

Investigating obesity-related risk factors for childhood asthma

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Abstract

Background

We tested the hypothesis that multiple obesity-related risk factors (obesity, physical activity, cardiopulmonary physical fitness, sleep-disorder breathing (SDB), and sleep quality) are associated with childhood asthma using a Mendelian randomization (MR) design. Furthermore, we aim to investigate whether these risk factors were associated with incident asthma prospectively.

Methods

In total, 7069 children aged 12 from the Taiwan Children Health Study were enrolled in the current study. Cross-sectional logistic regression, one-sample MR, summary-level MR sensitivity analyses, and prospective survival analyses were used to investigate each causal pathway.

Results

In MR analysis, three of the five risk factors (obesity, SDB, and sleep quality) were associated with asthma, with the highest effect sizes per inter-quartile range (IQR) increase observed for sleep quality (odds ratio [OR] = 1.42; 95% confidence interval [CI]: 1.06 to 1.92) and the lowest for obesity (OR = 1.08; 95% CI: 1.00–1.16). In the prospective survival analysis, obesity showed the highest risk of incident asthma per IQR increase (hazard ratio [HR] = 1.28; 95% CI: 1.05 to 1.56), followed by SDB (HR = 1.18; 95% CI: 1.08 to 1.29) and sleep quality (HR = 1.10; 95% CI: 1.03 to 1.17).

Conclusion

Among the examined factors, the most plausible risk factors for asthma were obesity, SDB, and poor sleep quality. For the prevention of childhood asthma, relevant stakeholders should prioritize improving children's sleep quality and preventing obesity comorbidities such as SDB.

Abbreviations

2SLS

two-stage least square

BMI

body mass index

CI

confidence interval

DTHM

discrete-time hazard model

Fe_{NO}

fractional exhaled nitric oxide

FEV1/FVC

forced expiratory volume in 1 second/forced vital capacity

GRS

genetic risk score

IV

instrumental variable

MR

Mendelian randomization

OR

odds ratio

SDB

sleep-disordered breathing

SNP

single nucleotide polymorphism

TCHS

Taiwan Children Health Study

Key Message

This study investigated multiple obesity-related risk factors, which are associated with childhood asthma using a Mendelian randomization (MR) design. In total, 7069 children aged 12 from the Taiwan Children Health Study were enrolled in the current study. Of the five risk factors examined, asthma was observationally and genetically associated with poor sleep quality, sleep-disordered breathing, and obesity. Prospective survival analysis also confirmed the temporal causality. Strategies for improving sleep quality and preventing obesity comorbidities such

as sleep-disordered breathing may be crucial to prevent childhood asthma.

1 INTRODUCTION

Childhood obesity and asthma have posed a parallel epidemic over the past three decades.¹ According to a meta-analysis of 6 prospective children studies, obesity was significantly associated with twofold times increased risk for incident asthma.² Obese asthma is a complex syndrome, including different phenotypes of diseases that warrant further investigations. Hence, identifying obesity-related risk factors behind this causal relationship is essential to inform preventive interventions. The obesity-related risk factors could be composed of hereditary factors and lifestyle factors, such as physical inactivity and inadequate sleep.

Multiple obesity-related risk factors may potentially contribute to the link of childhood asthma; for example, physical activity or physical fitness levels, poor sleep quality, and some obesity comorbidities, such as sleep-disordered breathing (SDB), may also play a role. We previously investigated the causal direction of the relationship between adiposity and asthma using genetic markers as instrumental variables (IVs) in bidirectional Mendelian randomization (MR) analysis, with the results suggesting that adiposity antedates asthma.³ Moreover, the causal relationships between physical activity or physical fitness levels and asthma have long been debated. Some studies have supported the causal relationship between physical fitness and asthma incidence in prospective studies,^{4, 5} whereas others have reported that physical fitness does not influence asthma directly.⁶ Moreover, poor sleep quality and SDB are common in children with asthma. Prospective studies of insomnia and new-onset asthma have been conducted in adults^{7, 8} but not in children. Using two-sample MR analysis, Dashti et al. reported a U-shaped association between sleep duration and asthma in an adult study.⁹ The mechanism behind poor sleep quality leading to asthma may be explained by the shifting of T helper (Th) cell activity toward a Th2 cytokine profile under chronic sleep deprivation.¹⁰ Moreover, protracted upregulation of inflammatory markers, such as increased interleukin (IL)-6, was also observed among patients with poor sleep.¹¹ IL-6 production induced by poor sleep quality might exacerbate airway hypersensitivity. Other potential mechanisms, such as poor sleep-induced chronic inflammatory status, manifesting as increased NF- κ B level¹² and decreased IFN- γ ,¹³ may also explain why poor sleep quality may trigger new-onset asthma. Although many studies have reported the obesity-related risk factors leading to asthma, accurately appraising the causality of these factors in asthma is essential for future preventive interventions.

Epidemiological studies have identified some obesity-related risk factors associated with asthma, but these associations can be subject to confounding and reverse causations. MR analysis can be used to strengthen causal inference indicated by observational studies by

using genetic variants as IVs for risk factors. A genetic risk score (GRS) for an individual obesity-related factor can be regarded as a genetic proxy for this risk factor. Therefore, if a certain obesity-related factor is causally related to asthma, a GRS for this risk factor should also be associated with asthma.

In this study, we addressed the aforementioned limitations of traditional observational methods and focused on several obesity-related risk factors (obesity, physical activity, cardiopulmonary physical fitness, SDB, and sleep quality) in which candidate genetic instruments could be defined. We aimed to (1) elucidate the causality of multiple obesity-related risk factors and childhood asthma by using MR, (2) conduct prospective analysis to strengthen the temporal relationship between these risk factors and asthma, and (3) describe the predicted prevalence of asthma from representative GRSs for each risk factor.

2 MATERIALS AND METHODS

2.1 Study participants

We obtained observational data on 7069 children aged 12 from the Taiwan Children Health Study (TCHS). The TCHS was a nationwide prospective study that comprised two cohorts of children, with 8.64% of the participants having physician-diagnosed asthma. The analysis herein included 3233 children in Cohort 1 and 3836 children in Cohort 2. The detailed study design and recruitment strategy were previously described.¹⁴ Obesity-related risk factors and oral mucosa samples for DNA extraction were collected in school. Follow-up surveys were performed through a home visit or telephone interview in 2012 and 2018 until these children were 17 years old. This study was approved by the Ethics Committees and was conducted according to the Declaration of Helsinki after obtaining informed consent from participating parents and children.

2.2 Definition of respiratory outcomes

We used answers from the parents to determine whether a child had physician-diagnosed asthma. The question was, “Has a doctor ever diagnosed your child as having asthma?” In the prospective survival analysis, incident asthma was calculated by excluding asthma history before the age of 11 years. Incident asthma was determined at age 12 and 17 years by parents’ affirmative answer to whether their child had been physician-diagnosed as having asthma during the follow-up period. The atopic status of asthma was determined by measuring the fractional exhaled nitric oxide (Fe_{NO}) by using a portable NO analyzer (NIOX MINO Airway Inflammation Monitor; Aerocrine AB, Solna, Sweden). We categorized children with asthma into the atopic or nonatopic group by using 20 ppb of Fe_{NO} as the cutoff value.¹⁵

A pulmonary function test was performed in accordance with a previously standardized protocol with two identical spirometers (Chestgraph HI-101)¹⁶ at age 12 years. The forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio, which is a marker of

obstructive type pulmonary function impairment, was also used as a respiratory outcome.

2.3 Measurement of multiple obesity-related risk factors

Five obesity-related risk factors were investigated at age 12, where suitable genetic instruments were available for inclusion in the analysis: obesity, physical activity, cardiopulmonary physical fitness, SDB, and sleep quality.

Physical activity was assessed using a questionnaire and evaluation at school. We used the Chinese version of the International Physical Activity Questionnaire¹⁷ to determine a child's physical activity levels. Participants were asked a series of questions pertaining to intensity, duration, and frequency of physical activity in the preceding week. Physical activities were categorized into vigorous, moderate, and mild, according to their metabolic equivalent (MET) values, namely >6 MET, 3–6 MET, and <3 MET. Physical activities were then quantified according to their average MET expenditure per day.¹⁸ Cardiorespiratory physical fitness was assessed through an 800-m sprint, a surrogate marker of predicted maximal oxygen consumption,¹⁹ during school visits by using a standardized protocol.²⁰ It was first converted into z-scores by using sex- and age-specific means and standard deviations. Hence, a higher cardiorespiratory physical fitness index signifies greater physical fitness.

SDB was determined by using a Chinese version of the Children's Sleep Habit Questionnaire, which was completed by the parent. Researchers compared this questionnaire with objective polysomnography-defined obstructive sleep apnea and found it to be a valid tool for detecting the presence of SDB.²¹ Sleep quality was evaluated through the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) questionnaire. The questionnaire consists of 19 self-rated questions that are grouped into seven subscale components: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, daytime dysfunction, sleep disturbances, and use of sleep medications.²² Each component score has equal weight and is measured on a Likert scale of 0 (*no difficulty*) to 3 (*severe difficulty*). The seven component scores are summed to yield a global PSQI score, with a range of 0–21; higher scores indicate poorer sleep quality.

We used body mass index (BMI) as a marker of obesity and calculated it by dividing body weight in kilograms by height in meters squared (kg/m^2). Subsequently, BMI was converted into age- and sex-specific z-scores (z-BMI) according to the World Health Organization growth standards for school-aged children and adolescents.²³

2.4 MR analysis

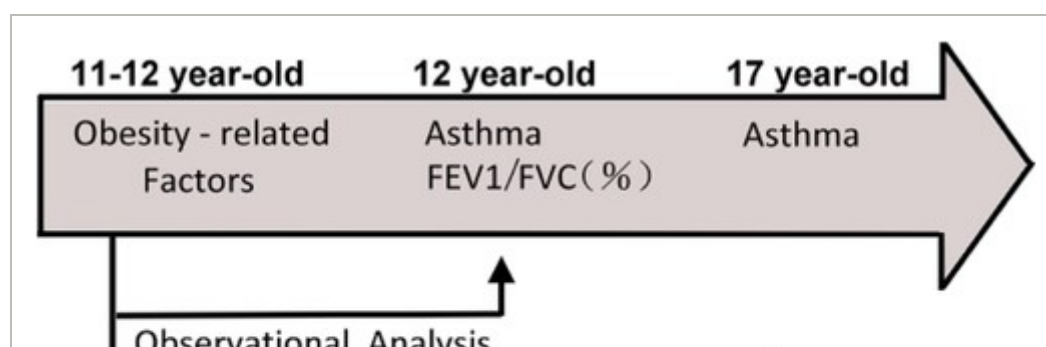
We performed MR²⁴ analyses by using genetic instrumental variables (IVs) to proxy for candidate obesity-related risk factors. The use of MR enables unbiased causal effects of risk factors on respiratory outcomes to be estimated if the following assumptions are met: (1) The genetic IVs are robustly associated with the risk factor of interest; (2) the genetic IVs are not associated with any confounding factors; and (3) the pleiotropic pathways through which

the IVs influence the outcome are all due to the risk factors. GRS composed of risk factor-associated single nucleotide polymorphism (SNP) was used as IVs. The dosage of the effect allele was multiplied by the regression coefficients of each SNP on associated traits divided by the mean value of all regression coefficients.

By referencing candidate SNPs from large genome-wide association studies, we collected well-known genetic variants associated with the five obesity-related risk factors. To avoid the pleiotropic effects of genetic variants, SNPs previously reported to be associated with asthma and confounders were excluded. After we selected SNPs for the obesity-related risk factors, some criteria were applied to filter the selected SNPs for quality control: (1) minor allele frequency of $\geq 5\%$, (2) genotyping call rate of $>98\%$ for all children, and (3) no linkage disequilibrium with candidate SNPs. The primers were designed using the National Genotyping Center of the Academia Sinica platform (<http://lims.ngc.sinica.edu.tw/service/>).²⁵ Genotyping was performed using Sequenom iPLEX matrix-assisted laser desorption/ionization time-of-flight mass spectrometry at the National Center for Genome Medicine, Taiwan. The online supplementary file provides details on how candidate SNPs were selected.

2.5 Statistical analysis

We initially conducted cross-sectional logistic models in the observational models (Figure 1). To investigate whether a factor is a causal factor for asthma, we conducted MR two-stage least squares (2SLS) and MR sensitivity analyses for all relationships. MR 2SLS analysis is a fundamental method in MR for both binary and continuous variables of exposure and outcomes.²⁶ MR sensitivity analyses (MR inverse-variance weighted, Egger's [slope], and weighted median method) were used to support the validity of the causal inference from the MR analysis.²⁷ To elucidate whether various factors predict incident asthma in later life, we also applied a discrete-time hazard model (DTHM). The DTHM is a survival analysis model that enables the estimation of hazard ratios (HRs) and 95% confidence intervals (CIs) when an event occurrence may be considered in a discrete period; baseline information on these risk factors was collected on disease-free individuals at age 11, and the outcomes were incident asthma at ages 12 and 17. Missing data were handled by applying the multiple imputation method.²⁸ The observational models and DTHM were adjusted for several potential confounders, such as age, sex, parental education, and family income. Odds ratios (ORs), HRs, and beta values were estimated using the IQR increase of the risk factors.



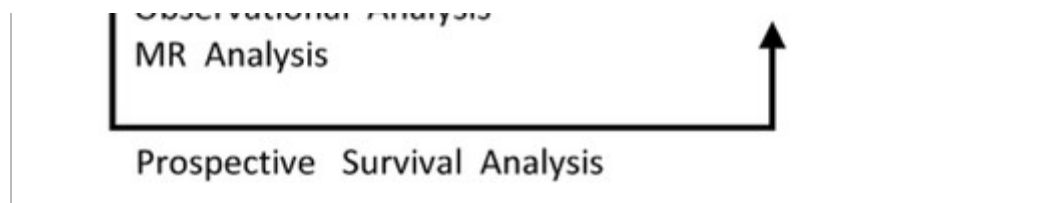


FIGURE 1

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Schematic drawing of analytical strategy

The GRS for a risk factor can be considered a genetic proxy. To compare the effect of these risk factors on asthma, as identified from observational and MR analyses, we further utilized the GRS to calculate the predicted prevalence of asthma. We computed the sample mean per quintile for each of the GRS to serve as the new dataset for prediction by logistic regression. To estimate the predicted probability of the GRS for an obesity-related factor, we included the means per quintile for asthma. Statistical significance was designated as a p -value $<.05$. All model regression and sensitivity analyses were performed using R software and R package (ivreg) MR 2SLS analysis (version 3.3.2, RStudio, Inc.).

3 RESULTS

In the present study, the TCHS population comprised 7069 children at age 12 (Table 1), and 4328 children received follow-up surveys at age 17 (Table S1). In Table 1, we observed a higher level of parental education and family income in Cohort 2 as compared to Cohort 1. Among them, 358 (9.33%) were children with physician-diagnosed asthma. The pulmonary function indicator, FEV1/FVC, was significantly higher in Cohort 2 as compared to Cohort 1.

TABLE 1. Characteristics of participants aged 12 years in the Taiwan Children Health Study.

Characteristics	Total		Cohort 1		Cohort 2		p value [§]
<i>N</i>	7069		3233		3836		
Age (years)	12.1	0.67	12.70	0.34	11.66	0.48	<.001
Male sex	3618	51.2%	1669	51.6%	1949	50.8%	.51
BMI (kg/m ²)	20.5	4.14	20.57	4.23	20.37	4.06	.08
Parental education							
High school or below	4110	58.1%	2085	64.5%	2025	52.8%	<.001
College or university	2520	35.7%	1026	31.7%	1494	39.0%	
Postgraduate	439	6.21%	122	3.77%	317	8.26%	

Characteristics	Total		Cohort 1		Cohort 2		<i>p</i> value [§]
Family income (NT\$)							
<600,000	3926	55.5%	2021	62.5%	1905	49.7%	<.001
600,001–1,000,000	2143	30.3%	848	26.2%	1295	33.8%	
>1,000,001	1000	14.2%	364	11.3%	636	16.6%	
Physician-diagnosed asthma	611	8.64%	253	7.83%	358	9.33%	.03

Note

All data are presented as means ± standard deviation or numbers (%). The number of participants does not add up to the total number because of missing data.

Abbreviations: BMI, body mass index; FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity; NT\$, new Taiwan dollars.

[§] *p* value indicates the difference between the two cohorts.

3.1 Observational and MR association

By using observational and MR 2SLS analysis, we calculated the causal associations between multiple obesity-related risk factors and asthma and pulmonary function (Table 2). The F-statistics for obesity, physical activity, cardiopulmonary physical fitness, sleep-disordered breathing, and sleep quality were 80.60, 18.62, 11.68, 10.27, and 7.09, respectively. Three of the five obesity-related risk factors exhibited robust associations with asthma in both the observational analysis and MR analysis. In order of decreasing effect sizes in MR analysis, these were sleep quality, SDB, and obesity, with the highest effect sizes per IQR increase observed for sleep quality (OR = 1.42; 95% CI, 1.06 to 1.92) and the lowest for obesity (OR = 1.08; 95% CI, 1.00 to 1.16). In detail, sleep quality was associated with increased risk of asthma in both observational and MR analyses (OR=1.01; 95% CI, 1.00–1.01 and OR =1.42; 95% CI, 1.06 to 1.92, respectively). SDB was associated with increased risk of asthma in both observational and MR analyses (OR=1.60; 95% CI, 1.36–1.88 and OR = 1.26; 95% CI, 1.00 to 1.58, respectively). Children with obesity suffered increased asthma risk in both observational and MR analyses (OR = 1.26; 95% CI, 1.07–1.47 and OR = 1.08; 95% CI, 1.00 to 1.16, respectively). Moreover, a one-IQR increase in z-BMI was also associated with a decrease in FEV1/FVC (β = −2.44; 95% CI, −4.24 to −0.65). Most of the MR sensitivity analysis results for the associations between obesity and respiratory outcomes were consistent with the main result (Table S2).

TABLE 2. Observational and MR analyses of obesity-related risk factors in relation to asthma at age 12

Risk factors	Category	Physician-diagnosed asthma			FEV1/FVC (%)		
		OR	95% CI		β	95% CI	
Obesity	Observational	1.26	1.07	1.47	-1.16	-1.37	-0.95
(28 SNPs, F = 80.60)	MR 2SLS	1.08	1.00	1.16	-2.44	-4.24	-0.65
Physical activity	Observational	1.01	1.00	1.01	-0.09	-0.24	0.06
(15 SNPs, F = 18.62)	MR 2SLS	0.91	0.82	1.00	0.77	-1.39	2.93
Cardiopulmonary physical fitness	Observational	0.99	0.98	1.01	0.74	0.37	1.11
(13 SNPs, F = 11.68)	MR 2SLS	0.88	0.69	1.13	4.92	-0.27	10.1
Sleep-disordered breathing	Observational	1.60	1.36	1.88	0.09	-0.27	0.45
(14 SNPs, F = 10.27)	MR 2SLS	1.26	1.00	1.58	6.40	1.15	11.7
Sleep quality	Observational	1.01	1.00	1.01	-0.13	-0.29	0.03
(15 SNPs, F = 7.09)	MR 2SLS	1.42	1.06	1.92	0.94	-4.82	6.70

Note

Observational models were cross-sectional logistic models, which were adjusted for age, sex, parental education, and family income. Odds ratios and beta values were estimated using the inter-quartile range increase of obesity-related risk factors.

Abbreviations: CI, confidence interval; FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity; MR 2SLS, Mendelian randomization two-stage least square; OR, odds ratio; SNP, single nucleotide polymorphism.

The GRSs for four tested risk factors (except for physical fitness) were robustly correlated with each factor and were associated with asthma (Table [S3](#)). To describe in detail, the GRSs for the 28 BMI-SNPs were correlated with z-BMI (F-statistics = 80.60, $p < .001$) and were associated with asthma ($p = .04$). The GRSs for the 15 physical activity-SNPs were associated with physical activity levels (F-statistics = 16.62, $p < .001$) and were associated with asthma ($p = .04$). The GRSs for the 13 physical fitness were correlated with physical fitness (F-statistics = 11.69, $p = .001$), but not asthma. The GRSs for the 14 SDB-SNPs were correlated with SDB (F-statistics = 10.27, $p = .001$) and were associated with asthma ($p = .049$). The GRSs for the 15 sleep quality-SNPs were correlated with sleep quality (F-statistics = 7.09, $p = .008$) and were associated with asthma ($p = .047$). Tables [S4–S8](#) reveal the associations between SNPs and factors and asthma. The data listed in Tables [S9–S13](#) verify that most SNPs were independent of confounders.

3.2 Prospective survival analysis

Table 3 presents the analysis of the five obesity-related risk factors for incident asthma at ages 12 and 17 years in the survival model. Three of the five factors (obesity, SDB, and sleep quality) were associated with increased incident asthma risk. Among the three risk factors, obesity presented the highest risk of incident asthma (HR: 1.28; 95% CI: 1.05 to 1.56), followed by a 1.18- and 1.10-fold higher risk of incident asthma per IQR increase for SDB (HR: 1.18; 95% CI: 1.08 to 1.29) and sleep quality (HR: 1.10; 95% CI: 1.03 to 1.17), respectively. In the subgroup analysis, SDB was associated with an increase in atopic asthma (HR: 1.50; 95% CI: 1.22 to 1.84).

TABLE 3. Hazard ratios of asthma for obesity-related risk factors in the longitudinal cohort

Risk factors	Means $\pm$ standard deviation	Incident asthma			Incident atopic asthma			Incident nonatopic asthma		
		HR	95% CI		HR	95% CI		HR	95% CI	
Obesity, BMI (kg/m ²)	20.37 $\pm$ 4.05	1.28	1.05	1.56	0.62	0.27	1.44	1.37	0.98	1.97
Physical activity, MET (kcal/kg/hr)	5.93 $\pm$ 7.25	1.02	0.96	1.08	1.03	0.77	1.23	1.09	1.00	1.18
Cardiopulmonary physical fitness (z-score)	0.16 $\pm$ 1.07	0.88	0.73	1.04	0.90	0.52	1.54	0.75	0.52	1.08
Sleep-disordered breathing (scores)	11.52 $\pm$ 4.67	1.18	1.08	1.29	1.50	1.22	1.84	1.11	0.95	1.30
Sleep quality (scores)	6.66 $\pm$ 2.69	1.10	1.03	1.17	1.10	0.85	1.38	1.08	0.91	1.26

Note

Hazard ratios were estimated using the inter-quartile range increase of obesity-related risk factors. Discrete-time hazard models were adjusted for age, sex, parental education, and family income.

Abbreviations: CI, confidence interval; HR, hazard ratio.

3.3 Genetic risk score–predicted risks

Figure 2 displays the inherited susceptibility of each risk factor on asthma from

representative GRSs. We demonstrated the predicted prevalence of asthma for the three risk factors (obesity, SDB, and sleep quality) corresponding to the mean GRS in each quintile. All three risk factors exhibited an increasing trend of predicted prevalence of asthma following the increase in quintile. To illustrate, the predicted prevalence of asthma was 6% for those whose GRS for SDB and sleep quality was in the lowest 20% of the sample (Q1) compared with 13% for those whose GRS was in the highest 20% (Q5). However, obesity revealed a less prominent increase. The predicted prevalence of asthma for those whose GRS for obesity was in Q1 was 7%, with an increasing trend to 11% for those with scores in Q5.

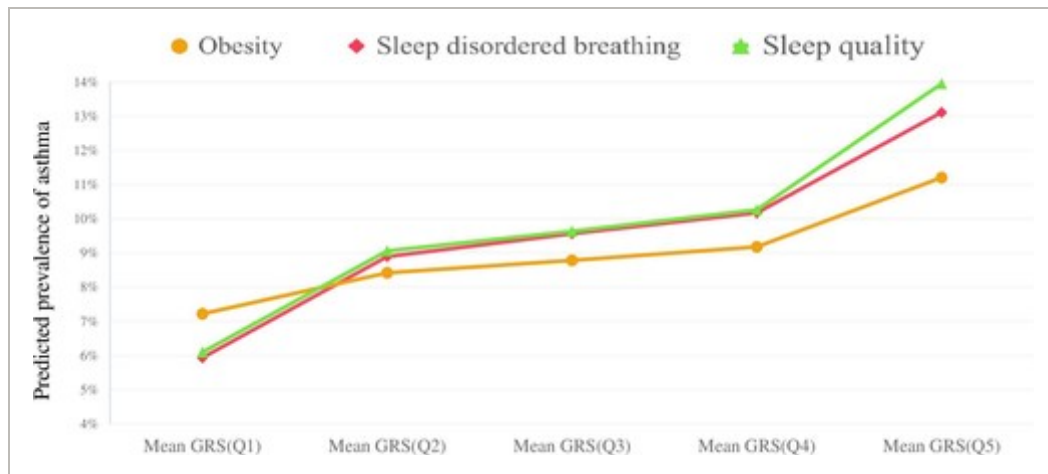


FIGURE 2

[Open in figure viewer](#) | [PowerPoint](#)

Predicted prevalence of asthma for the three obesity-related risk factors. GRS, genetic risk score

4 DISCUSSION

Among the five obesity-related risk factors examined for causality with childhood asthma, we obtained consistent evidence that obesity, SDB, and sleep quality are observationally and genetically associated with asthma. Among these, SDB and poor sleep quality were associated with a 1.26- and 1.42-fold risk of asthma. Furthermore, prospective survival analysis also confirmed the temporal relationship. The effect of SDB and poor sleep quality at age 11 on incident asthma continued to adolescence and early adulthood. When stratified by asthma subphenotypes, children with SDB had a 1.50-fold risk of developing atopic asthma. Under the global pandemic of sleep disturbance among children, detection and treatment of sleep-related symptoms in childhood could reduce the future risk of asthma.

In our data, poor sleep quality and SDB were the strongest risk factors contributing to asthma in the observational and MR analyses. Their predicted prevalence of asthma was also the highest in the Q5 GRS. Two previous prospective studies support our findings that insomnia increases the risk of asthma in adults.^{7, 8} Brumpton et al.⁸ reported an increased risk of asthma in those having problems initiating sleep, waking up too early, and

experiencing nonrestorative sleep. Moreover, Lin et al. conducted a population-based study in Taiwan and found that patients with insomnia had a twofold risk of having new-onset asthma during the 4-year follow-up.⁷ On the contrary, our study is the first to investigate this association among school-aged children. Although the prevalence of insomnia among school-aged children is not high, the global pandemic of sleep loss among children has gained the attention of public health and school officials.²⁹ According to a large-scale meta-analysis,³⁰ European adolescents sleep for an average of 500 min per day, whereas Asian adolescents sleep for only 400 min per day on weekdays. In our study, we used the PSQI questionnaire, representing a combination of various components of sleep parameters, to assess sleep quality in children. Poor sleep quality was a robust risk factor for asthma in the three models. Hence, our study might provide future lifestyle interventional perspectives to prevent and relieve asthma. Recent clinical trials have been designed to intervene in cognitive-behavioral treatment on sleep control to improve asthma symptoms.³¹ Another study also highlights the need for interventions targeting sleep problems among adolescents at high risk of asthma.³²

SDB was another strong risk factor for asthma in the present study. Although researchers have postulated that SDB and asthma exhibit similar airway inflammation, the temporal relationship between the two remains unclear.³³ The current study is the first to confirm the causal association using both MR analysis and a prospective cohort. SDB is associated with excessive daytime sleepiness, the release of proinflammatory cytokines, and increased leptin level, contributing to the development of asthma.³⁴ Our finding that SDB predicts atopic incident asthma is supported by one study³⁵ but contradicted by another related study, which found that SDB is associated with neutrophilic airway inflammation.³⁶ Further studies are warranted to explain relevant mechanisms linking SDB and asthma.

The strength of the current analysis centers on the use of three methods (observational, MR, prospective) to investigate the causal associations between risk factors and asthma. Our review of the literature suggests that no related study has employed three methods (observational, MR, and survival analysis) to investigate modifiable obesity-related factors for childhood asthma. The unique, population-based children cohort with prospective follow-up surveys and incident asthma enabled this analysis. Three of the five risk factors, SDB, sleep quality and physical activity, and incident asthma, were self- or parent-report rather than objective measures, representing a potential limitation. However, the TCHS employed globally used validated questionnaires to assess SDB, sleep quality, physical activity, and asthma outcomes, limiting the reporting bias. Moreover, F-statistic suggests that the GRS for sleep quality is a weak instrument, and we might be underpowered to detect small-moderate effect sizes, as compared to large sample GWAS. In addition, our study examined obesity-related risk factors for asthma in school-aged children and adolescents, rather than in infants and preschool-aged children. Considering the current obesity pandemic, we may identify specific risk factors contributing to the risk of asthma in adolescence or even young adulthood. On the contrary, the potential limitation of the

longitudinal study is that the loss to follow-up was 39% over the five years. However, the characteristics of those with follow-up and without follow-ups at age 17 were comparable, limiting the bias induced by loss to follow-up.

5 CONCLUSION

We found that obesity, SDB, and sleep quality were consistently associated with an increased risk of developing asthma. In addition, poor sleep quality and SDB emerged as potential causal risk factors, followed by obesity. Sleep quality and SDB are prevalent and manageable conditions for children. Hence, lifestyle interventions aimed at promoting high-quality sleep and reducing SDB symptoms, such as weight management, might effectively reduce asthma risk. For children with a high risk of developing asthma, evaluation for sleep disturbances may improve health status.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Yang-Ching Chen: Formal analysis (lead); Investigation (lead); Writing – original draft (lead).

Ming-Wei Su: Data curation (supporting); Methodology (supporting); Software (supporting).

Ben Brumpton: Supervision (supporting); Writing – review & editing (supporting). **Yungling**

Leo Lee: Conceptualization (lead); Data curation (lead); Funding acquisition (lead);

Investigation (lead); Methodology (lead); Resources (lead); Supervision (lead).

SUPPORTING INFORMATION

Additional supporting information may be found online in the supplementary files section.

Supporting Information



Filename	Description

Filename	Description
pai13710-sup-0001-AppendixS1.docx	Word 2007 document , 668.3 KB
pai13710-sup-0002-AppendixS2.doc	Word document, 101.5 KB

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Online supplement appendix
Investigating Obesity-related Risk Factors for Childhood Asthma

Candidate Single Nucleotide Polymorphism (SNP) Selection	2
Taiwan Children Health Study (TCHS)	3
Figure S1. Flowchart of Participant Recruitment	4
Table S1. Characteristics of participants aged 17 years in the follow-up survey of the Taiwan Children Health Study	5
Table S2. Observational, Mendelian randomization (MR), and MR sensitivity analyses on the associations of obesity-related factors with childhood asthma	6
Table S3. Associations of the genetic risk scores of obesity-related factors with the factors and childhood asthma	9
Table S4. Associations of individual body mass index (BMI)-SNPs (28 SNPs) with z-BMI and asthma at 12 years	10
Table S5. Associations of individual physical activity-SNPs (15 SNPs) with physical activity and asthma at 12 years.....	12
Table S6. Associations of individual cardiopulmonary physical fitness-SNPs (13 SNPs) with cardiopulmonary physical fitness and asthma at 12 years	13
Table S7. Associations of individual sleep-disordered breathing-SNPs (14 SNPs) with sleep-disordered breathing and asthma at 12 years	14
Table S8. Associations of individual sleep quality-SNPs (15 SNPs) with sleep quality and asthma at 12 years	15
Table S9. <i>P</i> values for the association of individual body mass index-SNPs (28 SNPs) with confounding factors.....	16
Table S10. <i>P</i> values for the association of individual physical activity-SNPs (15 SNPs) with confounding factors.....	17
Table S11. <i>P</i> values for the association of individual cardiopulmonary physical fitness-SNPs (13 SNPs) with confounding factors.....	18
Table S12. <i>P</i> values for the association of individual sleep-disordered breathing-SNPs (14 SNPs) with confounding factors.....	19
Table S13. <i>P</i> values for the association of individual sleep quality-SNPs (15 SNPs) with confounding factors.....	20

Candidate Single Nucleotide Polymorphism (SNP) Selection

Using genomic information from large genome-wide association studies, we chose well-known genetic variants associated with five obesity-related risk factors. To prevent the pleiotropic effects of genetic variants, SNPs previously reported to be associated with asthma and confounders were excluded. In summary, we selected 28, 15, 13, 14, and 15 SNPs for obesity, physical activity, cardiopulmonary physical fitness, sleep-disordered breathing, and sleep quality respectively. The 28 BMI-SNPs were identified by either Asian GWAS meta-analysis,¹⁷⁻²⁰ Chinese GWAS,²¹ or Chinese children studies.²²⁻²⁶ The 15 physical activity-SNPs were chosen from Genome-Wide Association Studies (GWAS),¹⁻³ and relevant studies.⁴⁻⁹ The 13 cardiopulmonary physical fitness-SNP were chosen from (GWAS),¹⁻³ and associated studies.⁴⁻⁹ The 14 SDB-SNPs were selected by GWAS,^{3, 10-13} Asian studies¹⁴ and meta-analysis.^{15, 16} Additionally, the 15 sleep quality-SNPs were selected from large GWAS,^{3, 10, 13, 27, 28} and several studies.^{12, 29}

Taiwan Children Health Study (TCHS)

In 2007 and 2010, we conducted a nationwide “Taiwan Children Health Study (TCHS)”, of 7,930 nine to twelve-years-old school children, recruited from 14 diverse Taiwanese communities from all over Taiwan. The first cohort of twelve to thirteen years-old children was enrolled in 2007, and the second cohort of nine to ten-years-old schoolchildren was enrolled in 2010. TCHS had a multi-purpose nationwide design, and was designed to study atopy, obesity, and social and behavioral issues in children. Communities in Taiwan were selected with the aim of maximizing the variability and minimizing the correlations of exposures to outdoor pollutants based on historic routine air monitoring data. In communities with pollution patterns of interest, neighborhoods with stable, primarily middle-income populations were identified from 2004 census data. To address community-level sources of variability, we randomly sought participating communities within existing financial constraints. Public school district representatives in participating communities were consulted to identify suitable schools based on demographic stability, likely parental cooperation, and absence of local pollution sources. A total of 19 different public schools participated in our study. Classroom-level incentives were used to encourage participation, and every student was invited to join our study. We excluded any special classes for gifted or learning-disabled subjects. On average, we recruited 350-450 participants from each of the study communities.

Figure S1. Flowchart of Participant Recruitment

At baseline, we collected questionnaires, oral mucosal genetic data, physical fitness, pulmonary function tests, and body weight and height. At follow-ups survey, we assessed asthma outcomes and self-reported body weight and height through a home visit or telephone interview.

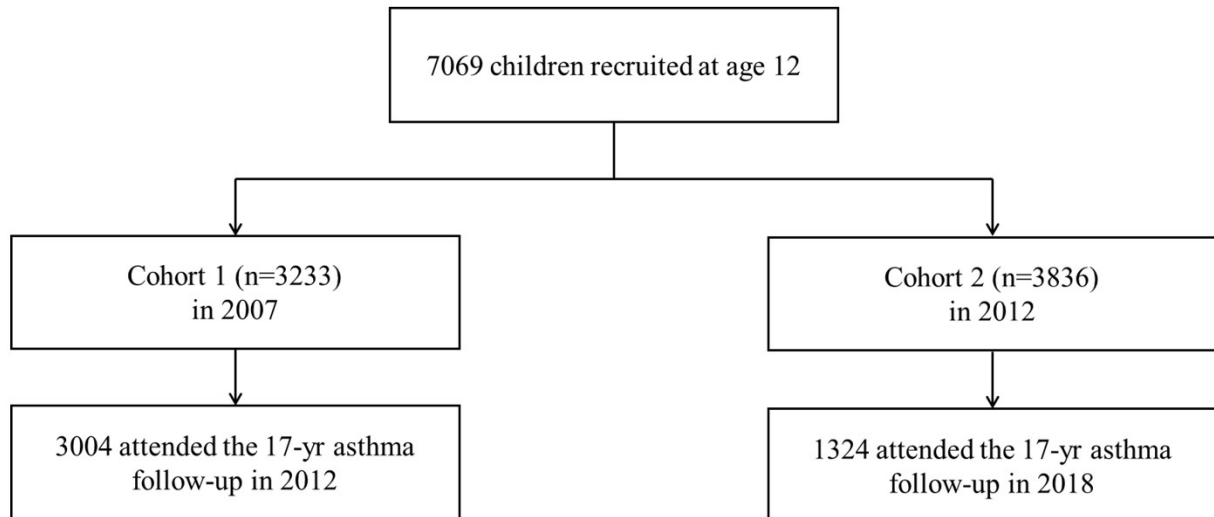


Table S1. Characteristics of participants aged 17 years in the follow-up survey of the Taiwan Children Health Study

Characteristics	Total		Cohort 1		Cohort 2		<i>P</i> value§
N	4328		3004		1324		
Age (years)	16.61	0.70	17.33	0.47	16.30	0.54	<0.001
Male sex	2121	49.01%	1447	48.17%	674	50.91%	0.10
BMI (kg/m²)	21.17	3.78	21.17	3.92	21.17	3.47	0.68
Parental education							<0.001
High school or below	2498	57.72%	1873	62.35%	625	47.21%	
College or university	1561	36.07%	1004	33.42%	557	42.07%	
Postgraduate	269	6.22%	127	4.23%	142	10.73%	
Family income (NT\$)							<0.001
<600,000	2385	55.11%	1803	60.02%	582	43.96%	
600,001–1,000,000	1330	30.73%	829	27.60%	501	37.84%	
>1,000,001	613	14.16%	372	12.38%	241	18.20%	
Physician-diagnosed asthma	368	8.50%	258	8.59%	110	8.31%	0.03

BMI, body mass index; NT\$, new Taiwan dollars.

All data are presented as means ± standard deviation or numbers (%).

The number of participants does not add up to the total number because of missing data.

§*P* value indicates the difference between the two cohorts.

Table S2. Observational, Mendelian randomization (MR), and MR sensitivity analyses on the associations of multiple obesity-related risk factors with childhood asthma

Risk factor	Category	<u>Physician-diagnosed asthma</u>			<u>FEV1/FVC (%)</u>		
		OR	95% CI		β	95% CI	
Obesity (28 SNPs, F = 80.60)	Observational	1.26	1.07	1.47	-1.16	-1.37	-0.95
	MR 2SLS	1.08	1.00	1.16	-2.44	-4.24	-0.65
	IVW fixed effect	1.01	1.00	1.01	0.08	-0.36	0.52
	IVW random effect	1.01	1.00	1.01	0.08	-0.36	0.52
	MR_Egger-intercept fixed effect	1.24	1.21	1.28	-2.98	-4.61	-1.35
	MR_Egger- intercept random effect	1.24	1.11	1.39	-2.98	-4.61	-1.35
	MR_Egger fixed effect	1.00	0.99	1.00	0.45	-0.04	0.93
	MR_Egger random effect	1.00	0.98	1.01	0.45	-0.24	1.14
	Simple median method	1.07	0.96	1.20	-4.06	-6.81	-1.32
	Weighted median method	1.00	1.00	1.01	0.33	-14.48	15.13
Physical activity (15 SNPs, F = 18.62)	Observational	1.01	1.00	1.01	-0.09	-0.24	0.06
	MR 2SLS	0.91	0.82	1.00	0.77	-1.39	2.93
	IVW fixed effect	0.91	0.83	1.00	1.29	-0.81	3.39
	IVW random effect	0.91	0.83	0.98	1.29	-0.81	3.39
	MR_Egger-intercept fixed effect	0.97	0.73	1.29	-14.31	-28.46	-0.16
	MR_Egger- intercept random effect	0.97	0.73	1.29	-14.31	-28.46	-0.16
	MR_Egger-slope fixed effect	0.96	0.51	1.83	15.40	1.29	29.50
	MR_Egger-slope random effect	0.96	0.51	1.83	15.40	1.29	29.50
	Simple median method	0.93	0.81	1.09	1.24	-2.08	4.56
	Weighted median method	0.91	0.77	1.07	0.64	-2.80	4.07
Cardiopulmonary physical fitness (13 SNPs, F = 11.68)	Observational	0.99	0.98	1.01	0.74	0.37	1.11
	MR 2SLS	0.88	0.69	1.13	4.92	-0.27	10.11
	IVW fixed effect	0.96	0.90	1.03	5.51	0.10	10.92

	IVW random effect	0.96	0.92	1.01	5.51	0.69	10.33
	MR_Egger-intercept fixed effect	1.04	0.47	2.27	-6.77	-44.61	31.07
	MR_Egger- intercept random effect	1.04	0.47	2.27	-6.77	-44.61	31.07
	MR_Egger-slope fixed effect	0.95	0.59	1.52	12.51	-26.98	52.00
	MR_Egger-slope random effect	0.95	0.59	1.52	12.51	-26.98	52.00
	Simple median method	1.01	0.93	1.09	9.69	1.96	17.43
	Weighted median method	0.97	0.87	1.08	2.44	-6.48	11.35
Sleep-disordered breathing (14 SNPs, F = 10.27)	Observational	1.60	1.36	1.88	0.09	-0.27	0.45
	MR 2SLS	1.26	1.00	1.58	6.40	1.15	11.65
	IVW fixed effect	1.47	0.92	2.31	6.53	1.29	11.77
	IVW random effect	1.47	0.95	2.27	6.53	1.48	11.58
	MR_Egger-intercept fixed effect	1.00	0.57	1.75	7.59	-21.92	37.10
	MR_Egger- intercept random effect	1.00	0.56	1.77	7.59	-21.92	37.10
	MR_Egger-slope fixed effect	1.47	0.46	4.69	-1.36	-32.47	29.75
	MR_Egger-slope random effect	1.47	0.46	4.83	-1.36	-32.47	29.75
	Simple median method	1.68	0.95	2.98	6.39	-1.93	14.70
	Weighted median method	1.75	0.87	3.46	6.48	-3.88	16.84
Sleep quality (15 SNPs, F = 7.09)	Observational	1.01	1.00	1.01	-0.13	-0.29	0.03
	MR 2SLS	1.42	1.06	1.92	0.94	-4.82	6.70
	IVW fixed effect	1.11	0.99	1.23	2.53	-1.60	6.65
	IVW random effect	1.11	0.99	1.23	2.53	-1.60	6.65
	MR_Egger-intercept fixed effect	1.00	0.75	1.32	-6.49	-19.89	6.91
	MR_Egger- intercept random effect	1.00	0.75	1.33	-6.49	-19.89	6.91
	MR_Egger fixed effect	1.11	0.82	1.48	7.29	-3.37	17.94
	MR_Egger random effect	1.11	0.82	1.48	7.29	-4.66	19.23
	Simple median method	1.15	0.99	1.32	3.18	-2.90	9.27
	Weighted median method	1.15	0.97	1.35	4.99	-1.11	11.08

CI, confidence interval; FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity; IVW, inverse-variance weighted; MR 2SLS, Mendelian randomization two-stage least square; OR, odds ratio; SNP, single-nucleotide polymorphism.

Observational models were adjusted for age, sex, parental education, and family income. Odds ratios and beta value were estimated by 1 unit increase in the interquantile range of risk factors, except for early puberty (binary variable).

Table S3. Associations of the genetic risk scores of obesity-related risk factors with the factors and childhood asthma

Genetic risk scores of risk factors	Association with the factors				Association with asthma			
	Regression coefficient	Standard error	F-statistic	<i>P</i> value	Regression coefficient	Standard error	F-statistic	<i>P</i> value
Obesity (28 SNPs, F = 80.60)	0.71	0.08	80.60	<0.001	0.04	0.02	4.07	0.04
Physical activity (15 SNPs, F = 18.62)	0.94	0.22	18.62	<0.001	0.02	0.01	3.52	0.06
Cardiopulmonary physical fitness (13 SNPs, F = 11.68)	0.94	0.28	11.69	0.001	0.09	0.10	0.94	0.33
Sleep-disordered breathing (14 SNPs, F = 10.27)	0.81	0.25	10.27	0.001	0.04	0.02	3.86	0.049
Sleep quality (15 SNPs, F = 7.09)	0.86	0.32	7.09	0.008	0.09	0.05	3.93	0.047

SNP, single-nucleotide polymorphism.

Table S4. Associations of individual body mass index (BMI)-SNPs (28 SNPs) with z-BMI and asthma at 12 years

Rs number	Nearby Gene	Allele	MAF*	Association with z-BMI				Association with asthma				References
				Coefficient	Standard error	F-statistics	P value	Coefficient	Standard error	F-statistics	P value	
rs2531995	ADCY9	C/T	0.33	0.06	0.03	6.00	0.01	0.07	0.07	0.87	0.35	17
rs671	ALDH2	G/A	0.27	0.02	0.03	0.37	0.54	0.31	0.30	1.05	0.31	17
rs651821	APOA5	C/T	0.27	0.01	0.03	0.21	0.65	0.88	0.40	4.85	0.03	22
rs662799	APOA5	G/A	0.27	0.02	0.02	0.45	0.50	0.94	0.27	12.15	<0.001	22
rs9356744	CDKAL1	C/T	0.35	0.06	0.02	5.57	0.02	0.04	0.08	0.27	0.61	17
rs10513801	ETV5	G/T	0.08	0.04	0.04	1.32	0.25	0.32	0.16	3.95	0.05	17
rs7647305	ETV5	C/T	0.09	-0.03	0.04	0.59	0.44	-0.22	0.24	0.88	0.35	23
rs9816226	ETV5	T/A	0.07	-0.04	0.05	0.79	0.38	0.16	0.21	0.62	0.43	30
rs888789	FLJ35779	G/A	0.47	0.01	0.02	0.16	0.69	-0.02	0.46	<0.001	0.97	17
rs11644943	FTO	T/A	0.16	0.01	0.03	0.04	0.85	-0.13	0.95	0.02	0.90	26
rs713586	GIPR	C/T	0.46	-0.03	0.02	1.95	0.16	0.11	0.13	0.73	0.39	31
rs12597579	GP2	C/T	0.26	-0.08	0.03	8.24	0.00	-0.10	0.06	2.32	0.13	17
rs13223383	INSIG2	G/T	0.33	0.03	0.03	1.59	0.21	0.20	0.14	1.85	0.17	20
rs4776970	MAP2K5	T/A	0.21	0.04	0.03	1.86	0.17	0.09	0.13	0.48	0.49	17
rs3746619	MC3R	C/A	0.23	0.01	0.03	0.19	0.66	0.73	0.42	3.06	0.08	17
rs6567160	MC4R	T/C	0.18	-0.08	0.03	7.42	0.01	-0.10	0.07	2.25	0.13	19
rs11604680	MTCH2	G/A	0.28	-0.07	0.02	8.13	0.00	-0.02	0.06	0.14	0.71	17
rs2815752	NEGR1	A/G	0.08	0.04	0.04	1.26	0.26	0.01	0.16	<0.001	0.96	23
rs3101336	NEGR1	C/T	0.08	0.01	0.05	0.09	0.77	0.73	0.61	1.42	0.23	18
rs11191580	NT5C2	C/T	0.28	-0.03	0.03	1.16	0.28	0.02	0.17	0.02	0.89	17
rs10160804	RPL27A	C/A	0.48	-0.02	0.02	1.08	0.30	-0.06	0.18	0.11	0.74	19
rs574367	SEC16B	T/G	0.15	0.17	0.03	23.91	0.00	0.05	0.04	1.65	0.20	17
rs4788102	SH2B1	G/A	0.10	0.10	0.04	5.24	0.02	-0.03	0.08	0.10	0.75	18
rs7498665	SH2B1	A/G	0.10	-0.08	0.04	3.92	0.05	-0.08	0.09	0.70	0.40	18

rs4715210	TFAP2B	T/C	0.14	0.09	0.04	6.15	0.01	−0.05	0.07	0.56	0.46	32
rs12463617	TMEM18	C/A	0.07	−0.12	0.05	5.89	0.02	0.13	0.08	2.87	0.09	33
rs3817334	MTCH2	C/T	0.29	0.09	0.03	11.79	<0.001	0.05	0.05	0.99	0.32	23
rs7701094	ZNF608	G/C	0.48	0.04	0.02	2.22	0.14	−0.13	0.12	1.07	0.30	17

*MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

Table S5. Associations of individual physical activity-SNPs (15 SNPs) with physical activity and asthma at 12 years

Rs number	Nearby gene	Allele	MAF*	Association with physical activity				Association with asthma				References
				Coefficient	Standard error	F-statistics	P value	Coefficient	Standard error	F-statistics	P value	
rs1815739	ACTN3	C/T	0.45	-0.10	0.19	0.29	0.59	-0.02	0.08	0.09	0.76	8
rs2268757	ACVR2B	C/T	0.27	-0.10	0.21	0.24	0.63	-0.02	0.09	0.07	0.79	6
rs6090314	BIRC7	G/A	0.37	0.27	0.20	1.90	0.17	-0.01	0.03	0.16	0.69	9
rs353625	CD44	C/T	0.18	0.04	0.23	0.04	0.85	-0.02	0.22	0.01	0.93	9
rs2253206	CREB1	G/A	0.39	0.26	0.19	1.76	0.18	-0.06	0.03	3.22	0.07	7
rs2273555	GBF1	G/A	0.22	-0.46	0.23	4.18	0.04	-0.05	0.02	6.10	0.01	2
rs1535628	GRIN3A	A/G	0.29	0.05	0.20	0.06	0.80	0.02	0.17	0.01	0.92	5
rs2288278	HOXB3	G/A	0.28	-0.02	0.21	0.01	0.94	-0.98	0.55	3.16	0.08	2
rs2296135	IL15Ra	C/A	0.42	0.12	0.19	0.39	0.53	0.02	0.07	0.07	0.80	6
rs10186876	LRPPRC	G/A	0.03	0.07	0.54	0.02	0.90	0.12	0.33	0.13	0.72	2
rs2267668	PPARD	A/G	0.27	-0.31	0.20	2.43	0.12	-0.04	0.03	2.04	0.15	4
rs10499043	PRDM1	T/C	0.08	0.27	0.35	0.59	0.44	-0.03	0.05	0.23	0.63	5
rs10751308	SHANK2	T/C	0.14	-0.43	0.27	2.52	0.11	0.02	0.03	0.84	0.36	1
rs26579	MEF2C	C/G	0.37	0.40	0.20	4.11	0.04	-0.01	0.02	0.33	0.57	3
rs3101340	NEGR1	A/G	0.13	-0.25	0.27	0.84	0.36	0.03	0.05	0.41	0.52	29

*MAF, minor allele frequency, SNP, single-nucleotide polymorphism.

Table S6. Associations of individual cardiopulmonary physical fitness-SNPs (13 SNPs) with cardiopulmonary physical fitness and asthma at 12 years

Rs number	Nearby gene	Allele	MAF*	Association with cardiopulmonary physical fitness				Association with asthma				References
				Coefficient	Standard error	F-statistics	P value	Coefficient	Standard error	F-statistics	P value	
rs1815739	ACTN3	C/T	0.46	0.02	0.02	1.51	0.22	-0.12	0.26	0.21	0.65	8
rs2268757	ACVR2B	C/T	0.27	-0.02	0.02	1.11	0.29	-0.05	0.31	0.02	0.87	6
rs6090314	BIRC7	G/A	0.37	-0.01	0.02	0.43	0.51	0.07	0.49	0.02	0.89	9
rs353625	CD44	C/T	0.18	0.00	0.03	0.01	0.92	0.35	3.12	0.01	0.91	9
rs2253206	CREB1	G/A	0.38	0.01	0.02	0.37	0.54	-0.74	0.53	1.97	0.16	7
rs2288278	HOXB3	G/A	0.27	-0.04	0.02	2.75	0.10	-0.31	0.19	2.57	0.11	2
rs2296135	IL15Ra	C/A	0.43	0.02	0.02	0.88	0.35	0.11	0.35	0.11	0.74	6
rs10186876	LRPPRC	G/A	0.05	0.04	0.06	0.53	0.47	-0.06	0.45	0.02	0.88	2
rs2267668	PPARD	A/G	0.28	0.00	0.02	0.03	0.87	2.20	2.01	1.20	0.27	4
rs10499043	PRDM1	T/C	0.08	0.04	0.04	1.30	0.25	-0.26	0.28	0.81	0.37	5
rs10751308	SHANK2	T/C	0.14	-0.04	0.03	1.89	0.17	0.11	0.24	0.22	0.64	1
rs26579	MEF2C	C/G	0.37	0.03	0.02	1.62	0.20	0.02	0.25	0.01	0.92	3
rs10252228	NPSR1	G/A	0.17	0.00	0.03	0.01	0.93	-1.63	3.80	0.18	0.67	34

*MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

Table S7. Associations of individual sleep-disordered breathing-SNPs (14 SNPs) with sleep-disordered breathing and asthma at 12 years

Rs number	Nearby gene	Allele	MAF*	Association with sleep-disordered breathing				Association with asthma				References
				Coefficient	Standard error	F-statistics	P value	Coefficient	Standard error	F-statistics	P value	
rs10097555	NRG1	G/A	0.22	−0.18	0.16	1.16	0.28	0.04	0.06	0.54	0.46	10
rs1137101	LEPR	G/A	0.11	−0.01	0.23	0.00	0.96	−1.37	1.26	1.18	0.28	14
rs12936587	RAI1	G/A	0.12	0.05	0.23	0.06	0.81	−0.33	0.26	1.53	0.22	35
rs6311	5HTR-2A	C/T	0.39	0.18	0.15	1.62	0.20	0.00	0.05	0.01	0.92	16
rs7412	APOE	C/T	0.08	−0.44	0.27	2.61	0.11	0.06	0.04	2.45	0.12	15
rs11046209	ABCC9	T/A	0.10	0.36	0.24	2.32	0.13	−0.02	0.04	0.34	0.56	27
rs11214607	DRD2	G/T	0.37	0.11	0.15	0.60	0.44	0.09	0.08	1.22	0.27	12
rs12635074	SGSM3	G/T	0.20	0.06	0.18	0.12	0.73	−0.09	0.18	0.23	0.63	11
rs2006810	AUTS2	C/T	0.33	0.16	0.15	1.13	0.29	0.00	0.06	0.00	0.99	3
rs3122163	HCRTR2	C/T	0.05	−0.51	0.44	1.34	0.25	0.08	0.05	2.29	0.13	13
rs3816358	ARNTL	C/A	0.17	−0.22	0.19	1.27	0.26	0.06	0.06	1.28	0.26	12
rs4821940	SGSM3	C/T	0.40	−0.01	0.14	0.00	0.95	−1.01	1.03	0.97	0.33	11
rs62158211	PAX8	G/T	0.17	−0.16	0.19	0.71	0.40	0.05	0.07	0.42	0.52	11
rs72720396	CALB1	G/A	0.19	−0.04	0.17	0.05	0.82	−0.08	0.27	0.08	0.78	11

*MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

Table S8. Associations of individual sleep quality-SNPs (15 SNPs) with sleep quality and asthma at 12 years

Rs number	Nearby gene	Allele	MAF*	Association with sleep quality				Association with asthma				References
				Coefficient	Standard error	F-statistics	P value	Coefficient	Standard error	F-statistics	P value	
rs6311	5HTR-2A	C/T	0.39	−0.07	0.06	1.21	0.27	0.14	0.11	1.41	0.24	16
rs7412	APOE	T/C	0.08	−0.07	0.08	0.67	0.41	−0.15	0.15	0.96	0.33	15
rs10097555	NRG1	A/G	0.22	0.06	0.05	1.16	0.28	−0.05	0.12	0.18	0.67	10
rs12936587	RAI1	A/G	0.12	−0.09	0.10	0.89	0.34	0.32	0.13	5.94	0.01	35
rs11046209	ABCC9	A/T	0.10	−0.02	0.09	0.03	0.86	−0.34	0.70	0.24	0.63	27
rs3816358	ARNTL	C/A	0.17	0.06	0.05	1.07	0.30	0.10	0.12	0.74	0.39	12
rs2006810	AUTS2	C/T	0.33	0.05	0.07	0.47	0.49	0.00	0.18	0.00	0.99	3
rs72720396	CALB1	A/G	0.18	−0.03	0.06	0.34	0.56	−0.11	0.22	0.25	0.62	11
rs5922858	CYCL1	T/G	0.32	0.05	0.15	0.11	0.74	−0.08	0.37	0.05	0.83	13
rs11214607	DRD2	G/T	0.36	0.05	0.07	0.57	0.45	0.07	0.17	0.19	0.66	12
rs9565309	FBXL3	C/T	0.12	0.02	0.05	0.13	0.72	0.58	0.35	2.85	0.09	28
rs3122163	HCRTR2	C/T	0.05	0.00	0.05	0.00	0.98	−4.19	5.53	0.57	0.45	13
rs62158211	PAX8	T/G	0.17	0.02	0.07	0.05	0.83	0.07	0.59	0.02	0.90	11
rs12635074	SGSM3	G/T	0.20	0.06	0.06	0.81	0.37	0.07	0.14	0.25	0.62	11
rs4821940	SGSM3	C/T	0.40	−0.05	0.08	0.42	0.52	0.16	0.19	0.70	0.40	11

*MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

Table S9. *P* values for the association of individual body mass index-SNPs (28 SNPs) with confounding factors

Rs number	Nearby gene	Age	Sex	Parental education	Family income
rs2531995	ADCY9	0.26	0.84	0.19	0.82
rs671	ALDH2	0.01	0.60	0.65	0.99
rs651821	APOA5	0.03	0.41	0.25	0.93
rs662799	APOA5	<0.001	0.78	0.96	0.69
rs9356744	CDKAL1	0.06	0.22	0.38	0.52
rs10513801	ETV5	0.30	0.58	0.90	0.16
rs7647305	ETV5	0.23	0.99	0.66	0.98
rs9816226	ETV5	0.81	0.81	0.70	0.19
rs888789	FLJ35779	0.01	0.46	0.01	0.02
rs11644943	FTO	0.16	0.04	0.43	0.48
rs713586	GIPR	0.37	0.02	0.92	0.11
rs12597579	GP2	0.15	0.64	0.99	0.95
rs13223383	INSIG2	0.00	0.67	<0.001	<0.001
rs4776970	MAP2K5	0.57	0.76	0.85	0.22
rs3746619	MC3R	0.24	0.27	0.51	0.25
rs6567160	MC4R	<0.001	0.32	0.01	0.12
rs11604680	MTCH2	<0.001	0.01	0.62	0.61
rs2815752	NEGR1	<0.001	0.86	0.13	<0.001
rs3101336	NEGR1	0.29	0.42	0.15	0.78
rs11191580	NT5C2	0.89	0.79	0.11	0.71
rs10160804	RPL27A	0.50	0.62	0.31	0.60
rs574367	SEC16B	<0.001	0.82	0.83	0.17
rs4788102	SH2B1	0.73	0.14	0.86	0.67
rs7498665	SH2B1	0.41	0.23	0.90	0.51
rs4715210	TFAP2B	0.76	0.36	0.41	0.98
rs12463617	TMEM18	0.58	0.70	0.06	0.01
rs3817334	MTCH2	0.07	0.13	0.40	0.10
rs7701094	ZNF608	<0.001	0.43	<0.001	0.44

SNP, single-nucleotide polymorphism. These *p* values have not been corrected for multiple testing. Under Bonferroni correction, the cutoff for significance is $\alpha = 0.05/28 = 0.002$

Table S10. *P* values for the association of individual physical activity-SNPs (15 SNPs) with confounding factors

Rs number	Nearby gene	Age	Sex	Parental education	Family income
rs1815739	ACTN3	0.41	0.89	0.75	0.41
rs2268757	ACVR2B	0.83	0.17	0.07	0.12
rs6090314	BIRC7	0.77	0.39	0.42	0.09
rs353625	CD44	0.92	0.87	0.98	0.18
rs2253206	CREB1	0.62	0.35	0.03	0.02
rs2273555	GBF1	0.86	0.17	0.58	0.15
rs1535628	GRIN3A	0.70	0.36	0.43	0.61
rs2288278	HOXB3	0.54	0.57	0.02	0.88
rs2296135	IL15Ra	0.04	0.31	0.55	0.32
rs10186876	LRPPRC	0.77	0.26	0.20	0.41
rs2267668	PPARD	0.12	0.23	0.10	0.37
rs10499043	PRDM1	0.71	0.21	0.64	0.82
rs10751308	SHANK2	0.14	0.76	0.31	0.26
rs26579	MEF2C	0.35	0.55	0.30	0.24
rs3101340	NEGR1	0.29	0.13	0.23	0.41

SNP, single-nucleotide polymorphism. These *p* values have not been corrected for multiple testing. Under Bonferroni correction, the cutoff for significance is $\alpha = 0.05/15 = 0.003$

Table S11. *P* values for the association of individual cardiopulmonary physical fitness-SNPs (13 SNPs) with confounding factors

Rs number	Nearby gene	Age	Sex	Parental education	Family income
rs1815739	ACTN3	0.77	0.96	0.89	0.79
rs2268757	ACVR2B	0.39	0.08	0.07	<0.001
rs6090314	BIRC7	0.87	0.11	0.99	0.14
rs353625	CD44	0.57	0.78	0.28	0.22
rs2253206	CREB1	0.56	0.25	<0.001	0.01
rs2288278	HOXB3	0.34	0.47	0.01	0.62
rs2296135	IL15Ra	0.13	0.11	0.57	0.51
rs10186876	LRPPRC	0.30	0.11	0.82	1.00
rs2267668	PPARD	0.01	0.01	0.07	0.26
rs10499043	PRDM1	0.89	0.46	0.21	0.22
rs10751308	SHANK2	0.27	0.79	0.04	<0.001
rs26579	MEF2C	0.15	0.42	<0.001	0.01
rs10252228	NPSR1	0.43	0.24	0.78	0.39

SNP, single-nucleotide polymorphism. These *p* values have not been corrected for multiple testing. Under Bonferroni correction, the cutoff for significance is $\alpha = 0.05/13 = 0.004$

Table S12. *P* values for the association of individual sleep-disordered breathing-SNPs (14 SNPs) with confounding factors

Rs number	Nearby gene	Age	Sex	Parental education	Family income
rs10097555	NRG1	0.55	0.03	0.40	0.91
rs1137101	LEPR	0.28	0.89	0.53	0.11
rs12936587	RAI1	0.62	0.95	0.83	0.93
rs6311	5HTR-2A	0.39	0.45	0.74	0.05
rs7412	APOE	0.32	0.10	0.36	0.53
rs11046209	ABCC9	0.45	0.51	0.15	0.26
rs11214607	DRD2	0.22	0.34	0.41	0.50
rs12635074	SGSM3	0.55	0.18	0.52	0.12
rs2006810	AUTS2	0.32	0.09	0.02	0.86
rs3122163	HCRT2	0.29	0.27	0.57	0.48
rs3816358	ARNTL	0.78	0.10	0.99	0.34
rs4821940	SGSM3	0.24	0.84	0.38	0.65
rs62158211	PAX8	0.97	0.72	0.52	0.81
rs72720396	CALB1	<0.001	0.15	0.37	0.14

SNP, single-nucleotide polymorphism. These *p* values have not been corrected for multiple testing. Under Bonferroni correction, the cut off for significance is $\alpha = 0.05/14 = 0.003$

Table S13. *P* values for the association of individual sleep quality-SNPs (15 SNPs) with confounding factors

Rs number	Nearby gene	Age	Sex	Parental education	Family income
rs6311	5HTR-2A	0.11	0.11	0.64	<0.001
rs7412	APOE	0.01	0.01	0.49	0.73
rs10097555	NRG1	<0.001	<0.001	0.29	0.12
rs12936587	RAI1	0.65	0.65	0.96	0.52
rs11046209	ABCC9	0.32	0.32	0.03	0.08
rs3816358	ARNTL	<0.001	<0.001	0.70	0.10
rs2006810	AUTS2	<0.001	<0.001	0.00	0.32
rs72720396	CALB1	0.01	0.01	0.57	0.01
rs5922858	CYCL1	<0.001	<0.001	0.28	0.98
rs11214607	DRD2	0.31	0.31	0.41	0.10
rs9565309	FBXL3	0.48	0.48	0.58	0.05
rs3122163	HCRT2	0.01	0.01	0.40	0.73
rs62158211	PAX8	0.80	0.80	0.40	0.68
rs12635074	SGSM3	0.12	0.12	0.94	0.01
rs4821940	SGSM3	0.53	0.48	0.27	0.52

SNP, single-nucleotide polymorphism. These *p* values have not been corrected for multiple testing. Under Bonferroni correction, the cutoff for significance is $\alpha = 0.05/15 = 0.003$

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	check	Brief Description
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	√	See both title and abstract.
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	√	See abstract.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	√	See introduction para 1-2.
Objectives	3	State specific objectives, including any prespecified hypotheses	√	See introduction para 3.
Methods				
Study design	4	Present key elements of study design early in the paper	√	See method para 1 and Figure 1.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	√	See method para 1.
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	√	See reference 10. (<i>Am J Respir Crit Care Med</i> 2014;189(10):1194-203.).
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	√	This is not a matched study.

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	√	See method adiposity measures, Outcome definition, statistical analysis
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	√	See method Definition of adiposity measures and asthma
Bias	9	Describe any efforts to address potential sources of bias	√	See method adiposity measures, Outcome definition
Study size	10	Explain how the study size was arrived at	√	See result para 1.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	√	See result para 1.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	√	See statistical analysis
		(b) Describe any methods used to examine subgroups and interactions	√	See statistical analysis
		(c) Explain how missing data were addressed	√	See statistical analysis
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	√	See result para 2-4.
		(e) Describe any sensitivity analyses	√	We used several different statistical analysis methods (regression and MR 2SLS) as main statistical analysis. MR sensitivity analyses (MR inverse-variance weighted, Egger [slope], and weighted median method) were used to support our result.

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	√	See result para 1.
		(b) Give reasons for non-participation at each stage	√	Due to school absence and children moving to other communities. Please also see Figure 1.
		(c) Consider use of a flow diagram	√	Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	√	See Table 1.
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	√	See result para 1.
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	√	See result para 1 and Table 1.
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	√	See Table 2-3 and Figure 2
		(b) Report category boundaries when continuous variables were categorized	√	See Method para 4.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	√	See page 6 result
Discussion				
Key results	18	Summarise key results with reference to study objectives	√	See discussion para 1.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	√	See discussion para 4.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	√	See discussion para 4.
Generalisability	21	Discuss the generalisability (external validity) of the study results	√	See discussion para 4.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	√	See title page

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.