Genetic pleiotropy between asthma and obesity in a community-based sample of twins

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Abstract

Background—Asthma and obesity are common conditions that are strongly associated. This association might be due to shared genetic or environmental causes.

Objective—We sought to determine whether a shared genetic cause is responsible for the association between asthma and obesity and to estimate the magnitude of shared genetic cause.

Methods—The analyses were performed with 1001 monozygotic and 383 dizygotic same-sex twin pairs within the University of Washington Twin Registry. The presence of asthma was determined by self-report of a physician diagnosis of asthma, and body mass index (BMI) was calculated by using self-reported height and weight. Obesity was defined as a BMI of 30 or greater. The association between asthma and BMI was assessed by means of mixed-effects ordinal regression. Twin correlations examined the association of asthma and obesity. Univariate and bivariate structural equation models estimated the components of variance attributable to genetic and environmental effects.

Results—A strong association between asthma and BMI was identified in the sample population ($P < .001$). Substantial heritability was detected for asthma (53%) and obesity (77%), which is indicative of additive genetic influences on each disorder. The best-fitting model of shared components of variance indicated that 8% of the genetic component of obesity is shared with asthma.

Conclusion—The covariation between obesity and asthma is predominantly caused by shared genetic risk factors for both conditions.

Keywords

Asthma; obesity; genetic; twin

Asthma and obesity are both common conditions of great public health concern worldwide.[1,2] Between 1980 and 1994, the prevalence of self-reported asthma increased by 73.4% in the United States.[3] Likewise, the prevalence of obesity increased from 12.5% in 1960 to 22.5% in 1994[5] and continues to increase.[5] These parallel trends in asthma and obesity in developed

countries[3,4] suggest that shared environmental and genetic factors affect both conditions.[1] The presence of shared genetic determinants for more than one condition is known as genetic pleiotropy.[6]

Asthma and obesity have been consistently related in cross-sectional[7–11] and longitudinal[12–15] epidemiologic studies. This relationship between asthma and obesity is stronger in women than in men.[3,4,12,15,16] Obesity is a significant independent predictor of the persistence of childhood asthma into adulthood.[17] Although asthma and obesity follow a polygenic mode of inheritance in which genes with low penetrance are responsible for the genetic susceptibility,[2] the extent to which the association is due to genetic factors shared by both conditions is unknown. Notably, linkage analyses of asthma and obesity demonstrate an overlap of chromosomal regions linked to each condition.[2]

Quantitative genetic analysis of twins can be used to identify a shared cause and ascertain whether genetic or environmental influences predominate.[18] Therefore we used data from a community-based American twin registry to (1) measure the association between asthma and obesity, (2) assess the genetic influence on each trait, and (3) estimate the magnitude of shared genetic cause that could explain the association between asthma and obesity.

METHODS

Sample population

The study population consisted of 1001 monozygotic (MZ) and 383 dizygotic (DZ) same-sex twin pairs registered in the University of Washington Twin Registry, which is a community-based sample of twins derived from the driver's license applications of the Washington State Department of Licensing. Unique to Washington State, all new applicants for a driver's license are asked if they are a twin. Because Washington State law allows state agencies to share data, a weekly electronic list of all new driver's license applicants who are twins is transmitted weekly to the University of Washington and forms the basis of the twin registry. These applicants are invited, along with their co-twin, to become members of the University of Washington Twin Registry. The University of Washington Human Subjects Review Committee and the Washington State Attorney General approved the procedures for establishing the twin registry and all data collection involved in this study. Informed consent was obtained from all participants.

Data collection

A brief survey was administered to all registry members by mail or telephone that included age, race-ethnicity, sex, education, and marital status. Zygosity was assigned by using standard questions on childhood similarity that correctly classify twins as MZ or DZ more than 95% of the time.[19–21] Health conditions, including asthma, were obtained by using a checklist of self-reported medical problems that asked specifically whether a physician ever diagnosed the condition.

Height and weight were obtained by self-report. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was divided into 7 categories reported in previous studies[10,14,22,23] to examine the relationship between asthma and obesity. The 7 categories represent low (BMI <20.0), normal (BMI ≥20.0 to ≤22.49 and ≥22.50 to ≤24.99), overweight (BMI ≥25.0 to ≤27.49 and ≥27.50 to ≤29.99), and obese (BMI ≥30) BMI.

Statistical analysis

The classical twin study analysis is based on a comparison of phenotypic similarity in MZ and DZ twins. MZ twins have identical genotypes, and DZ twins share, on average, half of their genes. Greater phenotypic similarity, indicated by a higher correlation in MZ than DZ twins, is indicative of a genetic component in the cause of the disease. Structural equation modeling is a general statistical approach useful for estimating genetic and environmental effects in classical twin studies.[24] In this approach genetic and environmental effects are modeled as latent variables representing an underlying liability for one or more phenotypes, such as asthma or obesity. Structural equation modeling is a highly flexible analysis that can determine the best-fitting and most parsimonious model for any phenotype and estimate the relative magnitude of the genetic, common environmental, and unique environmental effects. For example, by using structural equation modeling, it is possible to assess whether the MZ and DZ correlations for asthma are best explained by a model that includes genes alone, the common environment alone, or some combination of both genes and the common environment. For multiple phenotypes, such as asthma and obesity, structural equation modeling can be used to estimate how much of the variability in the 2 phenotypes is due to shared genetic, common environmental, and unique environmental effects. Structural equation models for twin studies typically use path diagrams to visually illustrate the relative magnitude of the hypothesized connections between the latent genetic, common environmental, and unique environmental effects with the observed phenotypes.

The distributions of age, race-ethnicity, physician-diagnosed asthma, BMI, and obesity were compared according to sex and zygosity by using χ^2 and t test statistics. The relationship between asthma and BMI was assessed by using mixed-effects ordinal regression.[25] Age was added to the mixed-effects ordinal regression model to determine whether age affected the relationship between asthma and obesity. The association between asthma and obesity in MZ and DZ pairs was initially assessed by 3 types of tetrachoric correlations: phenotypic, twin, and cross-twin, cross-trait. Structural equation modeling was used to estimate the components of phenotypic variance caused by additive genetic (A), common environment (C), and unique environment (E) from the within-pair twin correlations for asthma and obesity in MZ and DZ pairs.[24] A model was fit to the twin correlations on the basis of the additive genetic correlation of 1.0 for MZ and 0.5 for DZ twins and a shared environmental correlation of 1.0 for all twins. Parameter estimates for the full ACE model were then estimated. Reduced models were constructed by removing a specific parameter and comparing the goodness of fit of the full and reduced models by using a likelihood ratio χ^2 test. Parameters were removed from the model if the removal did not result in a significant degradation of model fit. A model parameter was considered significant if its omission resulted in a decrement in fit of the model at the .05 level of significance.

Models were also evaluated by using Akaike Information Criterion[26] to compare alternative models. The model with the lowest Akaike Information Criteria was judged to have superior fit over models with larger Akaike Information Criteria values. The proportions of variance for additive genetics, common environment, and unique environment were estimated from the final best-fitting model.

To test for the presence of shared genetic and environmental influence on asthma and obesity, we fit bivariate structural equation models of asthma and obesity. The model started with a full Cholesky decomposition that specifies a general multivariate covariance structure that allows for both shared and specific influences on asthma and obesity. Reduced models were then fit after removing shared or specific influences. The final best-fitting and most parsimonious model was identified by removing factors that did not significantly degrade the fit of the model on the basis of the likelihood ratio χ^2 test and Akaike Information Criteria. Estimates of the components of variance caused by both shared and specific genetic and environmental

influences were calculated from the path coefficients of the best-fitting bivariate model. The narrow genetic correlation was calculated from the path coefficients, as previously described. [27]

RESULTS

Sample characteristics

The University of Washington Twin Registry has enrolled 1042 pairs of MZ, 406 pairs of same-sex DZ, and 422 pairs of opposite-sex DZ twins. Because of the known sex differences in the association between asthma and obesity,[3,4,12,15,16] the analyses were restricted to 1001 MZ and 383 DZ same-sex twin pairs with complete asthma and BMI information (2768 individuals). The prevalence of physician-diagnosed asthma was 14.1%, and that of obesity was 13.5%. The characteristics of this sample according to sex are presented in Table I. The prevalence of asthma was higher in women than men. Conversely, the mean BMI was higher in men than in women (25.1 kg/m² in men vs 24.4 kg/m² in women, $P<.001$); however, the prevalence of obesity was slightly higher in women than men (14.1% in women and 12.5% in men). When we grouped the study population into 7 categories of BMI, the prevalence of asthma increased with greater BMI in women ($P < .001$, Fig 1) and marginally in men ($P = .07$). The association between asthma and BMI was not appreciably changed by adjustment for age ($P < .001$ in women and $P = .06$ in men).

The characteristics of the study population also differed according to zygosity. Compared with MZ twins, DZ twins were older (35.9 vs 31.7 years, $P < .0001$) and had higher BMI (25.4 vs 24.4 kg/m², $P < .0001$).

Biometric genetic models

Table II presents 3 types of tetrachoric correlations in MZ and DZ pairs for asthma and obesity: phenotypic, twin, and cross-twin, cross-trait. The within-pair similarity of the trait was measured by using the twin correlation. The higher twin correlation in MZ than DZ twins is indicative of genetic influence on each trait. Phenotypic correlations measure the association of obesity and asthma within individuals in the sample population. The phenotypic correlations indicate that asthma is associated with obesity, although the magnitude of this association is small. The cross-twin, cross-trait correlations assessed the degree of association for 2 traits; for example, the relationship of obesity in twin 1 and asthma in twin 2, as well as obesity in twin 2 and asthma in twin 1. The higher cross-twin, cross-trait correlations in MZ compared with DZ pairs is indicative of shared genes influencing both traits.

Table III shows the results of the univariate structural equation models for asthma and obesity. In the full model 35% of the phenotypic variance of asthma was due to additive genetic effects. By using sequential reduced models based on the likelihood ratio χ² test, the best-fitting model for asthma included both additive genetic effects (53%) and unique environmental effects (47%). Similarly, the full model for obesity indicated that 77% of the phenotypic variation was due to additive genetic effects. The best-fitting model, derived from sequential reduced models, included additive genetic effects (77%) and unique environmental exposures (23%). For both asthma and obesity, common environmental effects could be removed without deterioration in the fit of the models.

Bivariate genetic analysis

Bivariate models of asthma and obesity specified a structural equation model for shared and specific additive genetic, common, and unique environmental components of variance (Table IV). By using sequential reduced models based on the likelihood ratio χ² test and Akaike Information Criterion, the best-fitting and most parsimonious bivariate model included shared

additive genetic and shared unique environment influences for asthma and obesity, as well as specific genetic, common environmental, and unique environmental effects for each phenotype (Table V). There was no evidence of a shared common environmental influence on asthma and obesity. The full model with standardized pathway coefficients is illustrated in Fig 2. The narrow genetic correlation between asthma and obesity was 0.29. Therefore additive genetic effects, which are correlated 0.29, accounted for 65% of the covariance between asthma and obesity. On the basis of the best-fitting model shown in Table V, 8% of the genetic component of obesity is shared with asthma, and 5% of the specific environment component is shared. The findings indicate that the association between asthma and obesity is substantially due to shared genetic risk factors for both conditions, also known as genetic pleiotropy.

DISCUSSION

Asthma and obesity are common conditions in the United States and many other countries.[1,2] Several studies have shown that asthma and obesity are associated, especially in women.[3,4,12,15,16] The relationship between asthma and obesity was similarly identified in this community-based sample of twins. The magnitude of the association between asthma and obesity is modest in this and other studies; obesity is only one of the factors that influence the etiologically heterogeneous asthma phenotype. Like other studies, the prevalence of asthma was higher in women compared with that in men, even in the lower weight categories. This suggests that factors other than obesity are responsible for the difference in asthma prevalence between men and women. Although it is clear that obesity, defined as a BMI of 30 or greater, is associated with asthma, the relationship between a BMI of less than 30 and asthma is less clear. Some studies have shown a U-shaped distribution for the relationship between asthma and BMI in men,[23,28,29] and others have failed to show a clear relationship between asthma and BMI in men.[10,30,31]

The association between obesity and asthma could be due to the influence of each phenotype on the other, shared environmental determinants, or shared genetic factors. For example, obesity has a direct mechanical effect on airway smooth muscle that increases bronchial hyperresponsiveness.[32] Obesity alters the production of inflammatory mediators, such as TNF-α and IL-6, by constitutive expression in adipocytes.[2] Reduced activity is associated with asthma and is likewise associated with body weight.[33,34] Dietary factors, such as the intake of certain lipids and antioxidant vitamins, are associated with both asthma and obesity.[35,36] In addition to these phenotypic and environmental influences on asthma and obesity, both traits are highly heritable conditions,[37–40] a finding we replicated in this community-based sample of twins. In this study the presence and magnitude of the shared genetic influence on asthma and obesity was assessed by using structural equation models demonstrating significant genetic pleiotropy between the 2 conditions.

The additive genetic effects observed in the present study are the first to be reported from an American community-based sample of twins. The size of the additive genetic effect on asthma is similar to that found in twin studies from other countries.[37] The consistency of genetic effects across countries is remarkable because the prevalence of asthma varies markedly worldwide.[37]

Genetic pleiotropy occurs when a gene or set of genes influences 2 or more traits.[6] In this study we showed that 8% of the genetic component of obesity is shared with asthma. Although this is the first study to estimate the size of the shared genetic contribution, linkage studies of asthma and obesity have revealed regions of overlap at positions 2p, 5q, 6p, 7p, and 12q.[2] Recent studies have demonstrated the biologic plausibility of this genetic association. The β_2-adrenergic receptor is expressed on airway smooth muscle, inflammatory cells, and adipose tissue, where endogenous catecholamines influence energy expenditure, airway tone, and

airway inflammation.[41] Furthermore, insulin levels, which are altered in obesity, can influence β_2-adrenergic receptor sensitivity.[42] Polymorphisms of the β_2-adrenergic receptor, although not associated with asthma *per se*, are associated with bronchial hyperresponsiveness,[43,44] serum IgE,[45] and response to treatment with β_2-agonists.[46–48] Polymorphisms of the β_2-adrenergic receptor are also associated with obesity.[49,50] A polymorphism at the −308 position in relation to the gene encoding TNF-α is associated with asthma,[51,52] BMI,[53] and obesity.[54]

Asthma and obesity are both polygenic disorders, in which the influence at any single locus is likely small.[55] Therefore many genetic determinants will ultimately be identified for asthma, some of which will be shared with other polygenic traits. Although we identified significant overlap in the genetic determinants of asthma and obesity, as in other studies of pleiotropy, the magnitude of the shared influence was modest. For example, in a Finnish study of adult twins using comparable methods, the phenotypic variation between atopy and depression was due to shared additive genetic factors and shared unique environmental factors.[27] Although the magnitude of the additive genetic effects on atopy and depression were less than in the present study, the narrow genetic correlation between the 2 traits was similar to that described here. Similarly, significant overlap in the genetic determinants of atopy and asthma has been demonstrated among 381 young twins recruited from an Australian volunteer twin registry.[56]

Common environmental effects are those shared by MZ and DZ twins and reflect influences, such as *in utero* exposures, socioeconomic class, and diet. Consistent with previous twin studies, the environmental determinants of asthma identified in the present study were unique, rather than common environmental effects.[37] The absence of common environmental effects on atopic disease has also been demonstrated in a study of twins reared together and apart.[57] Notably, the absence of common environmental effects on asthma in twin studies is inconsistent with epidemiologic studies in which diverse exposures increase (eg, house dust mite[58]) or decrease (eg, endotoxin[59]) the risk of asthma. One explanation is that common environmental factors might only influence asthma in the presence of genetic factors. In this situation, environmental effects that are only manifest in the presence of a specific genetic background, also known as gene-by-environment effects, will be concealed in the genetic component of the disease.[37]

This study has several limitations. First, our measures of physician-diagnosed asthma and BMI were obtained by self-report. However, physician-diagnosed asthma obtained on a questionnaire has a specificity of 0.99 and positive predictive value of 0.82 compared with an asthma diagnosis based on pertinent symptoms, lung function, bronchodilator response, and bronchial hyperresponsiveness.[60] Self-reported weight and height might also underestimate actual BMI.[61] In this regard the young age of the sample is advantageous because misclassification of asthma[37] and obesity[61] increase with age. A second concern is the predominance of white subjects and women, thereby limiting the generalizability of our findings to groups with other demographic features. Despite these limitations, the strengths of this study include sophisticated genetic modeling and the use of a community-based twin registry that minimizes biases associated with selected twin samples identified from clinical sources or volunteer registries.

In conclusion, an association between asthma and obesity was identified in a young community-based sample of twins in the United States. By using structural equation modeling, both asthma and obesity were found to be heritable, indicating strong genetic influences on each phenotype. We also found that unique environmental factors that are not shared by siblings also influenced both phenotypes, indicating that certain environmental factors work independently of genetic background. In contrast, common environmental factors, which are shared by siblings, did not influence either phenotype, although these effects might be hidden

within the model if gene-by-environment effects are strong. Finally, our analyses demonstrated that a large part of the covariation between obesity and asthma is controlled by genetic factors. This is evidence of genetic pleiotropy, in which a common set of genes increases the susceptibility to both asthma and obesity. We also observed modest evidence for a shared unique environmental determinant for asthma and obesity. These findings also raise the possibility that both asthma and obesity are influenced by gene-by-environment interaction; for example, a specific environment, such as a westernized lifestyle, might be necessary for genetic effects to manifest on the asthma and obesity phenotypes. These gene-by-environment interactions would be concealed within the genetic covariation identified in this study. Diet is an important candidate for future studies of gene-by-environment interaction because it can effect the expression of genes through epigenetic mechanisms.[62] Identification of modifiable environmental factors that lead to both obesity and asthma in the genetically susceptible host will have important implications for future efforts to curb the increasing prevalence of obesity and asthma.

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Abbreviations used

BMI, Body mass index; DZ, Dizygotic; MZ, Monozygotic.
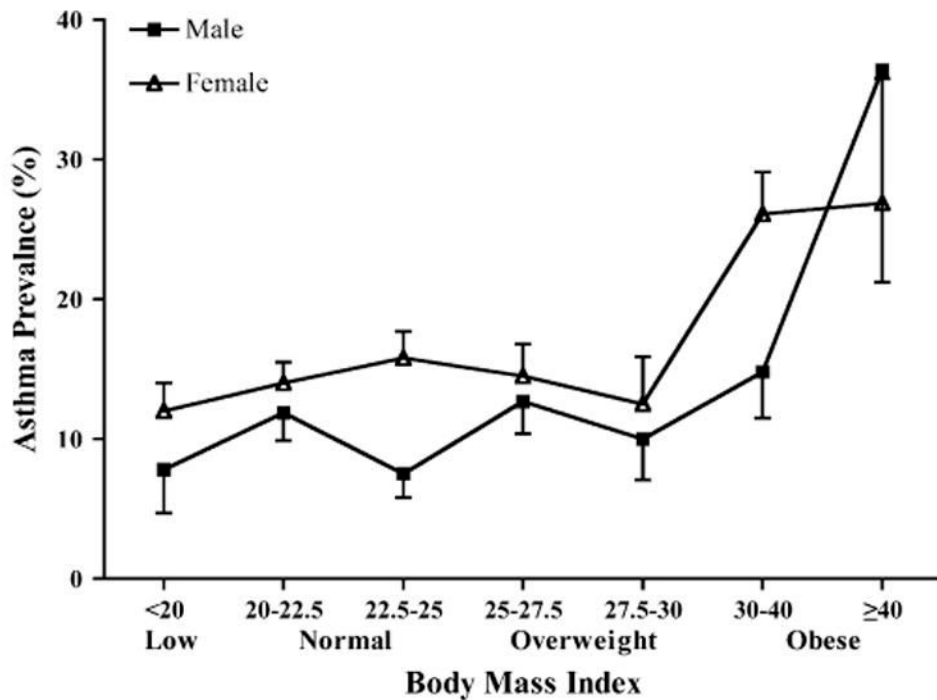
FIG 1.
Association between asthma and obesity in the University of Washington Twin Registry. The prevalence of asthma was assessed according to 7 categories of BMI. The association of asthma and obesity was assessed in each sex by using mixed-effects ordinal regression. The prevalence of asthma increased with greater BMI in women ($P < .001$) and marginally in men ($P = .07$).
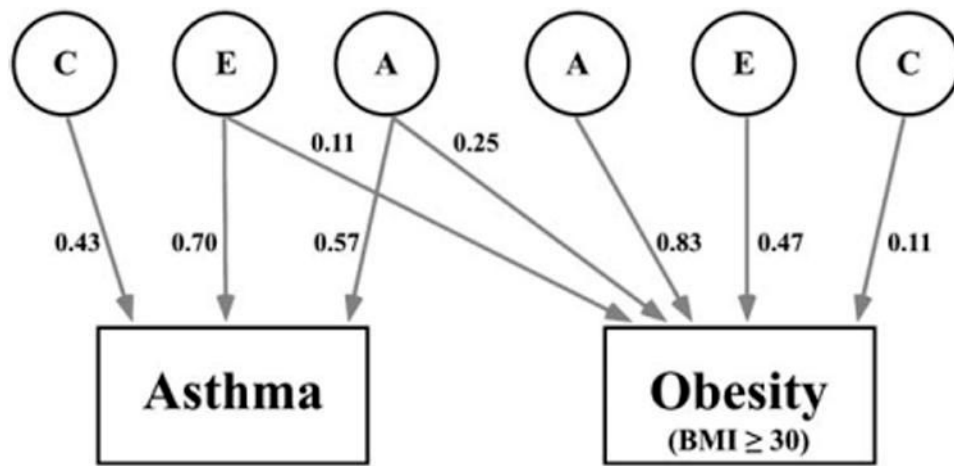
FIG 2.
Path model depicting the additive genetic effects that are common to asthma and obesity plus additive genetic *(A)*, unique environmental *(E)*, and common environmental *(C)* effects that are unique to each phenotype. The parameter estimates are path coefficients, indicating the relative importance of the latent variables A, E, and C to asthma and obesity.

TABLE I.

Characteristics of same-sex twins enrolled in the University of Washington Twin Registry

Characteristic	Men (n = 1010)	Women (n = 1758)
Zygosity		
Monozygotic, n (%)	736 (72.9)	1266 (72.0)
Dizygotic, n (%)	274 (27.1)	492 (28.0)
Age, mean y (SD)	32.3 (14.1)	33.2 (14.8)
Race-ethnicity, n (%)[*]		
White (non-Hispanic)	880 (87.1)	1528 (86.9)
African American	37 (3.7)	41 (2.3)
Asian–Pacific Islander	42 (4.2)	67 (3.8)
Hispanic	21 (2.1)	62 (3.5)
Native Indian–Alaska Native	8 (0.8)	30 (1.7)
Other	22 (2.2)	30 (1.7)
Physician-diagnosed asthma, n (%)[†]	112 (11.1)	278 (15.8)
BMI, mean (SD)[†]	25.1 (4.7)	24.4 (5.1)
BMI, n (%)[‡]		
<20	77 (7.6)	274 (15.6)
20–22.49	253 (25.1)	520 (29.6)
22.5–24.99	239 (23.7)	386 (22.0)
25–27.49 (overweight)	205 (20.3)	234 (13.3)
27.5–29.99 (overweight)	110 (10.9)	96 (5.5)
30–39.99 (obese)	115 (11.4)	222 (12.6)
≥ 40 (obese)	11 (1.1)	26 (1.5)

[*] $P < .05.$

[†] $P < .001.$

[‡] $P < .0001.$

TABLE II.

Tetrachoric correlations and 95% CIs for asthma and obesity according to zygosity[*]

	Twin 1		Twin 2	
	Asthma	**Obesity**	**Asthma**	**Obesity**
Monozygotic (n = 1001)				
Twin 1				
Asthma	1.000			
Obesity	0.13 (0.00–0.27)[†]	1.000		
Twin 2				
Asthma	0.51 (0.40–0.62)[‡]	0.13 (0.00–0.28)[§]	1.000	
Obesity	0.10 (0.00–0.25)[§]	0.77 (0.68–0.83)[‡]	0.20 (0.05–0.35)[†]	1.000
Dizygotic (n = 383)				
Twin 1				
Asthma	1.000			
Obesity	0.17 (0.00–0.38)[†]	1.000		
Twin 2				
Asthma	0.34 (0.14–0.52)[‡]	0.00 (0.00–0.19)[§]	1.000	
Obesity	0.13 (0.00–0.33)[§]	0.38 (0.18–0.55)[‡]	0.41 (0.21–0.58)[†]	1.000

[*] The correlations and 95% CIs have a lower bound of zero.

[†] Phenotypic correlation between asthma and obesity.

[‡] Twin correlations.

[§] Cross-twin, cross-trait correlation.

TABLE III.

Univariate biometric genetic models for asthma and obesity

Model[*]	Estimates of variance components[†]			Tests of model fit			
	Additive genetic (A)	Common environment (C)	Unique environment (E)	χ^2	df	P Value	AIC[‡]
Asthma							
ACE	0.35 (0.00–0.62)	0.17 (0.00–0.52)	0.49 (0.38–0.60)	-	-	-	-
AE	**0.53 (0.41–0.63)**	-	**0.47 (0.37–0.59)**	**0.62**	**1**	**.43**	**−1.38**
CE	-	0.46 (0.36–0.56)	0.54 (0.44–0.64)	2.37	1	.12	0.37
Obesity							
ACE	0.77 (0.40–0.83)	0.00 (0.00–0.34)	0.23 (0.17–0.32)	-	-	-	-
AE	**0.77 (0.68–0.83)**	-	**0.23 (0.17–0.32)**	**0.00**	**1**	**1.00**	**−2.00**
CE	-	0.66 (0.58–0.73)	0.34 (0.27–0.42)	17.89	1	<.0001	15.89

[*] *ACE* refers to a model that includes additive genetics (*A*), common environment (*C*), and unique environment (*E*); *AE* only includes additive genetics and unique environment; and *CE* only includes the common and unique environment.

[†] Proportion of variance caused by additive genetics (a^2), shared environment (c^2), and unique environment (e^2) according to each model.

[‡] Akaike's information criterion *(AIC)* is a global measure of goodness of fit; the best-fitting and most parsimonious models are shown in bold.

TABLE IV.

Bivariate structural equation models of asthma and obesity

Shared component	χ^2	df	P value	AIC[*]
ACE	-	-	-	-
CE	1.06	1	.30	−0.94
AE	**0.00**	**1**	**1.00**	**−2.00**
AC	1.13	1	.29	−0.87
A	2.20	2	.33	−1.80
C	6.85	2	.03	2.85
E	6.59	2	.04	2.59
None	21.26	3	<.0001	15.26

[*] Akaike's information criterion *(AIC)* is a global measure of goodness of fit; the best-fitting and most parsimonious model is shown in bold.

TABLE V.

Unique and shared additive genetic and environmental effects for asthma and obesity

Effect	Proportion of variance (95% CI)		
	Additive genetic (A)	**Common environment (C)**	**Unique environment (E)**
Trait specific			
Asthma	0.33 (0.01–0.62)	0.18 (0.00–0.26)	0.49 (0.38–0.58)
Obesity	0.76 (0.38–0.83)	0.01 (0.00–0.03)	0.23 (0.17–0.32)
Shared	0.08	-	0.05