

# Exploring Factors Underlying Poorly-Controlled Asthma in Adults by Integrating Phenotypes and Genotypes Associated with Obesity and Asthma: A Case-Control Study

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**Background:** Uncontrolled asthma in adults leads to poor clinical outcome, while the clinical heterogeneity of phenotypes interferes the applicable genetic determinants. This study aimed to identify phenotypes and genetic impact on poorly-controlled asthma to optimize individualized treatment strategies.

**Methods:** This propensity score-matched case-control study included 340 and 1020 asthmatics with poorly-controlled asthma and well-controlled asthma, respectively. Data were obtained from the 2008–2015 Taiwan Biobank Database and linked to the National Health Insurance Research Database. All asthmatics were aged  $\geq 30$  years, without cancer history, and each completed a questionnaire, physical examination, and genome-wide single nucleotide polymorphisms (SNPs). Multivariate adjusted odds ratios (ORs) for genetic risk scores were calculated using conditional logistic regression, stratified by age and sex. A model integrating obesity- and asthma-associated phenotypes and genotypes was applied for poorly-controlled asthma risk prediction.

**Results:** General obesity with body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> (OR:1.49, 95% confidence interval (CI) 1.09–2.03), central obesity with waist-to-height ratio (WHtR)  $\geq 0.5$  (OR:1.62, 95% CI 1.22–2.15), and parental history of asthma (OR:1.65, and 1.68; for BMI model and WHtR model, respectively) were significantly associated with poorly-controlled asthma in adults, and the combination effect of both obesity phenotypes was 1.66 (95% CI 1.17–2.35). A total of 16 obesity-associated SNPs and 9 asthma-associated SNPs were converted into genetic scores, and the aforementioned phenotypes were incorporated into the risk prediction model for poorly-controlled asthma, with an area under curve 0.72 in the receiver operating characteristic curve. The potential biological functions of genes are involved in immunity pathways.

**Conclusion:** The prediction model integrating obesity-asthma phenotypes and genotypes for poorly-controlled asthma can facilitate the prediction of high-risk asthma and provide potential targets for novel treatment.

**Keywords:** biobank, biomarker, obesity, genetic score, poorly-controlled asthma

## Introduction

Asthma is a highly heterogeneous chronic airway inflammatory disease that has emerged as a major public health threat with a rising prevalence in developing countries, affecting 262 million people in 2019 and causing 461,000 deaths.<sup>1</sup> Uncontrolled asthma, a precursor of severe asthma, is a multifactorial disease with marked phenotypic heterogeneity, involving the complex interaction of clinical characteristics, polygenetic, and environmental influences. It is defined as

worsening symptom control or frequent exacerbations refractory to high-dose inhaled steroid (ICS) despite adherence to maximal optimized therapy in line with the Global Initiative for Asthma and treatment of contributory factors.<sup>2</sup> Severe asthma afflicts 3.7–10% of the asthma population,<sup>3,4</sup> but drives the majority of the morbidity, mortality, psychological, and heavy socioeconomic burden.<sup>5,6</sup>

Recent studies have demonstrated that obesity is strongly associated with non-atopic asthma and contributes to uncontrolled asthma.<sup>7</sup> Our previous retrospective longitudinal study revealed that the annual increment of body mass index (BMI) is significantly associated with accelerated lung function decline, with a greater risk of acute exacerbation in asthmatics than non-asthmatics.<sup>8</sup> With the advancement of whole genome sequencing in decades, genome-wide association studies (GWAS) have revealed shared genetic risk factors of obesity-related traits, indicated by body-mass index and high-density lipoprotein with asthma.<sup>9–11</sup> Zhu et al indicated that the impact of BMI-based obesity trait-related genes on populations with later-onset and non-atopic asthma is greater than those with early onset and atopic asthma by conducting a GWAS of 457,822 individuals in the UK Biobank.<sup>11</sup> Additionally, they explored the shared loci between obesity and asthma that are involved in immune- and cell differentiation-related pathways. However, this BMI-based study does not provide the fat distribution of the body in obese patients.

Pharmacogenetic studies have been conducted to link genome-wide variants with treatment outcomes in patients with asthma. Single nucleotide polymorphism (SNP) variants of LTBP1 are mostly associated with a favorable ICS response, while GLCC11 and VDR genes are linked to attenuation of the response to ICS.<sup>12</sup> The clinical impact of the ADRB2 gene encoding the beta2 adrenergic receptor on the bronchodilator response in patients with asthma is still controversial.<sup>13,14</sup> However, there are no concise applicable genetic determinants for the clinical outcome of patients with severe asthma.

This matched case-control study aimed to comprehensively elucidate the phenotypes with genetic casualty impact on patients with poorly-controlled asthma, facilitate the understanding of poorly-controlled asthma-related pathophysiology, and develop a modifiable gene prediction model for treatment outcomes to optimize individualized treatment strategies.

## Materials and Methods

### Ethics Approval and Consent to Participate

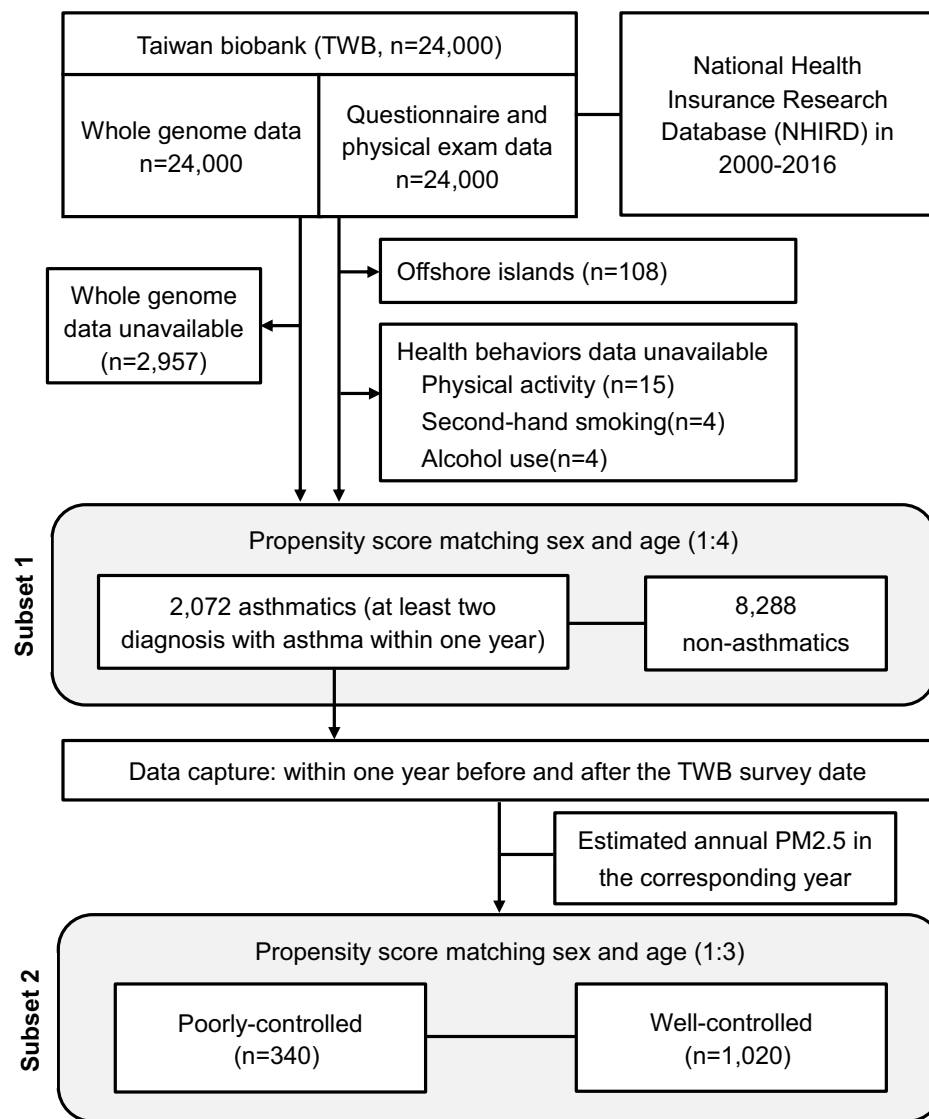
This study was approved by the Institutional Review Board (IRB) on Biomedical Science Research, Academia Sinica (AS-IRB01-17049). All data from human participants were obtained from the TWB database and NHIRD database, for which data sharing and data linkage were parts of the consent, so a waiver of consent was granted by the Academia Sinica IRB.

### Sample Size Calculation

The estimated sample size was based on the minimum sample size needed for a genetic association study (GAS) based on the following factors: (a) the prevalence of severe asthma was 0.037; (b) case control ratio was 1:3; (c) an alpha of  $1 \times 10^{-4}$  was used as the cutoff for significance; (d) a beta was set at 0.2 (power = 0.8); (e) the disease allele frequency was 0.19; and (f) genotype relative risk was 2.0.<sup>15</sup> The GAS Power Calculator ([http://csg.sph.umich.edu/abecasis/cats/gas\\_power\\_calculator/index.html](http://csg.sph.umich.edu/abecasis/cats/gas_power_calculator/index.html)) was used to determine the sample size. It was determined that 1067 participants (about 267 cases and 801 controls) would be required to prove an association between a particular SNP of interest and the development of severe asthma.

### Enrolled Population and Data Source

Figure 1 illustrates the study design and patient selection process. We first retrieved asthmatic patients aged 30–70 with no cancer history from the 24,000 participants of Taiwan Biobank (TWB) between 2008 and 2015,<sup>16</sup> who had at least two diagnoses of asthma (ICD-9-CM:483 and ICD-10-CM code: J45) and had regular medication intervals within one year from the National Health Insurance Research Database (NHIRD),<sup>17</sup> by linking encrypted personal identification numbers through the Health and Welfare Data Science Center, Ministry of Health and Welfare (MOHW), Taiwan. After excluding the participants living on offshore islands ( $n = 108$ ), with health behaviors unavailable ( $n = 23$ ), and the whole genome data



**Figure 1** Flow chart of the enrollment of study participants.

under quality control (QC) standards ( $n = 2,957$ ), a total of 2072 asthmatics and 8288 non-asthmatics randomly retrieved from TWB by age and sex using a propensity score matching algorithm (1:4) were enrolled in subset 1. We further identified poorly-controlled asthmatics among them. Poor asthma control (partly-controlled or uncontrolled) can lead to asthma exacerbation leading to increased emergency room (ER) or hospital admissions, which can be used as a surrogate for assessing the degree of asthma control.<sup>18</sup> The poorly-controlled asthmatics was defined as at least one ER visit or hospitalization due to asthma within one year before and after the TWB survey date, and each was age- and sex-matched to three controls with well-controlled asthma. A total of 1360 patients with asthma (340 poorly-controlled; 1020 well-controlled) were enrolled for the final analysis in subset 2. Each participant was assigned the 2-year average  $PM_{2.5}$  concentration of the residential area corresponding to the year of enrollment. Annual  $PM_{2.5}$  values were constructed using a two-step spatiotemporal prediction model that included 76 air quality monitoring sites and 1882 Airbox microsensors.<sup>19</sup>

## Phenotypes of General and Central Obesity

We assessed two phenotypes of obesity, general obesity and central obesity, using an index of BMI and waist-to-height ratio (WHtR). BMI is a value calculated by height and weight, and was stratified into four categories: underweight

(<18.5 kg/m<sup>2</sup>), normal (18.5 ≤BMI <24 kg/m<sup>2</sup>), overweight (24≤BMI <27 kg/m<sup>2</sup>), and obese (≥27 kg/m<sup>2</sup>).<sup>20</sup> WHtR is defined as WC divided by height, and the cutoff point for central obesity is 0.5.<sup>21</sup>

## Genetic Variants of Obesity and Asthma

### Genome-Wide SNP Genotyping and Quality Control (QC)

Whole genome genotyping analysis was performed using a customized Axiom-Taiwan Biobank Array Plate (TWB chip; Affymetrix, Inc., Santa Clara, CA, USA),<sup>22</sup> including 632,150 SNPs from autosomes (chromosomes 1 to 22) in the Taiwanese population.

The QC profiles for the SNPs were as follows: genotype call rate ≥ 0.95, minor allele frequency (MAF) ≥ 0.01, and Hardy-Weinberg equilibrium (HWE)  $p \geq 0.05/n$  (detailed QC procedure is shown in [Figure S1](#)). Sample and marker QCs analyses were performed using PLINK 1.9 (<https://www.cog-genomics.org/plink/1.9/>).<sup>23</sup>

### Genome-Wide Association Study (GWAS)

We used PLINK 1.9 to conduct association tests and clumping procedures to identify asthma- and obesity-related SNPs. First, we identified asthma-associated SNPs from subset 1 (10,360 participants, 606,086 SNPs) by logistic regression models. BMI- and WHtR-associated SNPs were identified from subset 2 by linear regression models. Both logistic and linear models were analyzed under additive, dominant, and recessive genetic effects and adjusted for age, sex, and 18 ancestry principal components used to control for population stratification.<sup>24</sup> Most studies focus on additive genetic effects; however, examining multiple genetic effects in meta-analysis may aid in the discovery of less common genetic variants.<sup>25</sup> Next, we combined the results of the three genetic models using fixed-effect meta-analysis, and heterogeneity was evaluated according to Cochrane's Q test.<sup>25</sup> Finally, a linkage disequilibrium-based clumping procedure ( $R^2$ -cutoff of 0.5 within a 250 kb window) was applied to the GWAS results to determine the most significant SNPs ( $p$ -value <  $10^{-4}$ ) that were independent of each other.

### Genetic Score

The genetic risk score (GRS) and genetic protective score (GPS) were established using poorly-controlled asthma-associated SNPs. The score was the weighted sum of the effect size (log (OR)) and coefficient of the SNPs determined by genetic models (details on [Text S1](#) of the supporting information).

## Statistical Analysis

The odds ratios (ORs) and 95% confidence intervals (CIs) for poorly-controlled asthma according to obesity-related traits and obesity-related SNPs were estimated using covariate-adjusted conditional logistic regression models stratified by age and sex. Moreover, we analyzed the impact of asthma-related SNPs on asthma control. We selected common sociodemographic variables and all possible confounders, including the presence of asthma in one parent, disease history, medication history, physical activity, smoking, and PM<sub>2.5</sub>, as covariates, and applied a stepwise regression method to determine the final model. Finally, presence of asthma in one parent was included as the confounding factor in the final model. Furthermore, we used the Change-in-Estimate (CIE) criterion with a 10% cut-off to check whether the model was affected by other unselected variables.<sup>26</sup> Receiver operating characteristic (ROC) curve analysis was applied to test the accuracy of obesity-related traits and obesity genetic scores in predicting the risk of poor asthma control. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and drawn using the R software version 3.6.3 (R Core Team, Vienna, Austria). Statistical significance was set at  $p < 0.05$ .

## Expression Quantitative Trait Loci (eQTL) Analysis

Expression quantitative trait loci (eQTL) have been widely used to identify the effects of genetic variation on gene expression across human tissues ( $p < 10^{-4}$ ). We accessed the Genotype Tissue Expression (GTEx) portal (<https://www.gtexportal.org/home/>)<sup>27</sup> to obtain publicly available eQTL data.

## Gene and Pathway Enrichment Analysis

We performed gene set enrichment analysis of gene ontology and pathways to assess the biological processes and functional pathways of obesity-related genes in asthma control, and over-representation analysis was used to identify the overrepresentation of genes of interest in related pathways. All functional analyses were performed using the default parameters in WebGestalt (<http://www.webgestalt.org/>) with KEGG, Panther, Reactome, and WikiPathway as functional databases.<sup>28</sup> Benjamini-Hochberg (BH) adjustment was used for multiple tests, and a p value <0.05 was statistically significant.

## Results

### Baseline Characteristics of Enrolled Population

Characteristics of the 1360 asthmatics (340 poorly-controlled and 1020 well-controlled) are summarized in Table 1. Participants with poorly-controlled asthma had significantly higher proportions of one of the parents with asthma (15.0% vs 9.22%), chronic obstructive pulmonary disease (36.5% vs 30.0%), gastroesophageal reflux disease (13.8% vs 7.65%), steroid treatment (oral:

**Table 1** Baseline Characteristics of Included Participants

Characteristic	Total (n = 1360)	Poorly- Controlled (n = 340)	Well-Controlled (n = 1020)	p-value
<b>Demography</b>				
Age (year)				0.969
30–39	216 (15.9)	55 (16.2)	161 (15.8)	
40–49	279 (20.5)	69 (20.3)	210 (20.6)	
50–59	348 (25.6)	84 (24.7)	264 (25.9)	
60–70	517 (38.0)	132 (38.8)	385 (37.8)	
Female	739 (54.3)	181 (53.2)	558 (54.7)	0.637
Education				0.625
Primary and below	136 (10.0)	37 (10.9)	99 (9.71)	
Junior/ senior high school	535 (39.3)	138 (40.6)	397 (38.9)	
College and above	689 (50.7)	165 (48.5)	524 (51.4)	
<b>Family history</b>				
One of the parents has asthma	145 (10.7)	51 (15.0)	94 (9.22)	0.003
<b>Disease history</b>				
COPD	430 (31.6)	124 (36.5)	306 (30.0)	0.026
GERD	125 (9.19)	47 (13.8)	78 (7.65)	<0.001
<b>Medication history</b>				
Metformin	29 (2.13)	9 (2.65)	20 (1.96)	0.448
Statin	22 (1.62)	2 (0.59)	20 (1.96)	0.082
Aspirin	152 (11.2)	39 (11.5)	113 (11.1)	0.843
Beta-blockers	146 (10.7)	36 (10.6)	110 (10.8)	0.919
Steroid	981 (72.1)	275 (80.9)	706 (69.2)	<0.001

(Continued)

**Table 1** (Continued).

Characteristic	Total (n = 1360)	Poorly- Controlled (n = 340)	Well-Controlled (n = 1020)	p-value
Steroid for Asthma				
Oral	759 (55.8)	272 (80.0)	487 (47.8)	<0.001
Injection	117 (8.60)	66 (19.4)	51 (5.00)	<0.001
<b>Anthropometry</b>				
BMI (kg/m <sup>2</sup> )	24.8±3.84	25.3±3.83	24.6±3.83	0.002
Underweight (<18.5)	31 (2.28)	5 (1.47)	26 (2.55)	0.032
Normal (18.5–23.9)	581 (42.7)	132 (38.8)	449 (44.0)	
Overweight (24.0–26.9)	423 (31.1)	103 (30.3)	320 (31.4)	
Obesity (≥27.0)	325 (23.9)	100 (29.4)	225 (22.1)	
WHtR	0.53±0.06	0.54±0.06	0.53±0.06	<0.001
Obesity	901 (66.3)	251 (73.8)	650 (63.7)	<0.001
Non-obesity	459 (33.8)	89 (26.2)	370 (36.3)	
<b>Health behaviors</b>				
Physical activity				0.252
Light-intensity (<3METs)	1041 (76.5)	268 (78.8)	773 (75.8)	
High-intensity (≥3METs)	319 (23.5)	72 (21.2)	247 (24.2)	
<b>Smoking</b>				
Never	941 (69.2)	236 (69.4)	705 (69.1)	0.301
Former	314 (23.1)	72 (21.2)	242 (23.7)	
Current use	105 (7.72)	32 (9.41)	73 (7.16)	
Secondhand smoke	119 (8.75)	34 (10.0)	85 (8.33)	0.346
PM <sub>2.5</sub> (μg/m <sup>3</sup> )	23.2±10.5	23.9±11.3	23.0±10.2	0.176
<b>Medical service utilization<sup>a</sup></b>				
Total OPD visits	16.0 (2.00, 51.5)	20.0 (3.0, 60.0)	14.0 (1.50, 48.0)	<0.001
Asthma OPD visits	0.00 (0.00, 8.00)	1.00 (0.00, 14.5)	0.00 (0.00, 4.00)	<0.001
Total ER visits	13.0 (2.00, 48.5)	18.0 (4.00, 57.5)	12.0 (1.00, 46.0)	<0.001
Asthma ER visits	0.00 (0.00, 4.00)	1.00 (0.00, 8.00)	0.00 (0.00, 2.00)	<0.001
Total hospitalization visits	0.00 (0.00, 1.00)	0.00 (0.00, 2.00)	0.00 (0.00, 1.00)	<0.001
Asthma hospitalization visits	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	0.00 (0.00, 0.00)	<0.001

**Notes:** Continuous variables are presented as mean ± SD, and categorical variables are expressed as n (%). <sup>a</sup>indicates that descriptive statistics for variables are presented as medians (P5, P95).

**Abbreviations:** COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; BMI, body mass index; WHtR, waist-to-height ratio; OPD, outpatient department; ER, emergency department.

80.0% vs 47.8%; injected: 19.4% vs 5.00%), and obesity ( $\text{BMI} \geq 27 \text{ kg/m}^2$ : 29.4% vs 22.1%;  $\text{WHtR} \geq 0.5$ : 73.8% vs 63.7%) than participants with well-controlled asthma. The median number of visits in the outpatient department (OPD) (20.0 vs 14.0), asthma OPD (1.00 vs 0.00), total ER (18.0 vs 12.0) and asthma ER (1.00 vs 0.00), were significantly higher among patients with poorly-controlled asthma than among those with well-controlled asthma.

## The Effect of Phenotypes of Obesity on Poorly-Controlled Asthma

Covariate-adjusted conditional logistic regression models (Table S1) showed that both general ( $\text{BMI} \geq 27 \text{ kg/m}^2$ ) and central obesity ( $\text{WHtR} \geq 0.5$ ) were independent risk factors for poor asthma control in patients with asthma, with adjusted ORs (95% CI) of 1.49 (1.09, 2.03) and 1.62 (1.22, 2.15), respectively.

To clarify the effect of obesity phenotypes on asthma control, cross-categorization was performed based on a combination of BMI and WHtR (Table 2). We found that participants with both central ( $\text{WHtR} \geq 0.5$ ) and general obesity ( $\text{BMI} \geq 27.0 \text{ kg/m}^2$ ) had the highest risk (OR:1.66, 95% CI:1.17, 2.35) of poorly-controlled asthma compared with participants without both central and general obesity.

## The Effect of Genotypes of Obesity on Poorly-Controlled Asthma

The meta-analysis identified 119 and 135 SNPs which met the  $P < 5 \times 10^{-8}$  threshold for genome-wide significance associated with BMI (Table S2) and WHtR (Table S3). Quantile-quantile (Q-Q) plot and Manhattan plot of the GWAS meta-analyses results for BMI and WHtR are shown in Figure S2. The effects of obesity-associated SNPs on poorly-controlled asthma are shown in Table 3. Three BMI-associated SNPs, rs720631, rs7323765, and rs117777319 were independent risk factors for poorly-controlled asthma, with ORs [95% CI] for dominant model as 1.46 [1.09, 1.95], 1.32 [1.02, 1.71], and 1.76 [1.17, 2.63], respectively. Seven WHtR-associated SNPs were associated with poorly-controlled asthma, including rs11735097 (1.34 [1.04, 1.73]), rs4873644 (1.32 [1.02, 1.72]), rs16936559 (1.40 [1.01, 1.73]), and rs6020323 (1.49 [1.16, 1.90]) in the dominant model, and rs26956 (1.49 [1.09, 2.04]), rs12153582 (2.16 [1.13, 4.12]), and rs2151317 (5.07 [1.40, 18.3]) in the recessive model. In contrast, four BMI-associated SNPs (dominant model: rs318773, rs17531088, rs2075050, and rs72971630) and two WHtR-associated SNPs (recessive model: rs6533014 and dominant model: rs75080842) were significantly associated with a lower risk of poorly-controlled asthma.

The meta-analysis identified 117 SNPs which met the  $P < 5 \times 10^{-8}$  threshold for genome-wide significance associated with asthma (Table S4). Q-Q plot and Manhattan plot of the GWAS meta-analyses results for asthma are shown in Figure S3. Five asthma-associated SNPs, rs4688261, rs3800570, rs4497664, rs437587, and rs1926075, were significantly associated with poorly-controlled asthma (Table 4). In the additive model, allele A of rs4688261 and allele C of rs1926075 were associated with an approximately 20% increase in the odds of poorly-controlled asthma. In the dominant model, the “A1A1” genotype of rs3800570, rs4497664, and rs437587 were associated with an approximately 200%, 130%, and 100% increased risk of poorly-controlled asthma as compared to the “A1A2/A2A2” genotype. In contrast, four SNPs (rs4663568, rs210774, rs981710, and rs10143946) were significantly associated with a lower risk of poorly-controlled asthma.

**Table 2** Combination Effect of Central Obesity and General Obesity, Stratified by WHtR and BMI on Poorly-Controlled Asthma

	BMI ( $\text{kg/m}^2$ )			
	Underweight (<18.5)	Normal (18.5–23.9)	Overweight (24.0–26.9)	Obesity ( $\geq 27.0$ )
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<b>Non-central obesity (WHtR &lt; 0.5)</b>	0.58 (0.20, 1.73)	Ref	0.51 (0.21, 1.24)	-
<b>Central obesity (WHtR <math>\geq 0.5</math>)</b>	-	1.41 (<1.00, 2.15) <sup>†</sup>	1.34 (0.94, 1.90)	1.66 (1.17, 2.35)*

**Notes:** Adjusted for one of the parents has asthma. \* $p < 0.05$ , <sup>†</sup> $0.05 \leq p < 0.1$ .

**Abbreviations:** BMI, body mass index; WHtR, waist-to-height ratio; OR, odds ratio; CI, confidence interval.

**Table 3** Genetic Model of Obese-Associated SNPs and Poorly-Controlled Asthma (Only Show Results with p-values <0.05)

SNPs	Chr: Position	A1/ A2	Nearby Gene(s)	Regulated Gene(s) <sup>a</sup> (p <10 <sup>-4</sup> )	Poor Asthma Control				
					BMI-Associated		WHtR-Associated		
					AM	DM	AM	DM	RM
					OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Risk SNPs									
rs720631	2: 208693307	C/ T	PLEKHM3	FZD5		1.46 (1.09, 1.95)			
rs11735097	4: 174559666	G/ T	RANP6	RP11-475B2.1				1.34 (1.04, 1.73)	
rs26956	5: 59790985	A/ C	PART1 PDE4D	ELOVL7 DEPDC1B ERCC8			1.21 (1.01, 1.45)		1.49 (1.09, 2.04)
rs12153582	5: 89008780	C/ T	LINC02161	-			1.28 (1.03, 1.59)		2.16 (1.13, 4.12)
rs2151317	6: 64468738	C/ T	PHF3 EYS	LGSN					5.07 (1.40, 18.3)
rs4873644	8: 53379300	C/ T	Intergenic	ALKAL1				1.32 (1.02, 1.72)	
rs16936559	11: 42379607	A/ C	Intergenic	-			1.36 (1.00, 1.84)	1.40 (1.01, 1.73)	
rs7323765	13: 20807243	C/ G	GJB6	GJB6		1.32 (1.02, 1.71)			
rs117777319	14: 59363486	C/ T	LINC01500	-	1.64 (1.15, 2.35)	1.76 (1.17, 2.63)			
rs6020323	20: 48785923	G/ A	RP11-112L6.2 RP11-112L6.3 RP11-112L6.4	LINC01273 TMEM189 RP11-112L6.3 CEBPB-AS1 UBE2V1			1.45 (1.19, 1.77)	1.49 (1.16, 1.90)	2.06 (1.24, 3.41)
Protective SNPs									
rs318773	3: 64778758	G/ A	ADAMTS9-AS2	-	0.80 (0.65, 0.98)	0.73 (0.57, 0.93)			
rs17531088	3: 174893775	C/ T	NAALADL2	-	0.78 (0.65, 0.93)	0.69 (0.53, 0.89)			
rs6533014	4: 103349740	G/ A	SLC39A8	SLC39A8			0.80 (0.66, 0.95)		0.64 (0.45, 0.9)
rs2075050	4: 13526386	G/ A	Intergenic	-		0.76 (0.59, 0.99)			
rs72971630	6: 136115951	A/ G	Intergenic	-	0.77 (0.61, 0.96)	0.76 (0.59, 0.99)			
rs75080842	18: 74270848	C/ T	LINC00908	-			0.63 (0.40, 0.97)	0.63 (0.41, 0.99)	

**Notes:** Adjusted for obesity phenotype and one of the parents has asthma. SNPs information were obtained from the SNP database (dbSNP, GRCH 37.p13: <https://www.ncbi.nlm.nih.gov/snp>) of the National Center for Biotechnology Information (NCBI) and the Taiwan Biobank v3 (<https://taiwanview.twbiobank.org.tw/index>). "a" means the gene expression is regulated by the SNPs, and the information of SNPs was obtained from GTEx portal (<https://www.gtexportal.org/home/>).

**Abbreviations:** AM, additive model; DM, dominant model; RM, recessive model; BMI, body mass index; WHtR, waist-to-height ratio; OR, odd ratio; CI, confidence interval.

## Biological Process and Functional Pathways of Obesity-Associated SNPs and Asthma-Associated SNPs on Poorly-Controlled Asthma

High gene expression of obesity-associated SNPs was observed in visceral adipose tissue, adrenal gland, esophagus, lung, cultured fibroblasts, and whole blood (Figures S4-S5). Simultaneously, the genotype of asthma-associated SNPs was also significantly correlated with the expression of genes in tissues such as visceral adipose, whole blood, lung, and cultured fibroblasts (Figure S6).

The results of the top 10 GO biological processes analysis (Figure S7) indicated that FZD5, ELOVL7, LGSN, GJB6, DEPDC1B, and ERCC8 were involved in different biological processes, including sensory organ morphogenesis, response to molecules of bacterial origin, apoptotic processes involved in development, developmental induction, organic acid biosynthetic process, embryonic organ development, response to electrical stimulus, cell-cell signaling by wnt, protein

**Table 4** Effects of Asthma-Associated SNPs on Poorly-Controlled Asthma Under Three Genetic Model (Only Show Results with p-values <0.05)

SNPs	Chr: Position	A1/ A2	Nearby Gene(s)	Regulated Gene(s) <sup>a</sup> (p <10 <sup>-4</sup> )	Poor Asthma Control					
					BMI			WHtR		
					AM	DM	RM	AM	DM	RM
					OR (95%CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Risk SNPs										
rs4688261	3: 61620775	A/ G	PTPRG	–	1.21 (1.01, 1.44)			1.20 (1.01, 1.44)		
rs3800570	7: 138411332	G/ C	ATP6V0A4	–	1.31 (1.04, 1.66)		2.97 (1.44, 6.13)	1.35 (1.07, 1.72)		3.14 (1.51, 6.52)
rs4497664	15: 89261134	C/ T	Intergenic	ISG20 ACAN	1.27 (1.03, 1.57)		2.27 (1.30, 3.98)	1.28 (1.03, 1.58)		2.36 (1.34, 4.15)
rs437587	2: 79272737	T/ C	Intergenic	REG3G	1.24 (1.02, 1.52)		2.02 (1.25, 3.27)	1.23 (1.01, 1.51)		1.97 (1.21, 3.18)
rs1926075	20: 54880817	C/ A	Intergenic	–	1.24 (1.03, 1.49)		1.43 (1.01, 2.03)	1.22 (1.01, 1.46)		
Protective SNPs										
rs4663568	2: 236207394	G/ C	Intergenic	–	0.79 (0.65, 0.97)			0.78 (0.63, 0.95)	0.77 (0.60, 0.99)	
rs210774	4: 27428596	C/ A	Intergenic	–	0.67 (0.52, 0.85)	0.60 (0.45, 0.79)		0.67 (0.53, 0.86)	0.60 (0.45, 0.80)	
rs981710	4: 27658939	C/ T	Intergenic	–	0.77 (0.64, 0.92)	0.76 (0.58, 0.99)	0.64 (0.46, 0.89)	0.76 (0.63, 0.91)	0.75 (0.57, 0.98)	0.64 (0.46, 0.88)
rs10143946	14: 39040391	G/ T	Intergenic	–	0.81 (0.67, 0.98)	0.67 (0.52, 0.86)		0.82 (0.68, 0.99)	0.68 (0.53, 0.87)	

**Notes:** Adjusted for obesity phenotype and one of the parents has asthma. SNPs information were obtained from the SNP database (dbSNP, GRCH 37,p13: <https://www.ncbi.nlm.nih.gov/snp>) of the National Center for Biotechnology Information (NCBI) and the Taiwan Biobank v3 (<https://taiwanview.twbiobank.org.tw/index>). “a” means the gene expression is regulated by the SNPs, and the information of SNPs was obtained from GTEx portal (<https://www.gtexportal.org/home/>).

**Abbreviations:** AM, additive model; DM, dominant model; RM, recessive model; BMI, body mass index; WHtR, waist-to-height ratio; OR, odd ratio; CI, confidence interval.

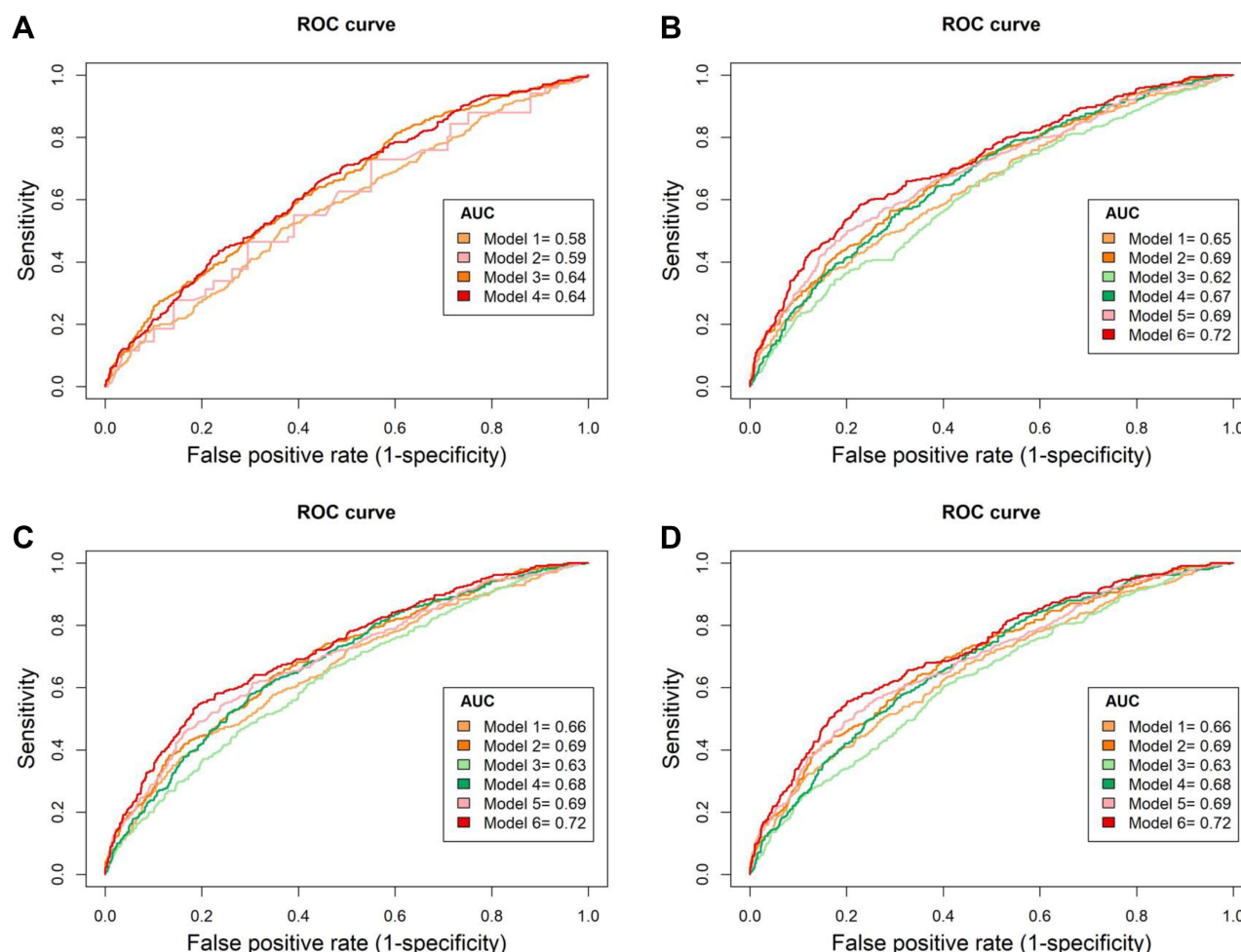
autoubiquitination, and establishment of tissue polarity. The top 10 pathway analyses indicated that the FZD5, UBE2V1, and SLC39A8 genes were involved in zinc ion transmembrane transport and immunity pathways (Figure S8).

## Predictive Model of Poorly-Controlled Asthma

The best area under the covariate-adjusted ROC curve (AUC) of the predictive model for poorly-controlled asthma was 0.72 by incorporating phenotypes and genetic scores (combination of gene traits from Table 3) for general obesity and central obesity (Figure 2). ROC curves for predicting poorly-controlled asthma based on general obesity-related traits and genetics scores and central obesity-related traits and genetics scores are shown in Figures S9 and S10, respectively.

## Discussion

In the current study, we found that concomitant central and general obesity is an independent risk factor with a 1.66-folds higher risk of poorly-controlled asthma than non-obese adult asthmatics. We also identified the shared prioritized risk genes for obesity and asthma involving inflammation-related pathways by conducting a comprehensive genomics integrative analysis. The AUC of the predictive model compromising phenotypes and genotypes of general and central obesity was 0.72. To our knowledge, this is the first model for severe asthma anchoring phenotype and genotype, which aids physicians in prognosticating adult asthma patients. This also provides novel targets for treatment.



**Figure 2** Covariate-adjusted ROC curve of combination effect of WHtR and BMI. **(A)** The effect of BMI and WHtR traits on poorly-controlled asthma. Model 1: BMI (CONT.) + WHtR (CONT.). Model 2: BMI (BIN.) + WHtR (BIN.). Model 3: Model 1 + asthma genetic score + one of the parents has asthma. Model 4: Model 2 + asthma genetic score + one of the parents has asthma. **(B)** The effect of BMI- and WHtR - related genetic score on poorly-controlled asthma. Model 1: BMI-related GRS + WHtR-related GRS. Model 2: Model 1 + asthma genetic score + one of the parents has asthma. Model 3: BMI-related GPS + WHtR-related GPS. Model 4: Model 3 + asthma genetic score + one of the parents has asthma. Model 5: Model 1 + Model 3. Model 6: Model 5 + asthma genetic score + one of the parents has asthma. **(C)** The effect of BMI, WHtR and genetic score on poorly-controlled asthma. Model 1: BMI (CONT.) + WHtR (CONT.) + BMI-related GRS + WHtR-related GRS. Model 2: Model 1 + asthma genetic score + one of the parents has asthma. Model 3: BMI (CONT.) + WHtR (CONT.) + BMI-related GPS + WHtR-related GPS. Model 4: Model 3 + asthma genetic score + one of the parents has asthma. Model 5: Model 1 + Model 3. Model 6: Model 5 + asthma genetic score + one of the parents has asthma. **(D)** The effect of obesity phenotype and genetic score on poorly-controlled asthma. Model 1: BMI (BIN.) + WHtR (BIN.) + BMI-related GRS + WHtR-related GRS. Model 2: Model 1 + asthma genetic score + one of the parents has asthma. Model 3: BMI (BIN.) + WHtR (BIN.) + BMI-related GPS + WHtR-related GPS. Model 4: Model 3 + asthma genetic score + one of the parents has asthma. Model 5: Model 1 + Model 3. Model 6: Model 5 + asthma genetic score + one of the parents has asthma. The asthma genetic score was established using asthma-associated SNPs from Table 4.

**Abbreviations:** BMI, body mass index; WHtR, waist-to-height ratio; CONT, continuous; BIN, binary; GRS, genetic risk score; GPS, genetic protective score.

Several longitudinal epidemiological studies have reported that obesity often precedes incident asthma in adults, and obese adults tend to have worse asthma control, with a greater risk of acute exacerbation than the lean population.<sup>29,30</sup> The clinical impact of central or abdominal obesity on obesity-related comorbidities compared to that of general obesity, as measured by BMI.<sup>31</sup> In accordance with a previous meta-analysis,<sup>32</sup> we reported that both general and central obesity adversely influence asthma control in adults, and central obesity is regarded as a greater contributor to poorly-controlled asthma. Additionally, we emphasize the integrated effect of both phenotypes and genotypes on poorly-controlled asthma, indicating that central obesity is independent of BMI and is a significant determinant of poorly-controlled asthma in adults. Possible mechanisms involving physiological and inflammation-mediated mechanics. The restriction of total lung capacity with lower expiratory reserve volume by the accumulation of adiposity around the chest wall and abdomen.<sup>33</sup> In contrast to allergic phenotypic asthma, obesity may polarize asthmatics to a neutrophil-dominant phenotype, attributed to

adipocytes and macrophage-mediated low-grade systemic inflammation,<sup>34</sup> thus resulting in greater bronchial hyper-responsiveness to airway remodeling<sup>35</sup> and poor response to steroids.

Asthma and obesity are highly heritable diseases, and known family history is a predictor for developing asthma and obesity. Genetic factors account for approximately 70% of the susceptibility to developing asthma<sup>36</sup> and 40–70% to obesity from studies of identical and fraternal twins.<sup>37</sup> The current study demonstrates the association between asthma and obesity overlap genes and poorly-controlled asthma, indicating the associated effect of genetic tendency toward poorly-controlled asthma.

In contrast to the reported SNPs associated with poorly-controlled asthma in previous studies,<sup>38</sup> we obtained 16 obesity-associated SNPs from a matched-case control study in an Asian population, which might be attributed to ethnic differences, and we did not access pharmacogenomic analysis for therapeutic responses to ICS or bronchodilators. The current predictive biological function of SNPs genes reflects the possible obesity-asthma shared genetic effects, involving the pro-inflammatory effects of adipose tissue fetal programming and epigenetics.<sup>39</sup> The FZD5 gene is regulated by rs72063, a receptor for the smooth muscle-specific WNT5A involved in  $\beta$ -catenin-independent wingless-integrase-1 (WNT) signaling, and is characterized to augment asthmatic inflammation with mast cells, eosinophils, and lymphocytes and remodeling.<sup>40</sup> The SNP rs6020323 reported in our study is associated with UBE2V1 gene expression, which is enriched in the innate immune responses involving the NF- $\kappa$ B pathway to regulate pro-inflammatory cytokines in airway smooth muscle and is positively correlated with the risk of asthma.<sup>41</sup> The SLC39A8, regulated by rs6533014, is involved in the zinc ion transmembrane transport pathway, guiding zinc into the cytosol to inhibit IKK $\beta$ , thereby negatively regulating NF- $\kappa$ B.<sup>42</sup>

Our study has several limitations. First, the inflammatory phenotype of patients with asthma cannot be distinguished from the current registry database because of the lack of laboratory data. In addition, we cannot differentiate between allergic and non-allergic asthmatic patients because skin prick testing was not performed. Second, the obesity status in the current dataset was only recorded on the day of the interview for each participant. Therefore, we cannot consider how the evolution of obesity status affected asthma control. Third, we could not access the modifiable risk factors, medication adherence, inhaler technique, and gene-environment interactions in asthma patients. Fourth, the use of GWAS arrays rather than next-generation sequencing has limited the exploration of genetic variation outside of protein-coding regions and variants beyond common SNPs. Fifth, this genetic study was restricted to an Asian population, and the results cannot be generalized to other racial populations. Sixth, we lack replication cohort for further validation. Seventh, PM<sub>2.5</sub> was a potential confounding factor in our study; hence, we included PM<sub>2.5</sub> into the model selection at the initial stage. However, PM<sub>2.5</sub> was not significant to be retained in the final model. Additionally, the current temporal resolution of PM<sub>2.5</sub> is the annual concentration and its short-term acute effect on asthma relapse may be difficult to observe.

## Conclusion

Assessing obesity phenotypes, including general obesity and central obesity, and asthma-obesity associated gene traits simultaneously, will facilitate the identification of high-risk populations of poorly-controlled asthma in adults, and the obesity-asthma overlap genes for poorly-controlled asthma might be a potential target for developing novel treatments.

## Data Sharing Statement

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 analyzed in person in the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. The researchers who meet the criteria can apply the data from the Taiwan Biobank and Ministry of Health and Welfare, Taiwan to access to confidential data.

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## Author Contributions

TCC, HLH, and JSH designed this study. YJH and YCC reviewed the literature, refined the data, performed statistical analyses, and drafted the manuscript. CWC helped in the preparation of the genetic data and quality control. HCY, JSH, and CHC provided statistical consultation and helped interpret the results. HLH provided clinical suggestions and helped to interpret the results. YJH and HLH drafted the manuscript. TCC revised the manuscript accordingly. All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests in this work.

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