suggest that obesity precedes asthma.^{4–6} The mechanism linking obesity and asthma is not clear, but systematic inflammation, a mechanical effect and genetic factors are possible explanations for the association.^{7–8} One previous study from one large retrospective cohort also found obesity is significantly associated with decreased lung function in asthmatics, but the effect of genetic factors is not considered.⁹

Obesity and asthma are highly heritable traits that share genetic variants, leading to coexistence within the same person.^{10–11} Exploring the pleiotropy of genetic variants of obesity and asthma can not only better clarify the link between obesity and asthma, but is also beneficial to reduce the risk of incident asthma and improve the poor prognosis of asthma patients with obesity. Previous studies exploring the association between obesity-related genetic variants and asthma have reported several common characteristics. First, the candidate gene approach is the most common method for selecting single-nucleotide polymorphisms (SNPs). Limited



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research has assessed the obesity-related polygenic risk score (PRS) to explore its association with asthma risk; moreover, this approach has not been reported for Asian adults.¹² Second, most studies have focused on children,^{13–15} and few have assessed adult participants, who might be affected by genetic traces and obesity phenotypes. Third, most studies have not addressed the impact of multiple confounders on the results, especially objective disease histories.¹⁶ Fortunately, the linkage between the Taiwan Biobank (TWB) and National Health Insurance Research Database (NHIRD) provides us with a unique opportunity to perform genome-wide association study (GWAS) analysis of asthma and the three obesity indicators—body mass index (BMI), waist circumference (WC) and waist-to-height ratio (WHtR). The linked data enabled us to explore the association between genetic variants for obesity-related traits and asthma risk in adults at three levels—SNPs, genes and overall genetic risk (PRS). Additionally, since we integrated data from the micro to macro level including the health behaviours questionnaire, physical examination, genome-wide SNPs, clinical diagnosis data and PM_{2.5} exposure data, we were able to explore the relationship among obesity-related genetic variants, obesity traits and asthma risk and adjust multiple confounders simultaneously.

There are two aims of the study. The first is to elucidate the relationship among obesity-related PRS, obesity phenotypes and the risk of having asthma via multivariable analysis, interaction tests and mediation analyses. The second aim is to identify what obesity-related SNPs affect the risk of having asthma and explain the role of these SNPs in biological pathways to explore the pathogenesis of asthma.

METHODS

Patient and public involvement

This study obtained secondhand data; participants did not receive feedback on the results and were not involved in the study.

Data source

This is a matched case–control study. Participants' phenotypic and genotype data were from the TWB database,¹⁷ and the data of asthma and other disease diagnoses were collected from the NHIRD between 2000 and 2016.^{18 19} Two data sets were linked using encrypted personal identification numbers through the Health and Welfare Data Science Center, Ministry of Health and Welfare. In accordance with the year and month of enrolment, the 2-year average PM_{2.5} concentration of each participant's residential area was identified. Annual PM_{2.5} values were determined using a two-step spatiotemporal prediction model that included 76 air quality monitoring sites and 1882 Airbox microsensors. The detailed computation method was presented in another study.²⁰

Participants

The study participants consisted of volunteers who were between 30 and 70 years of age with no history of cancer and were recruited from 2008 to 2015 into the TWB. The flowchart of study participants is shown in figure 1. Of the 24 000 participants, we excluded those persons were living on offshore islands (n=108), those for whom health behaviours data was unavailable (n=23) or the genetic data did not meet quality control (QC) standards (n=2957).

Whole-genome genotyping analysis was performed using a customised Axiom-Taiwan Biobank Array Plate (TWB chip: Affymetrix, Santa Clara, California, USA).²¹ The QC criteria for samples were as follows: genotype call rate (GCR)≥0.95, average heterozygosity within three SD of the mean, no chromosomal aberrations, identity by descent≤0.1875 and no divergent ancestry. The following criteria were used to determine the quality of SNPs: GCR≥0.95, minor allele frequency≥0.01 and Hardy-Weinberg equilibrium $p \geq 8.185999e-08$. All QC analyses were conducted using the PLINK V.1.9 (<https://www.cog-genomics.org/plink/1.9/>).²² A total of 21 043 participants and 606 086 autosomal SNPs met the QC standards. A QC flowchart is presented in figure 2.

Participants diagnosed with asthma (ICD-9-CM/ ICD-10-CM code 493/J45) at least two times within a 1-year period between 2000 and 2016 were included in the case group. By contrast, participants without asthma formed the control group. Propensity score matching of asthmatics versus non-asthmatics was generated by 1:4 matching with age and sex. A total of 10 360 participants (asthma 2072; non-asthma 8288) were included in the analysis.

Obesity indicators

BMI, WC and WHtR from the TWB data were indicators for defining obesity in our study. BMI is a value calculated by height and weight and was stratified into four categories: underweight (<18.5 kg/m²), normal (18.5≤BMI<24 kg/m²), overweight (24≤BMI<27 kg/m²) and obese (≥27 kg/m²).²³ WC≥90 cm for men and ≥80 cm for women means central obesity.²³ WHtR is defined as WC divided by height, and the cut-off point for central obesity is 0.5.²⁴

GWAS analysis

We used PLINK V.1.9 to conduct association tests. Quantitative traits (obesity indicators) and the disease trait (asthma) were analysed with linear and logistic regression under the additive, dominant and recessive genetic models and both were adjusted for age, sex and 18 ancestry principal components used to control for population stratification.²⁵ The scree plot (online supplemental figure S1) of principal components analysis was drawn by R software V.3.6.3 (R Core Team, Vienna). Most studies only consider additive genetic effects, but testing different genetic effects in meta-analysis may help to detect less common genetic variants.²⁶ We combined

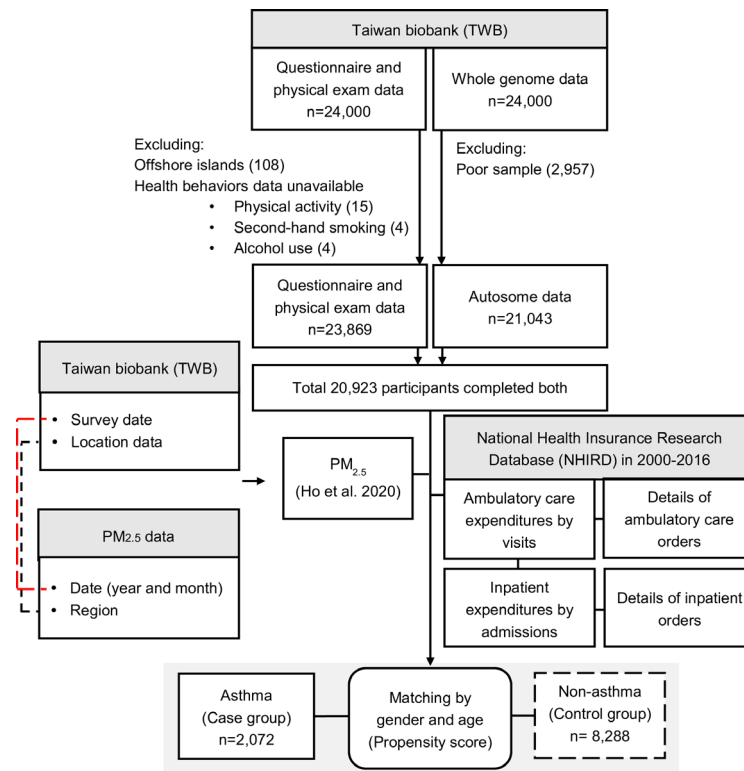


Figure 1 Participant flow chart.

the results of three genetic models by fixed-effect meta-analysis, and the heterogeneity was evaluated according to Cochrane's *Q* test.

Analysis of obesity-related SNPs and asthma

We examined the association between obesity-related SNPs and the risk of asthma using logistic regression with adjustment for age and sex under three genetic models (PLINK V.1.9).²⁷ To identify the genetic components shared between asthma and obesity, we used the R software's CUMP package to identify pleiotropic SNPs.²⁸ The information of SNPs was obtained from the SNP database (dbSNP, GRCH 37.p13: <https://www.ncbi.nlm.nih.gov/snp>) of the National Center for Biotechnology Information and the Taiwan Biobank V.3 (<https://taiwanview.twbiobank.org.tw/index>). Additionally, the expression quantitative trait loci information, a method to identify the effect of genetic variation on gene expression across human tissue (p value $< 10^{-4}$), was obtained from the Genotype-Tissue Expression (GTEx) portal database (<https://www.gtexportal.org/home/>).²⁹

Over-representation enrichment analysis

To determine the biological pathways involved in obesity-related SNPs that are associated with asthma risk, we used the WebGestalt tool (<http://www.webgestalt.org/>) to assess gene ontology (GO) biological process functional and biological pathways (KEGG, Panther, Reactome and WikiPathways) with a significance threshold of 0.05.³⁰

Polygenic risk score (PRS)

Polygenic risk score (PRS), a method to calculate the effect of many genetic variants on an individual's phenotype, is widely used to identify and predict an individual's trait or disease risk^{31 32} and to study genetic pleiotropy between diseases or/and traits.³³ A linkage disequilibrium (LD)-based clumping procedure (R^2 cut-off of 0.05 within a 500 kb window) was applied to the GWAS results to determine the most significant SNPs (p value $< 5 \times 10^{-8}$) that were independent of each other. Then, PRS were calculated using the score procedure. A PRS was constructed for each individual by weighted sum of the number of allele 1 (usually minor) carried, by using the effect size: log (OR) for binary traits, or the beta coefficient for continuous traits. PRSs were standardised to mean=0 and SD=1 for the analysis. The procedure of clumping and score calculation was implemented in PLINK V.1.9.

Statistical analysis

Continuous and categorical variables are expressed as mean \pm SD and percentage, respectively. A conditional logistic regression was stratified by age and sex, and was used to analyse the association between obesity and asthma. We selected common sociodemographic variables and risk factors for asthma as covariates and used the stepwise regression method (selection criterion: $\alpha=0.10$) to determine the covariates in the model. The model was checked by the 10% change-in-estimate method.³⁴ Estimates of the

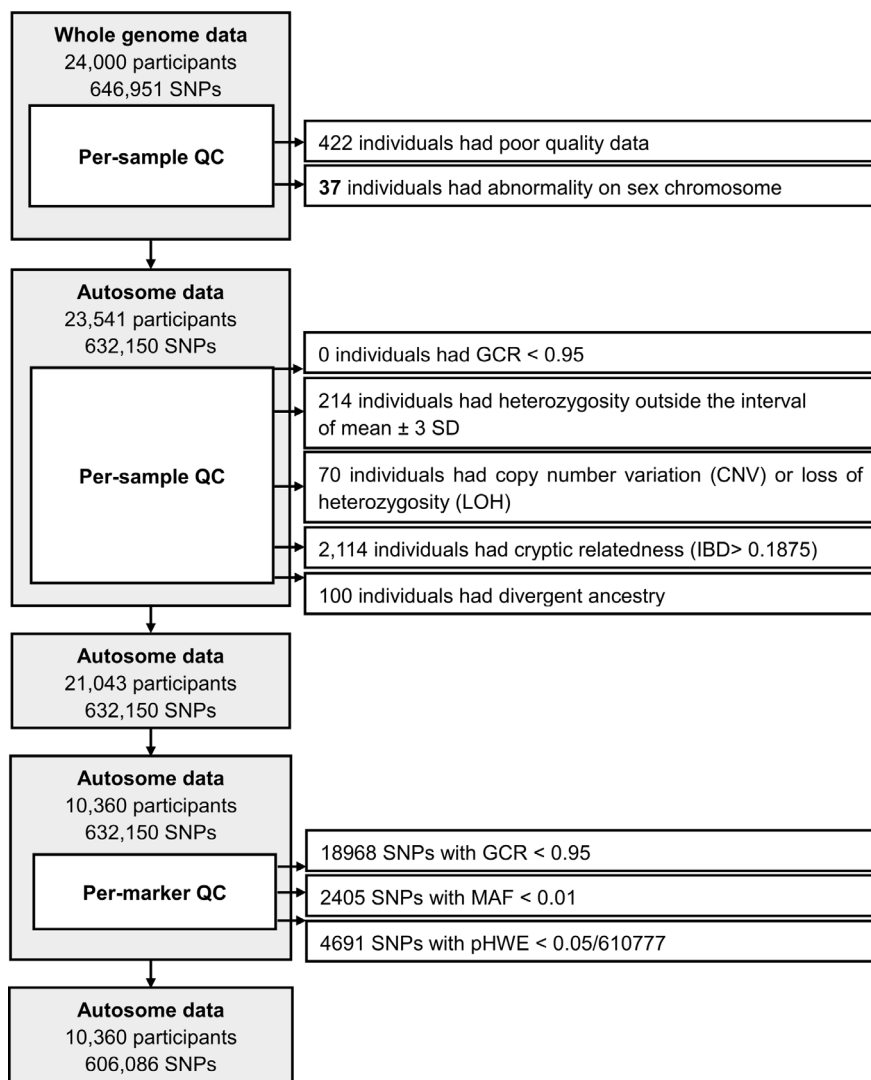


Figure 2 Quality control flow chart. GCR, genotype call rate; HWE, Hardy-Weinberg equilibrium; IBD, identity by descent; MAF, minor allele frequency; QC, quality control; SNPs, single-nucleotide polymorphisms.

receiver operating characteristic (ROC) curve were used for the area under the ROC curve (AUC) to evaluate the accuracy of predicting the risk of asthma. A generalised linear model with binary and normal distribution was used for mediation analysis to explore the relationship between PRS of obesity indicators (independent variable), obesity indicators (mediator) and asthma (dependent variable). The same covariates were adjusted for all models: PRS of asthma, education, at least one parent has (or had) asthma, at least one sibling has (or had) asthma, chronic obstructive pulmonary disease (COPD), depression, gastro-oesophageal reflux disease (GERD), hypertension and $PM_{2.5}$. All analyses were performed by SAS V.9.4 (SAS Institute, Cary, North Carolina, USA) and drawn by R software V.3.6.3 (R Core Team, Vienna). A p value less than 0.05 indicates statistical significance.

RESULTS

Baseline characteristics of the enrolled population

This case–control study included 10 360 participants, including 2072 asthma patients and 8288 non-asthmatic controls. The characteristics of the asthma and non-asthma groups are summarised in [table 1](#). The prevalence of obesity calculated by BMI (25.1% vs 19.3%), WC (48.8% vs 40.6%) and WHtR (65.1% vs 56.7%) was significantly different between the groups. Moreover, compared with the non-asthmatic group, the asthma group had significantly higher proportions of low education (primary and below: 9.17% vs 5.88%; junior/senior high school: 40.1% vs 37.9%), light-intensity physical activity (77.9% vs 75.2%) and various medical histories, including hypertension (33.3% vs 25.0%), diabetes (20.0% vs 15.2%), hyperlipidaemia (16.1% vs 10.4%), COPD (28.9% vs 7.34%), depression (16.1% vs 10.4%) and GERD (8.93% vs 4.44%) and had significantly higher $PM_{2.5}$ exposure (24.3 ± 11.1 vs 21.9 ± 9.85 $\mu\text{g}/\text{m}^3$).

Table 1 Characteristics of asthma and non-asthma participants in adults at 30–70 years, Taiwan Biobank

Characteristic	Sample (%)	Asthma	Non-Asthma	Crude OR (95% CI)	p value
n (%)		2072 (20)	8288(80)		
Demography					
Age (years)					–
30–39	19.5	19.5	19.5	–	
40–49	23.5	23.5	23.5	–	
50–59	27.5	27.2	27.6	–	
60–70	29.5	29.8	29.4	–	
Female	56.3	56.0	56.4	–	–
Education					<0.001
Primary and below	6.53	9.17	5.88	Ref	
Junior/senior high school	38.3	40.1	37.9	0.64 (0.53 to 0.78)	<0.001
College and above	55.2	50.8	56.3	0.53 (0.43 to 0.64)	<0.001
Family history					
One of the parents has asthma	6.60	10.1	5.72	1.87 (1.58 to 2.22)	<0.001
One of the siblings has asthma	3.38	5.16	2.93	1.79 (1.42 to 2.26)	<0.001
One of the parents has depression	3.09	3.86	2.90	1.35 (1.04 to 1.75)	0.023
Disease history					
Hypertension	26.7	33.3	25.0	1.63 (1.45 to 1.84)	<0.001
Diabetes	16.2	20.0	15.2	1.45 (1.27 to 1.65)	<0.001
Hyperlipidaemia	11.5	16.1	10.4	1.66 (1.45 to 1.90)	<0.001
Chronic obstructive pulmonary disease	11.7	28.9	7.34	5.51 (4.82 to 6.31)	<0.001
Depression	11.5	16.1	10.4	1.66 (1.45 to 1.90)	<0.001
Gastro-oesophageal reflux disease	5.34	8.93	4.44	2.10 (1.75 to 2.52)	<0.001
Obesity indicators					
WC (cm)					
Obese	42.2	48.8	40.6	1.41 (1.28 to 1.56)	<0.001
Non-obese	57.8	51.3	59.5	Ref	
WHtR					
Obese	58.4	65.1	56.7	1.45 (1.31 to 1.61)	<0.001
Non-obese	41.6	34.9	43.3	Ref	
BMI (kg/m ²)					
Underweight	2.82	2.36	2.93	0.93 (0.67 to 1.27)	0.630
Normal	48.4	42.9	49.8	Ref	
Overweight	28.3	29.7	28.0	1.26 (1.12 to 1.41)	<0.001
Obese	20.5	25.1	19.3	1.54 (1.36 to 1.75)	<0.001
BMI+WC*					
Obese	18.9	23.3	17.8	1.41 (1.26 to 1.59)	<0.001
Non-obese	81.1	76.7	82.8	Ref	
BMI+WHtR*					
Obese	20.3	24.9	19.1	1.41 (1.26 to 1.58)	<0.001
Non-obese	79.7	75.1	80.9	Ref	
Health behaviours					
Physical activity					
Light intensity (<3 METs)	75.8	77.9	75.2	Ref	0.011

Continued

**Table 1** Continued

Characteristic	Sample (%)	Asthma	Non-Asthma	Crude OR (95% CI)	p value
High intensity (≥ 3 METs)	24.2	22.1	24.8	0.86 (0.76 to 0.96)	0.010
Environment					
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	22.4 \pm 10.2	24.3 \pm 11.1	21.9 \pm 9.85	1.02 (1.02 to 1.03)	<0.001

*Individuals with both central and general obesity were defined as obese.

BMI, body mass index; MET, metabolic equivalent of task; PRS, polygenic risk scores; WC, waist circumference; WHtR, waist-to-height ratio.

Obesity-related SNPs and their overlap with asthma-related SNPs

The meta-analysis identified 234 SNPs that met the $p < 5 \times 10^{-8}$ threshold for genome-wide significance associated with BMI, 236 that were associated with WC and 263 that were associated with WHtR (online supplemental tables S1–S3). Overall, 32 BMI-related, 24 WC-related and 33 WHtR-related SNPs were associated with asthma (online supplemental table S4). We used cross-phenotypic association analyses to identify the loci shared between asthma and obesity. Among the obesity-related SNPs associated with an increased risk of asthma, we identified 41 SNPs shared by asthma and obesity. Of these, 13 SNPs contained information from the GTEx portal database (online supplemental table S5). These involved 15 genes, including MBL2, PIAS1 and HPSE2, which are expressed across various human tissues (online supplemental figure S2). In the over-representation enrichment analysis, we identified several possible biological pathways for the genes shared between asthma and obesity. For instance, MBL2 gene is involved in the complement cascade of innate immunity. PIAS1 plays a role in both interferon signalling, including the regulation of interferon-gamma (IFN- γ) signalling, JAK/STAT signalling pathway and IFN- γ signalling pathway in the immune system, and the transcriptional regulation of transcription factors (SUMOylation). HPSE2 is involved in glycosaminoglycan (heparin sulfate/heparin, HS-GAG) degradation. The top 10 GO terms and pathways are shown in online supplemental figures S3 and S4, respectively.

Asthma and obesity PRS

The PRS for asthma, BMI, WC and WHtR were calculated using 80 asthma-related SNPs (online supplemental table S6), 140 BMI-related SNPs (online supplemental table S7), 132 WC-related SNPs (online supplemental table S8) and 148 WHtR-related SNPs (online supplemental table S9), respectively. The mean PRS of asthma (0.63 ± 0.95 vs -0.16 ± 0.95), PRS of BMI (0.08 ± 1.02 vs -0.02 ± 1.00), PRS of WC (0.10 ± 1.01 vs -0.02 ± 1.00) and PRS of WHtR (0.07 ± 1.00 vs -0.02 ± 1.00) were significantly different between asthma patients and non-asthmatic controls (table 2). The ability of the PRS of asthma, BMI, WC and WHtR to predict asthma was evaluated using ROC curves, as shown in online supplemental figure S5.

In addition to the obesity indicator PRS, we were also interested in obesity PRS; consequently, we further used discrete criteria to determine PRS for obesity. Obesity PRS includes general obesity PRS ($\text{BMI} \geq 27 \text{ kg}/\text{m}^2$), central obesity PRS ($\text{WC} \geq 80 \text{ cm}$ in women or $\geq 90 \text{ cm}$ in men; $\text{WHtR} \geq 0.05$) and obesity PRS meeting both criteria for obesity. A comparison of this PRS between the two groups is presented in table 2, and online supplemental figure S6 shows the results of the ROC curve analysis for the accuracy of predicting asthma. The accuracies of the five obesity PRS in predicting asthma were comparable to those of the three obesity-indicator PRS.

Genetic variants, obesity traits and asthma

The covariate-adjusted conditional logistic regression model that identified the obese phenotype and obese-related PRS as risk factors for asthma is presented in table 3. In model 1, both general obesity (OR of BMI=1.32, 95% CI=1.14 to 1.52, $p < 0.001$) and central obesity (OR of WC=1.26, 95% CI=1.12 to 1.41; OR of WHtR=1.27, 95% CI=1.13 to 1.44; p all < 0.001) indicated significantly higher odds of asthma. In model 2, a one-standardised score increase in PRS of BMI and PRS of WC significantly increased the odds of asthma by 7% (95% CI=1.01 to 1.13, $p=0.020$) and 10% (1.04 to 1.17, $p < 0.001$), respectively. A one-standardised score increase in PRS of WHtR increased the odds of asthma by 5% (0.99 to 1.11, $p=0.103$), but this increase was not statistically significant. However, when we used WHtR (0.5 as the cut-off point) to define central obesity, a one-standard-score increase in the PRS of central obesity significantly increased the odds of asthma by 9% (1.03 to 1.15, $p=0.003$). There was no significant interaction effect for obesity-related PRS \times asthma PRS (not shown here). Additionally, lower education level, family history of asthma, disease history of COPD, history of depression, history of GERD, history of hypertension and increased PM_{2.5} are also independent risk factors for asthma. The details of the model for each indicator are shown in online supplemental tables S10 to S16. In the covariate-adjusted ROC curve, the AUC for predicting asthma was 0.82 (online supplemental figures S7–S9).

We examined the relationship between the traits of obesity indicators, obesity-related PRS and asthma, as shown in figure 3. Obesity-related PRS is an indirect risk

Table 2 Asthma-related and obesity-related PRS in asthma and non-asthma participants among adults aged 30–70 years, Taiwan Biobank

Characteristic	Sample	Asthma, n=2072	Non-asthma, n=8288	Crude OR (95% CI)	P value
Asthma PRS	0.00±1.00	0.63±0.95	-0.16±0.95	2.40 (2.26 to 2.54)	<0.001
Obesity indicators PRS*					
BMI	0.00±1.00	0.08±1.02	-0.02±1.00	1.10 (1.05 to 1.16)	<0.001
WC	0.00±1.00	0.10±1.01	-0.02±1.00	1.14 (1.08 to 1.19)	<0.001
WHtR	0.00±1.00	0.07±1.00	-0.02±1.00	1.09 (1.04 to 1.15)	<0.001
General obesity PRS†					
BMI	0.00±1.00	0.05±0.99	-0.01±1.00	1.07 (1.02 to 1.12)	0.010
Central obesity PRS†					
WC	0.00±1.00	0.06±1.02	-0.02±1.00	1.08 (1.03 to 1.13)	0.002
WHtR	0.00±1.00	0.07±0.99	-0.02±1.00	1.09 (1.04 to 1.14)	<0.001
General–central obesity PRS‡					
BMI+WC	0.00±1.00	0.05±0.99	-0.01±1.00	1.07 (1.02 to 1.12)	0.008
BMI+WHtR	0.00±1.00	0.05±1.00	-0.01±1.00	1.06 (1.01 to 1.11)	0.018

Polygenic risk scores were standardised to mean=0 and SD=1 for the analysis.
 *Obesity measures were continuous variables.
 †Obesity measures were binary variables (obese vs non-obese groups).
 ‡Obesity measures were binary variables (two obesity traits vs other groups).
 BMI, body mass index; PRS, polygenic risk scores; WC, waist circumference; WHtR, waist-to-height ratio.

factor for asthma, with the link being fully mediated by traits of obesity. The indirect effects of BMI, WC and WHtR were 1.05 (1.03–1.07), 1.06 (1.04–1.08) and 1.07 (1.04–1.09), respectively. The indirect effects of general, central and general–central obesity were 1.04 (1.01–1.06), 1.05 (1.02–1.07) and 1.04 (1.01–1.06), respectively.

DISCUSSION

We used the GWAS approach to scan the genomes from Taiwan adults to look for obesity-related and asthma-related SNPs and summarised multiple effects to estimate the PRS of obesity and asthma. As far as we know, no studies have found a relationship among obesity-related PRS, obesity traits and asthma risk by mediation analyses. Through a clinical or public health lens, identifying genetic variants related to both obesity and asthma might provide opportunities for preventing or treating asthma and obesity simultaneously, and establishment of a prediction model could be useful for disease management.

Several epidemiological and genetic studies have suggested that obesity is a risk factor for asthma. For example, Beuther and Sutherland performed a meta-analysis of prospective epidemiologic studies and found a dose–response relationship between body weight and asthma in adults.³⁵ Bidirectional Mendelian randomisation studies in European adult suggested that BMI is causal factor in asthma, particularly in later-onset and non-atopic asthma.^{36,37} Our findings are similar to these observations, and our ROC analysis also suggested that obesity and obesity-related PRS have excellent discrimination in

predicting asthma. Nevertheless, this finding requires further confirmation in a different cohort.

Using over-enrichment analysis, we also identified potential immunological mechanisms for the association between obesity and asthma. The MBL2 gene, regulated by rs11003136, involves the lectin pathway of complement activation. Complement is an ancient danger-sensing component of the innate immune system, which is activated through three independent pathways—the classical pathway, the alternative pathway and the lectin pathway. The low-molecular-weight anaphylactic toxins (AT) C3a and C5a produced during complement activation have many important proinflammatory and immunomodulatory properties, and regulate the development of Th2 immunity during allergen sensitisation.³⁸ It is well known that the immune mechanism of asthma is predominantly mediated by Th2 cells. MBL is a component of the lectin pathway, and its concentration is regulated by a polymorphism in the promoter region of the MBL2 gene. Aittoniemi *et al* have demonstrated that carriage of -221 base pair promoter region variants (G>C) caused low MBL expression and increased the risk of asthma in the Finnish population.³⁹ Our results found that allele T of rs11003136 was associated with increased asthma risk (OR (95% CI) of additive model=1.093 (1.015, 1.177); OR (95% CI) of recessive model=1.184 (1.005, 1.395)). The PIAS1 gene, which is regulated by rs4776990, is involved in both IFN signalling (IFN- γ signalling pathway, JAK/STAT signalling pathway and regulation of IFN- γ signalling) in the immune system and the SUMOylation of transcription factor pathways. IFN- γ , a Th1

**Table 3** Associations between obesity and asthma in adults aged 30–70 years, Taiwan Biobank

Variable	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
BMI				
Phenotype 1 (ref: normal)				
Underweight	0.83 (0.57 to 1.19)	0.307	–	–
Overweight	1.13 (0.99 to 1.30)	0.068	–	–
Obese	1.32 (1.14 to 1.54)	<0.001	–	–
Phenotype 2 (ref: non-obese)				
Obese	1.26 (1.10 to 1.45)	<0.001	–	–
BMI PRS	–	–	1.07 (1.01 to 1.13)	0.020
General obesity PRS	–	–	1.04 (0.98 to 1.10)	0.236
WC				
Phenotype (ref: non-obese)				
Obese	1.26 (1.12 to 1.41)	<0.001	–	–
WC PRS	–	–	1.10 (1.04 to 1.17)	<0.001
Central obesity PRS	–	–	1.06 (<1.00 to 1.12)	0.057
WHtR				
Phenotype (ref: non-obese)				
Obese	1.27 (1.13 to 1.44)	<0.001	–	–
WHtR PRS	–	–	1.05 (0.99 to 1.11)	0.103
Central obesity PRS	–	–	1.09 (1.03 to 1.15)	0.003
Two obesity traits				
Phenotype				
BMI (obese)+WC (obese)	1.27 (1.10 to 1.46)	<0.001	–	–
BMI (obese)+WHtR (obese)	1.27 (1.11 to 1.46)	<0.001	–	–
General–central obesity PRS				
BMI (obese)+WC (obese)	–	–	1.06 (1.00 to 1.12)	0.036
BMI (obese)+WHtR (obese)	–	–	1.03 (0.98 to 1.09)	0.241

Adjustments include PRS of asthma, education, one of the parents has asthma, one of the siblings has asthma, chronic obstructive pulmonary disease, depression, gastro-oesophageal reflux disease, hypertension and PM_{2.5}.
 BMI, body mass index; PRS, polygenic risk scores; WC, waist circumference; WHtR, waist-to-height ratio.

cytokine primarily generated by natural killer and activated T cells, is crucial for the induction and regulation of a range of immune responses. Studies have reported that severe asthma is associated with higher IFN- γ levels.⁴⁰ The cellular responses to IFN- γ are mediated by the IFN- γ receptor (IFNGR), which comprises two chains. Both IFNGR chains lack intrinsic kinase/phosphatase activity and thus rely on JAK1, JAK2 and STAT1 for signal transduction to regulate gene expression, thereby mediating the biological functions of IFN- γ .^{41 42} Protein inhibitors of activated STATs (PIAS) are a class of negative regulators that affect IFN- γ signalling by inhibiting various steps in the IFN- γ cascade.⁴² O'Connell *et al* suggested that the IFN- γ -induced JAK/STAT-associated signalling pathway is insensitive to glucocorticoid action, an insensitivity that is reversed by STAT1 inhibition.⁴³ PIAS1 is a negative regulator of STAT1. It blocks STAT1 from interacting with DNA and inhibits STAT1-mediated gene activation in

response to interferons.⁴⁴ SUMOylation is an important post-translational mechanism that affects transcriptional regulation by altering transcription factors and chromatin structures. SUMO3 and SUMO E3 ligase PIAS1 may mediate the crosstalk mechanism between androgen receptor SUMOylation and ubiquitination to modulate the androgen receptor cellular distribution and stability.⁴⁵ Androgen receptor signalling stabilises Treg suppressive function to reduce allergen-induced type II airway inflammation and airway hyper-responsiveness.⁴⁶ HPSE2 is regulated by rs10883230 and involves the HS-GAG degradation pathway. Increased extracellular matrix deposition in the airway wall is characteristic of airway remodelling. HS is a linear GAG that functions as an HS proteoglycan (HSPG). Ge *et al* demonstrated in a mouse model that HSPG influences the development of airway remodelling during chronic allergic asthma by promoting the recruitment of inflammatory cells and

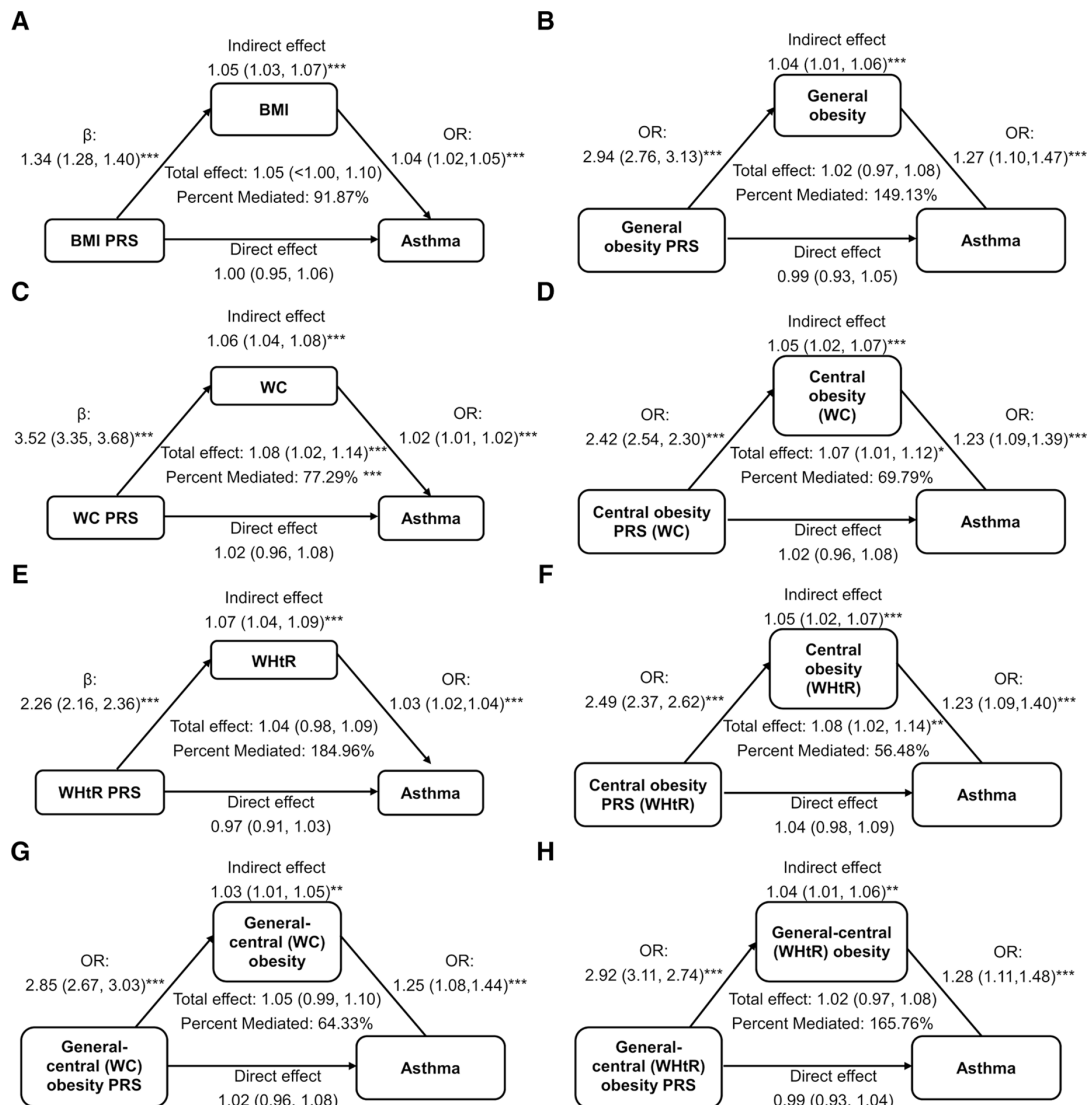


Figure 3 Mediation analysis using generalised linear models with binary and normal distribution of obesity-related PRS, obesity trait and asthma. Adjusted for age, sex, PRS of asthma, education, one of the parents has asthma, one of the siblings has asthma, chronic obstructive pulmonary disease, depression, gastro-oesophageal reflux disease, hypertension and PM_{2.5}. ***p value <0.001. BMI, body mass index; PRS, polygenic risk score; WC, waist circumference; WHtR, waist-to-height ratio.

regulating the expression of proremodelling factors in the lung.⁴⁷ Our results suggest that the AA/GA genotype of rs10883230, which regulates *HPSE2*, is associated with an increased asthma risk by 12%. Additionally, we found that five SNPs are involved in *ALCAM* gene expression and associated with asthma risk. *ALCAM* is a trans-membrane protein highly expressed in dendritic cells. It combines with *CD6*, a receptor on T-cells, to form an immune synapse, mediating the activation and differentiation of T cells to regulate the immune response. There is evidence that *ALCAM* promotes the development of allergic asthma by stimulating T helper cell type 2 immune response.⁴⁸ The *ALCAM*–*CD6* pathway is a target for severe asthma.⁴⁹ Our results reported that minor alleles of four SNPs (rs28588542-T, rs9857705-C, rs6769329-C and rs2399047-T) were associated with an 8% increase in asthma risk.

In addition to immunological mechanisms, a mechanical effect in which obesity narrows the airways and affects airway closure and hyper-responsiveness is a well-known explanation for the relationship between obesity and asthma. Abdominal and thoracic fat are more likely to contribute to lung function impairment than general obesity is, which is independent of the fat distribution. This is because they directly affect the mechanical expansion of the chest wall and diaphragm during forced inspiration.⁸ A recent study in a Chinese population identified a strong negative genetic correlation between central obesity and lung function.⁵⁰ Our study also found that WC and WHtR (indicators of central obesity) are genetic mediators of asthma.

However, our results should be interpreted with caution due to the following limitations. First, the cross-sectional survey data cannot be used to infer a causal or temporal

relationship between obesity and asthma. Several studies have confirmed that obesity may predispose individuals to asthma, but as our study design is not prospective, we should interpret results cautiously when exploring the association and mediated effect. Second, only adults who are 30–70 years old without a history of cancer were recruited in the TWB, so our results should not be extrapolated to all populations in Taiwan. Third, we do not control all factors related to obesity and asthma due to the limitations of the secondhand data. Fourth, owing to their distinctive genetic backgrounds,⁵¹ obesity may have heterogeneous effects on different subtypes of asthma. However, we lacked the diagnosis of asthma subtypes, which prevented us from further exploring the relationship between obesity and different asthma subtypes. Additionally, we generated obesity and asthma PRS using the traditional PRS methods. Because LD is not considered in traditional PRS approaches, their predictive value is restricted. Adopting advanced PRS approaches, such LDpred,^{52–54} will be beneficial in future analyses to address the LD structural problem and improve power.

In conclusion, we found that adults with obesity have a significantly higher risk of asthma, and observed a significant positive relationship between the overall genetic risk for obesity and the risk of asthma. Furthermore, overall genetic risk for obesity increases the risk of asthma by affecting the obese phenotype.

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Contributors T-CC, H-LH and J-SH designed the study. Y-JH and Y-CC reviewed the literature, refined the data and performed statistical analysis and wrote the draft of the manuscript. C-WC helped on preparing genetic data and quality control. H-CY, J-SH and C-HC provided statistical consulting and helped interpret the results. H-LH provided clinical suggestions and helped interpret the results. T-CC, H-LH and J-SH helped edit the manuscript. T-CC is the guarantor of the study. All authors have read and approved the final manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This study was approved by the institutional review board (IRB) on Biomedical Science Research, Academia Sinica (AS-IRB01-17049). All data from human participants were obtained from

the Taiwan Biobank database and National Health Insurance Research Database database, for which data sharing and data linkage were parts of the consent, so a waiver of consent was granted by the Academia Sinica IRB. This study obtained secondhand data; participants did not receive feedback on the results and were not involved in the study.

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Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from the Taiwan Biobank and Ministry of Health and Welfare, Taiwan, but restrictions apply to the availability of these data, which were under approval for the current study and so are not publicly available. The linked data set used in this study had to be analysed in person in the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan.

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REFERENCES

- 1 GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 2020;396:1204–22.
- 2 World Health Organization (WHO). Asthma 3 may 2021. Available: <https://www.who.int/news-room/fact-sheets/detail/asthma>
- 3 World Health Organization (WHO). Obesity and overweight 9 June 2021. Available: <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- 4 Chen YC, Dong GH, Lin KC, et al. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev* 2013;14:222–31.
- 5 Chen Y-C, Fan H-Y, Huang Y-T, et al. Causal relationships between adiposity and childhood asthma: bi-directional Mendelian randomization analysis. *Int J Obes* 2019;43:73–81.
- 6 Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169–79.
- 7 Litonjua AA, Gold DR. Asthma and obesity: common early-life influences in the inception of disease. *J Allergy Clin Immunol* 2008;121:1075–84.
- 8 Boulet L-P. Asthma and obesity. *Clin Exp Allergy* 2013;43:8–21.
- 9 Huang Y-J, Chu Y-C, Huang H-L, et al. The effects of asthma on the association between pulmonary function and obesity: a 16-year longitudinal study. *J Asthma Allergy* 2021;14:347–59.
- 10 Hallstrand TS, Fischer ME, Wurfel MM, et al. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol* 2005;116:1235–41.
- 11 Zhu Z, Guo Y, Shi H, et al. Shared genetic and experimental links between obesity-related traits and asthma subtypes in UK Biobank. *J Allergy Clin Immunol* 2020;145:537–49.
- 12 Guo Y, Moon J-Y, Laurie CC, et al. Genetic predisposition to obesity is associated with asthma in US Hispanics/Latinos: results from the Hispanic community health Study/Study of Latinos. *Allergy* 2018;73:1547–50.
- 13 Melén E, Himes BE, Brehm JM, et al. Analyses of shared genetic factors between asthma and obesity in children. *Journal of Allergy and Clinical Immunology* 2010;126:631–7.
- 14 Melén E, Granell R, Kogevinas M, et al. Genome-Wide association study of body mass index in 23 000 individuals with and without asthma. *Clin Exp Allergy* 2013;43:463–74.
- 15 Santos Coelho R, Paula Castro Melo A, Dos Santos Silva H, et al. ADIPOQ and Lep variants on asthma and atopy: genetic association modified by overweight. *Gene* 2021;781:145540.

- 16 Zhu Z, Guo Y, Shi H, *et al*. Shared genetic and experimental links between obesity-related traits and asthma subtypes in UK Biobank. *J Allergy Clin Immunol* 2020;145:537–49.
- 17 Fan C-T, Lin J-C, Lee C-H. Taiwan Biobank: a project aiming to aid Taiwan's transition into a biomedical island. *Pharmacogenomics* 2008;9:235–46.
- 18 Hsing AW, Ioannidis JPA. Nationwide population science: lessons from the Taiwan National health insurance research database. *JAMA Intern Med* 2015;175:1527–9.
- 19 Lin L-Y, Warren-Gash C, Smeeth L, *et al*. Data resource profile: the National health insurance research database (NHIRD). *Epidemiol Health* 2018;40:e2018062.
- 20 Ho C-C, Chen L-J, Hwang J-S. Estimating ground-level PM_{2.5} levels in Taiwan using data from air quality monitoring stations and high coverage of microsensors. *Environ Pollut* 2020;264:114810.
- 21 Chen C-H, Yang J-H, Chiang CWK, *et al*. Population structure of Han Chinese in the modern Taiwanese population based on 10,000 participants in the Taiwan Biobank project. *Hum Mol Genet* 2016;25:ddw346–31.
- 22 Chang CC, Chow CC, Tellier LCAM, *et al*. Second-Generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* 2015;4:s13742-015-0047-8.
- 23 Taiwan Health Promotion Administration (THPA). Evidences-based guideline on adult obesity prevention and management 2018. Available: https://www.hpa.gov.tw/File/Attach/10042/File_12271.pdf
- 24 Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev* 2010;23:247–69.
- 25 Price AL, Patterson NJ, Plenge RM, *et al*. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006;38:904–9.
- 26 Gögele M, Minelli C, Thakkinian A, *et al*. Methods for meta-analyses of genome-wide association studies: critical assessment of empirical evidence. *Am J Epidemiol* 2012;175:739–49.
- 27 Melén E, Himes BE, Brehm JM, *et al*. Analyses of shared genetic factors between asthma and obesity in children. *J Allergy Clin Immunol* 2010;126:e1-8:631–7.
- 28 Yang Q, Wang Y. Methods for analyzing multivariate phenotypes in genetic association studies. *J Probab Stat* 2012;2012:1–13.
- 29 GTEx Consortium. Human genomics. The Genotype-Tissue expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* 2015;348:648–60.
- 30 Wang J, Vasaikar S, Shi Z, *et al*. WebGestalt 2017: a more comprehensive, powerful, flexible and interactive gene set enrichment analysis toolkit. *Nucleic Acids Res* 2017;45:W130–7.
- 31 Belsky DW, Sears MR, Hancox RJ, *et al*. Polygenic risk and the development and course of asthma: an analysis of data from a four-decade longitudinal study. *Lancet Respir Med* 2013;1:453–61.
- 32 Torkamani A, Wineinger NE, Topol EJ. The personal and clinical utility of polygenic risk scores. *Nat Rev Genet* 2018;19:581–90.
- 33 Loika Y, Irincheeva I, Culminkaya I, *et al*. Polygenic risk scores: pleiotropy and the effect of environment. *Geroscience* 2020;42:1635–47.
- 34 Budtz-Jørgensen E, Keiding N, Grandjean P, *et al*. Confounder selection in environmental epidemiology: assessment of health effects of prenatal mercury exposure. *Ann Epidemiol* 2007;17:27–35.
- 35 Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175:661–6.
- 36 Sun Y-Q, Brumpton BM, Langhammer A, *et al*. Adiposity and asthma in adults: a bidirectional Mendelian randomisation analysis of the HUNT study. *Thorax* 2020;75:202–8.
- 37 Xu S, Gilliland FD, Conti DV. Elucidation of causal direction between asthma and obesity: a bi-directional Mendelian randomization study. *Int J Epidemiol* 2019;48:899–907.
- 38 Zhang X, Köhl J. A complex role for complement in allergic asthma. *Expert Rev Clin Immunol* 2010;6:269–77.
- 39 Aittoniemi J, Soranummi H, Rovio AT, *et al*. Mannose-Binding lectin 2 (MBL2) gene polymorphism in asthma and atopy among adults. *Clin Exp Immunol* 2005;142:120–4.
- 40 Naumov D, Gassan D, Kotova O, *et al*. Role of interferon-gamma as a marker of asthma severity and control. *European Respiratory Journal* 2019;54:PA4378.
- 41 Tau G, Rothman P. Biologic functions of the IFN-gamma receptors. *Allergy* 1999;54:1233–51.
- 42 Fabregat A, Sidiropoulos K, Viteri G, *et al*. Reactome diagram viewer: data structures and strategies to boost performance. *Bioinformatics* 2018;34:1208–14.
- 43 O'Connell D, Bouazza B, Kokalari B, *et al*. IFN- γ -induced JAK/STAT, but not NF- κ B, signaling pathway is insensitive to glucocorticoid in airway epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2015;309:L348–59.
- 44 Liu B, Liao J, Rao X, *et al*. Inhibition of Stat1-mediated gene activation by PIAS1. *Proc Natl Acad Sci U S A* 1998;95:10626–31.
- 45 Yang N, Liu S, Qin T, *et al*. Sumo3 modification by PIAS1 modulates androgen receptor cellular distribution and stability. *Cell Commun Signal* 2019;17:153.
- 46 Gandhi VD, Cephus J-Y, Norlander AE, *et al*. Androgen receptor signaling promotes Treg suppressive function during allergic airway inflammation. *J Clin Invest* 2022;132. doi:10.1172/JCI153397. [Epub ahead of print: 15 Feb 2022].
- 47 Ge XN, Ha SG, Rao A, *et al*. Endothelial and leukocyte heparan sulfates regulate the development of allergen-induced airway remodeling in a mouse model. *Glycobiology* 2014;24:715–27.
- 48 Kim MN, Hong JY, Shim DH, *et al*. Activated leukocyte cell adhesion molecule stimulates the T-cell response in allergic asthma. *Am J Respir Crit Care Med* 2018;197:994–1008.
- 49 Mukherjee M, Zhao N, Radford K. CD6-ALCAM pathway is elevated in patients with severe asthma. *European Respiratory Journal* 2020;56:5283.
- 50 Zhu Z, Li J, Si J, *et al*. A large-scale genome-wide association analysis of lung function in the Chinese population identifies novel loci and highlights shared genetic aetiology with obesity. *Eur Respir J* 2021;58. doi:10.1183/13993003.00199-2021. [Epub ahead of print: 14 10 2021].
- 51 Zhu Z, Hasegawa K, Camargo CA, *et al*. Investigating asthma heterogeneity through shared and distinct genetics: insights from genome-wide cross-trait analysis. *J Allergy Clin Immunol* 2021;147:796–807.
- 52 Vilhjálmsson BJ, Yang J, Finucane HK, *et al*. Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *Am J Hum Genet* 2015;97:576–92.
- 53 Zhu Z, Hasegawa K, Ma B, *et al*. Association of asthma and its genetic predisposition with the risk of severe COVID-19. *J Allergy Clin Immunol* 2020;146:e4:327–9.
- 54 Zhu Z, Hasegawa K, Ma B, *et al*. Association of obesity and its genetic predisposition with the risk of severe COVID-19: analysis of population-based cohort data. *Metabolism* 2020;112:154345.