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Original article

Association between obesity and asthma in a twin cohort

Background: Obesity is linked to asthma in a yet poorly understood manner. We examined the relationship between obesity and asthma in a population-based sample of twins.
Methods: From the cohorts born between 1953 and 1982, who were enrolled in The Danish Twin Registry, a total of 29 183 twin individuals participated in a nationwide questionnaire study, where data on height, weight and asthma were collected. Latent factor models of genetic and environmental effects were fitted using maximum likelihood methods.
Results: The age-adjusted risk of asthma was increased both in obese females, OR = 1.96 (1.45–2.64), $P \leq 0.001$ and in obese males, OR = 1.59 (1.08–2.33), $P = 0.02$. According to best-fitting models, the heritability for obesity was 81% in males and 92% in females, whereas the heritability for asthma was 78% and 68% in males and females respectively. The age-adjusted genetic liabilities to obesity and asthma were significantly correlated only in females, $r = 0.28$ (0.16–0.38).
Conclusions: Obese subjects have an increased risk for asthma, which in females seems partly because of common genes.

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There has been a substantial worldwide increase in the prevalence of asthma in recent decades, but thus far the causes for this increase are poorly identified (1). In the search for explanatory determinants, several studies have found that increased body weight is associated with development of asthma, particularly among females (2–5). Furthermore, several studies report an association between obesity and objective markers of asthma, such as airway hyper-responsiveness and atopy, although evidence is circumstantial (6, 7). Finally, some studies have evaluated asthmatic patients who have undergone either surgical or medical weight loss and shown an improvement in symptoms of asthma, asthma severity, use of medication and several measures of pulmonary function in those patients following treatment (8, 9).

Much speculation has arisen as to the mechanisms that cause asthma and obesity to be associated. In particular, genetics, immune mechanisms, lung mechanics, diet and endocrine factors have been suggested to act in a developmental context to link the two disorders (10, 11). Asthma and obesity are both multifactorial disorders. This means that the individual susceptibility to develop the conditions is the result of several genes that can interact with one another and with environmental risk factors (12). A powerful way to study multifactorial disorders is to examine the pattern of disease susceptibility between groups of relatives (13). Particularly, studies of identical and fraternal twins provide an ideal framework within which causes for potential covariation between multifactorial disorders can be elucidated (13). We analysed the questionnaire data from a large population-based twin sample to estimate to what extent genetic and environmental risk factors influence obesity and asthma.

Methods

Sample

The population comprised twin cohorts born between 1953 and 1982 who were enrolled in the nationwide Danish Twin Registry (14). In these cohorts, zygosity was established in 1991 using four

questions of similarity and mistaken identity, which assign zygosity correctly in more than 96% of the cases (15). In 1994, 34 076 twin individuals, who in 1991 have declared their willingness to participate in future studies, were sent a questionnaire with items aimed at identifying multiple phenotypes including height, weight and asthma. Asthma cases were identified based on affirmative response to the question 'Do you have, or have you ever had, asthma?' (16). This procedure has been shown to be reliable with respect to identifying subjects with asthma in population-based studies, which use questionnaire responses as the sole diagnostic criterion (17). Body mass index (BMI) was calculated from the self-reported values of weight in kilograms divided by the square of height in metres. Subjects were regarded as obese if their BMI was above 30 kg/m^2. The participation rate was 86%, comprising 29 183 subjects (12 356 intact twin pairs and 4471 single responders). Among these, 11 302 intact pairs had complete data on zygosity, BMI and asthma. See Table 1.

Statistical analysis

The analyses were performed under the assumptions of the multifactorial threshold model (18). This model assumes that: (i) many factors (genetic and environmental) contribute to the development of a disorder, (ii) each member of a twin pair is assumed to have his or her own liability, the pair of liabilities for a twin pair being assumed to be bivariate normally distributed and (iii) as the number of causal factors for the disorder increases in an individual, the liability for the disorder increases. When a threshold is reached, the burden of liability becomes so great that disease results. The threshold then represents the population prevalence of that disorder and is equivalent to a *z*-value of the (standard) normal distribution.

To estimate the extent to which genetic and environmental risk factors contributed to the susceptibility to obesity and asthma, latent factor models of genetic and environmental effects were fitted to the raw data using maximum likelihood methods. These models are standard within twin research and assumed – in this case – that the susceptibility to obesity and asthma was a linear function of additive genetic effects (loci contributing additively to disease risk, A), shared environmental effects (environmental factors that increase the resemblance between members of the same family, C) and nonshared-random-environmental effects (influences unique to an individual, E) (18). From biometrical genetic theory, the expected covariance for identical twin pairs is A + C while for fraternal twins it is $0.5 \times A + C$. In males, identical twins were considerably more concordant for asthma than were fraternal twins pointing to the presence of more complex genetic mechanisms such as genetic dominance (interaction between alleles at the same locus). Because of this we fitted an alternative model for male asthma that included effects of A, E and D (genetic dominance) where D was assumed to be correlated 1.0 across identical twins and 0.25 across fraternal twins (18). Nested sub-models were subsequently fitted by successively fixing the different variance components to zero. The difference in log-likelihood between the saturated and the nested models provided a test for the significance of the individual variance components to the disease susceptibility. Since neither shared environment nor genetic dominance contributed significantly to the trait variability, our preferred model comprised only of components A and E. Subsequently, bivariate model-fitting was conducted between obesity and asthma using an AE-model. See Fig. 1. The magnitude of genetic and environmental sharing between obesity and asthma was expressed as the genetic and environmental correlations respectively between the disorders. These were estimated as the additive genetic or the random environmental covariance between the two conditions divided by the square root of the product of the additive genetic or the random environmental variances of the two conditions respectively (19). The analysis was stratified on sex whereas age was incorporated into the threshold model as a covariate for obesity and asthma. The raw ordinal data option in the

Table 1. Prevalence and resemblance between twins for obesity and asthma in a sample of 11 302 twin pairs, 12–41 years of age

Zygosity	Pairs	Prevalence (%)	Discordant pairs (*n*)	Concordant pairs (*n*)	Probandwise concordance (95% CI)*	Tetrachoric correlation (95% CI)†
Obesity						
MZ	3574	152 (2.1)	76	38	0.50 (0.42–0.58)	0.86 (0.79–0.91)
Males	1634	58 (1.8)	38	10	0.34 (0.22–0.46)	0.74 (0.57–0.86)
Females	1940	94 (2.4)	38	28	0.60 (0.50–0.70)	0.90 (0.83–0.95)
DZ-ss	4201	246 (2.9)	194	26	0.21 (0.16–0.26)	0.52 (0.41–0.63)
Males	2059	97 (2.4)	77	10	0.21 (0.13–0.29)	0.54 (0.36–0.69)
Females	2142	149 (3.5)	117	16	0.21 (0.15–0.28)	0.51 (0.35–0.64)
DZ-os	3527	229 (3.2)	189	20	0.17 (0.12–0.22)	0.45 (0.31–0.56)
Males		115 (3.3)	95‡			
Females		114 (3.2)	94‡			
Asthma						
MZ	3574	437 (6.1)	249	94	0.43 (0.38–0.48)	0.72 (0.66–0.77)
Males	1634	196 (6.0)	102	47	0.48 (0.41–0.55)	0.77 (0.69–0.84)
Females	1940	241 (6.2)	147	47	0.39 (0.33–0.45)	0.67 (0.58–0.75)
DZ-ss	4201	468 (5.6)	384	42	0.18 (0.14–0.23)	0.36 (0.26–0.45)
Males	2059	214 (5.2)	176	19	0.18 (0.13–0.23)	0.37 (0.23–0.51)
Females	2142	254 (5.9)	208	23	0.18 (0.13–0.23)	0.35 (0.22–0.48)
DZ-os	3527	451 (6.4)	399	26	0.12 (0.09–0.15)	0.17 (0.06–0.28)
Males		216 (6.1)	190‡			
Females		235 (6.7)	209‡			

MZ, monozygotic; DZ-ss, dizygotic same sex; DZ-os, dizygotic opposite sex.

*The probandwise concordance rate estimates the risk of disease in a twin given the co-twin has the disease.

†The tetrachoric correlation estimates what the correlation between obesity and asthma would be if they were measured on a continuous scale.

‡Males and females being the affected twin respectively.

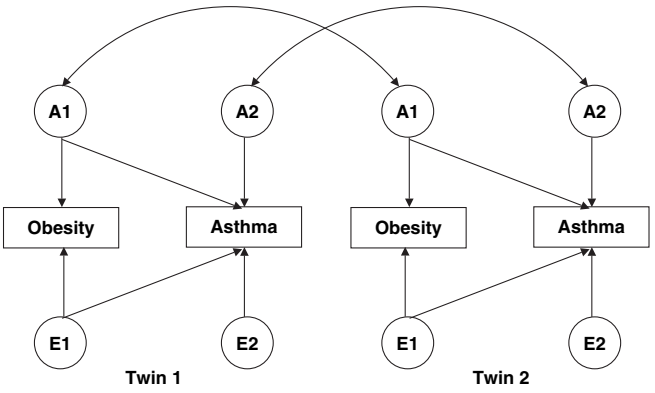

Figure 1. Classical bivariate twin model showing latent additive genetic influences (A) and nonhared influences (E) on obesity and asthma measured in a pair of twins. The arrows pointing from each of the latent factors to the trait directly below or above (from A1 and E1 on obesity and from A2 and E2 on asthma), account for genetic and environmental factors unique to that trait, whereas oblique arrows pointing to the adjacent trait (from A1 and E1 on asthma) assign genetic and environmental factors shared between the two traits. Additive genetic factors (A) are correlated 1.0 across identical twins and 0.5 across fraternal, whereas nonshared environment (E) is uncorrelated across twin pairs.

statistical package Mx was used for the analyses (20). A *P*-value <0.05 was considered to be statistically significant. The Scientific Ethics Committee approved the protocol.

Results

The mean age of the population was 27 years (age-range 12–41) and 52% were females. The prevalence of obesity was 2.7% in males and 3.2% in females, whereas the cumulative prevalence of asthma was 6.0% and 6.4% in males and females respectively.

The risk of obesity increased with increasing age both in males OR(per year) = 1.08 (1.07–1.10), $P \leq 0.001$ and in females, OR(per year) = 1.07 (1.06–1.08), $P \leq 0.001$. On the contrary, the risk of asthma decreased slightly with age in males, OR(per year) = 0.98 (0.97–0.99), $P \leq 0.001$ but not in females, OR(per year) = 1.00 (0.99–1.01), $P = 0.55$, consistent with a higher incidence of asthma in adult females. In both sexes, concordance rates for obesity and asthma were higher in identical twins than in fraternal twins indicating that genetic factors influence both disorders (Table 1).

Figure 2 shows the prevalence of asthma by BMI. In females, the age-adjusted risk of asthma increased with increasing BMI, OR(per unit) = 1.04 (1.02–1.06), $P \leq 0.001$, whereas in males this effect was absent, OR(per unit) = 1.00 (0.98–1.03), $P = 0.87$.

There was an increased age-adjusted risk of asthma in obese females, OR = 1.96 (1.45–2.64), $P < 0.001$ and in

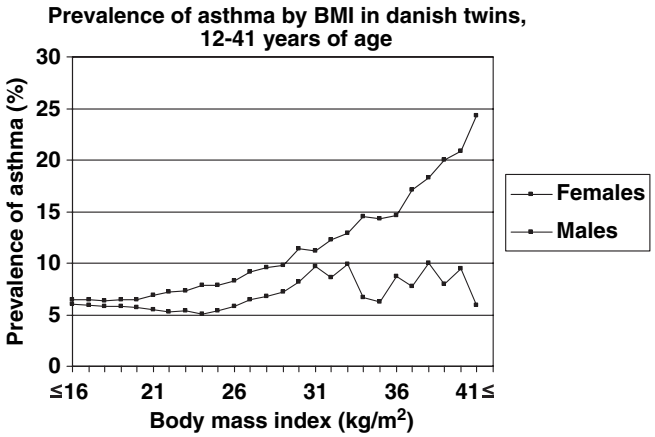

Figure 2. Prevalence of asthma by body mass index in Danish twins, 12–41 years of age.

obese males, OR = 1.59 (1.08–2.33), $P = 0.02$. Cross-twin cross-trait risks in females were higher in identical than in fraternal twins; OR = 2.09 (1.13–3.88) *vs* OR = 1.07 (0.56–2.06) suggestive of a common genetic source for obesity and asthma, whereas the difference was less pronounced in males, OR = 0.92 (0.28–2.97) *vs* OR = 1.29 (0.56–2.99).

Table 2 shows the results from univariate variance components analysis. A model that included effects of additive genetic factors and nonshared environment best described the individual susceptibility to develop obesity and asthma respectively.

Bivariate variance components analysis based on the model depicted in Fig. 1 showed that the age-adjusted genetic liabilities to obesity and asthma were significantly positively correlated only in females, $r = 0.28$ (0.16–0.38). On the contrary, the genetic correlation for males was $r = 0.09$ (−0.12 to 0.23). The correlation between environmental risk factors was statistically significant and negative in females, $r = -0.17$ (−0.33 to −0.12) pointing to opposite effects of environmental risk factors in the two disorders. The environmental correlation was statistically insignificant in males, $r = -0.13$ (−0.67 to 0.35).

Discussion

This study showed a significant relationship between obesity and asthma that was most pronounced in females. Our analysis suggested that some of the same genes, which contribute to obesity, also increase the susceptibility to asthma. We estimated the magnitude of genetic sharing between obesity and asthma and found it to be considerably less than unity indicating that several additional genetic factors influence the variation of the two disorders independently. The present study is thus consistent with and expands upon a recent study by

Table 2. Variance components analysis of obesity and asthma in a sample of 11 302 twin pairs, 12–41 years of age

	Variance components*			Fit statistics		
Model	A	C/D	E	Δ−2 logQ	Δdf	*P*-value
Obesity						
Males						
ACE	0.45 (0.02–.86)	0.33 (0.00–0.36)	0.22 (0.11–0.38)			
AE	**0.81 (0.68–0.89)**	-	**0.19 (0.11–0.32)**	**2.92**	**1**	**0.09**
CE	-	0.65 (0.53–0.75)	0.34 (0.25–0.47)	4.27	1	0.04
E	-	-	1.00	79.11	2	<0.001
Females						
ACE	0.86 (0.58–0.96)	0.06 (0.00–0.32)	0.08 (0.04–0.14)			
AE	**0.92 (0.86–0.96)**	-	**0.08 (0.04–0.14)**	**0.16**	**1**	**0.69**
CE	-	0.72 (0.64–0.79)	0.28 (0.21–0.36)	38.07	1	<0.001
E	-	-	1.00	213.47	2	<0.001
Asthma						
Males						
ACE	0.78 (0.49–0.84)	0.00 (0.00–0.26)	0.22 (0.16–0.30)			
ADE	0.75 (0.17–0.84)	0.03 (0.00–0.62)	0.22 (0.16–0.30)			
AE	**0.78 (0.70–0.84)**	-	**0.22 (0.20–0.30)**	**0.01**	**1**	**0.91**
DE	-	0.79 (0.71–0.85)	0.21 (0.17–0.29)	6.24	1	0.01
E	-	-	1.00	196.99	2	<0.001
Females						
ACE	0.67 (0.37–0.76)	0.01 (0.00–0.27)	0.31 (0.27–0.41)			
AE	**0.68 (0.63–0.76)**	-	**0.32 (0.24–0.40)**	**0.01**	**1**	**0.95**
CE	-	0.53 (0.46–0.61)	0.47 (0.39–0.54)	19.24	1	<0.001
E	-	-	1.00	161.41	2	<0.001

*Standardized parameter estimates (95% confidence intervals) of additive genetic factors (A), genetic factors due to dominance (D), shared environmental factors (C) and nonshared environmental factors (E).

Δ−2 logQ, difference in model fit (log-likelihood) between saturated model and nested model.

Δdf, difference in degrees of freedom between saturated model and nested model.

Preferred models are shown in bold.

Hallstrand et al., which in an American population suggested a similar degree of genetic overlap between obesity and asthma (21).

Our finding of pleiotropy furthermore agrees with several molecular genetic studies of asthma and obesity. As outlined by Tantisira and Weiss, specific regions of the human genome that harbour candidate genes for obesity are known also to be important in asthma (22). These regions include chromosomes 5q23-34, 6p21-23, 11q13 and 12q13-14 (10, 22). The 5q23-34 contains the β_2-adrenergic receptor gene and the glucocorticoid receptor gene, the former encoding receptors involved in the regulation of airway tone and metabolic rate through sympathetic nervous system activity and the latter encoding receptors that modulate inflammation in both asthma and obesity (10). Chromosome 6p21-23 harbours the tumour necrosis factor alpha (TNF-α) gene complex within which several polymorphisms have been associated with asthma, intermediate asthmatic phenotypes and obesity (23–25). The low affinity immunoglobulin E receptor and uncoupling protein (UCP2 and UCP3) genes are positioned on chromosome 11q13 and polymorphisms of these have been associated with measures of asthma, objective measures of atopy and fat distribution respectively (26, 27). Finally, several genes encoding various cytokines such as STAT6, IFNγ, IL1A and LTA4H are situated on chromosome 12q13-14, all of which are known to influence inflammatory processes of asthma and obesity (10, 22). Although these findings imply that the genetic susceptibility to asthma may be shared with that for obesity, it is important to realize that the two conditions could be associated due to factors that mimic pleiotropy. Consider, for example co-segregation of obesity candidate genes with genes that influence the expression of asthma. Such a phenomenon would increase the genetic correlation between the two traits even though the genes involved are not the same (22). In the same instance, if some genes predispose to the development of obesity and the obesity phenotype increases the risk of asthma it would appear as if the same genes influence both traits. This, in turn, would induce a genetic correlation between the two traits that is misleading. Furthermore, increased production of several inflammatory products in the obese such as TNF-α, IL-6, leptin, C-reactive protein and nitric oxide is speculated to influence the development of asthma directly while at the same time being increased in asthma (10, 22). This is signified for instance by TNF-α, which increases following allergen exposure but which is also known to upregulate the T-helper cell 2 type cytokines IL-4 and

IL-5 produced by bronchial epithelial cells in obese nonasthmatic subjects (10). Additionally, C-reactive protein and leptin levels are increased in obesity. The latter is expressed by adipocytes and is known to regulate satiety and basic metabolic rate. Leptin receptors are also expressed in T cells and through interaction with these it is speculated to increase the production of inflammatory cytokines, in addition to activating the autonomic nervous system (28). Finally, exhaled nitric oxide has been proposed as a possible link, implied by the finding of a positive correlation between levels of that substance and BMI in healthy nonasthmatic subjects (29). Based on these findings it is evident that basic functions alluding to metabolism, autonomic nervous system activity and immune mechanisms are common to the two traits. It is therefore not surprising that genetic studies uncover a certain degree of agreement between loci contributing to their variation. Studies of other inflammatory disorders such as rheumatoid arthritis, inflammatory bowel disease and diabetes find that those diseases seem to be influenced by several of the same loci that are also involved in asthma and obesity (30). These findings support that at least part of the genetic correlation between asthma and obesity is on the level of fundamental aspects of inflammation.

Other factors also likely to contribute to the association between obesity and asthma (22). These have been shown to include effects on lung mechanics relating to decreased cycling rates of airway smooth muscle in turn leading to decreased functional capacity, airflow obstruction and increased airway reactivity (31). Also, a significant relationship exists between gastroesophageal reflux and bronchoconstriction with obesity perhaps linking the two conditions (32). Furthermore, hormonal factors undoubtedly play a role in the pathogenesis of asthma among the obese. Oestrogens are produced from androgens in adipose tissue and are observed in excess amounts in obese subjects. Studies of postmenopausal hormone replacement therapy and early menarche associate effects of oestrogens with development and severity of asthma (4, 33, 34). These observations point to a general susceptibility underlying obesity, gastroesophageal reflux, hormonal changes, female sex and asthma, which may be genetically determined.

We used self-reported measures of height, weight and asthma and therefore our conclusions may be affected by imprecise reporting. Most people tend to underestimate their weight while at the same time overestimate their height, especially if being overweight (35). Furthermore, other measures of excess weight such as hip/waist ratio, waist circumference or objective techniques could perhaps have captured some additional information.

In conclusion, our study showed that obese subjects have an increased risk of asthma, which in females seems partly because of common genes.

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