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

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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. (J Allergy Clin Immunol 2005;116:1235-41.)

Key words: *Asthma, obesity, genetic, twin*

Abbreviations used
BMI: Body mass index
DZ: Dizygotic
MZ: Monozygotic

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[4] 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,

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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)

*$P < .05$.
†$P < .001$.
‡$P < .0001$.

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]