

Original article

Risk factors for asthma in young adults: a co-twin control study

Background: The liability to asthma is influenced both by genetic and environmental factors. The objective of this study was to identify risk factors for asthma in young adult twin pairs during an 8-year period.

Methods: From the birth cohorts 1953–1982 of the Danish Twin Registry, 6090 twin pairs who were initially unaffected with respect to asthma at a nationwide questionnaire-based study in 1994 participated in a similar follow-up study in 2002. Subjects were regarded incident asthma cases when responding affirmatively to the question 'Do you have, or have you ever had asthma?' in 2002. Pairs in which only one twin developed asthma – discordant pairs – were identified and conditional logistic regression was applied to detect effects of risk factors.

Results: A total of 126 monozygotic (MZ) and 273 dizygotic (DZ) discordant twin pairs were identified. In MZ twins hay fever (OR = 3.16, 95% CI: 1.29–7.73, $P = 0.007$) and exercise (OR for inactivity = 0.35, 95% CI: 0.13–0.91, $P = 0.023$) were significantly associated with asthma, whereas in DZ twins, hay fever (OR = 2.44, 95% CI: 1.44–4.13, $P = 0.001$), eczema (OR = 1.96, 95% CI: 1.02–3.78, $P = 0.040$), female sex (OR between males and females = 0.54, 95% CI: 0.36–0.80, $P = 0.002$), and increasing levels of body mass index (BMI; OR per unit = 1.11, 95% CI: 1.02–1.20, $P = 0.009$) were significant predictors of asthma.

Conclusions: Hay fever, eczema, female sex, exercise and increasing levels of BMI were risk factors for asthma in young adults. The different risk profile observed in MZ twins compared with DZ twins may reflect an underlying genetic vulnerability shared between those risk factors and asthma.

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Twins have been used for research purposes for more than a century. Initially unaware of the distinction between identical and fraternal twins, Sir Francis Galton – Darwin's cousin – proposed in 1875 that twins could be used to study inheritance. He argued that twins were a perfect natural experiment, quite like a living laboratory (1).

The classical twin study compares the phenotypic similarity of identical twins with that of fraternal twins. The basic idea being that if identical twins, who are perfectly genetically matched, are more similar for a trait than are fraternal twins, who like ordinary siblings, on average, share half of their segregating genes, a genetic contribution to the trait can be inferred (2). The majority of the previous twin studies of asthma have used this design to distinguish influences of genes from influences of upbringing on the disease. These studies provide evidence of substantial genetic causation in asthma, but still with a considerable portion of the disease liability being due to environmental differences between people (3).

Another slightly less common type of twin study is called the co-twin control study. The co-twin control study uses identical twin pairs of which only one twin in each pair is diseased (discordant pairs). The idea behind

this approach is that if two individuals are genetically identical only the environment makes them dissimilar. Therefore, by comparing affected with unaffected twins, effects of specific environmental risk factors can be isolated (4). The strength of the co-twin control study is the ability to control confounding (genotype effects, age effects, sex effects, etc.), and therefore this type of design is inherently more powerful to detect effects of the environment than are ordinary epidemiological studies of genetically unrelated individuals. The clearest signal of co-twin control studies comes from studies where hereditary influences on the risk factors in question are negligible. Many perceived environmental factors, for example, smoking and alcohol consumption, show a great deal of familial aggregation making identical twins more similar for these factors than is expected by chance (5). This diminishes the twin to co-twin variation within each pair for a given risk factor in turn making a study that uses identical twins suboptimal for detecting an effect of that particular risk factor. Furthermore, if the risk factors studied are genetically associated with the trait on which the twin pairs are selected, the results can be difficult to interpret. In order to face these objections the co-twin

control study can be extended to include fraternal twin pairs as controls.

During the past decades there has been a substantial increase in the prevalence of asthma but so far the causes for this increase are poorly identified (6). It is well documented that the incidence of asthma is greater in childhood compared with adulthood and that the male/female ratio of incident asthma diminishes with increasing age. Adult-onset asthma has, however, received an increasing amount of attention in recent years not least because of reports coming from large collaborative studies such as the European Community Respiratory Health Survey and the Nutrition Examination Study (7, 8). In particular, female sex (9), hay fever (9, 10), sensitization to aeroallergens (10, 11), obesity (12), exposures encountered at work (13) and perhaps hormone replacement therapy (14) are all suspected to be causal factors for asthma in adults. Still, prospective studies of asthma in adults are sparse, especially among twins, and conduction of such studies may therefore further elucidate the causes for development of the disease.

In order to assess the possible effects of hay fever, eczema, sex, body mass index (BMI), smoking, leisure time physical activity and educational level on risk of asthma in young adults we undertook a prospective co-twin control study, nested within a larger nationwide questionnaire survey. We studied these risk factors both in identical and in fraternal twins and compared the risk estimates of the two zygosity groups with each other.

Methods

Study design

The study population is based on the birth cohorts from 1953 to 1982 that were ascertained from the nationwide Danish Twin Registry (15). In these cohorts, zygosity was established in 1991 using questions of similarity and mistaken identity, which have a frequency of misclassification of <5% (16).

In 1994, a questionnaire with items aimed at identifying multiple phenotypes including asthma and possible risk factors for asthma, was answered by 29 180 twin individuals (48% males; response rate 86%; 17), and for an 8-year follow-up study in 2002, by 21 162 of those (45% males; response rate 73%). Subjects were 12–41 years of age in 1994 and 18–49 years of age in 2002. There were similar response rates across ages. Of the 21 162 responders to both questionnaires, a total of 7411 intact twin pairs were identified. These comprised 2343 identical (monozygotic, MZ) pairs, 2559 fraternal (dizygotic, DZ) same-sex pairs, 2133 DZ opposite-sex pairs and 376 pairs of unknown zygosity, leaving 6340 single responders. Of the 7411 intact twin pairs responding to both questionnaires, a total of 6090 pairs with known zygosity were unaffected with respect to self-reported asthma in 1994, and this sample was used to identify twin pairs in which only one twin in each pair developed asthma in the period from 1994 to 2002.

Incident asthma cases were identified on the basis of responses to the question 'Do you have, or have you ever had asthma?' Individuals who were initially unaffected in 1994 and who responded affirmatively to that question in 2002 were classified as incident

asthma cases. This procedure has previously 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 (18).

Information on possible risk factors for development of new asthma from 1994 to 2002 was collected in 1994. Possible risk factors included a history of hay fever, a history of eczema, sex, height and weight (BMI), smoking history, intensity of leisure time physical activity and years of schooling.

Statistical analysis

We applied conditional logistic regression analysis separately for the MZ and DZ twin pairs to estimate the effects of the possible risk factors for asthma. Only pairs that had become discordant for asthma in the study period were considered in the analysis. A 1 : 1 matching was done with the affected twin in each pair being the case, the unaffected being the control. Asthma was the dependent variable; hay fever, eczema, sex (for DZ pairs only), smoking, physical activity and years of schooling were binary explanatory variables, BMI continuous. Subjects with incomplete data on any of the explanatory variables were omitted from the analysis. The effects of the explanatory variables were estimated from the difference in likelihood for removing one of the explanatory variables from a model with all explanatory variables included. Risk estimates are given as odds ratios (ORs). A *P*-value of <0.05 was considered to be statistically significant.

Co-twin control studies are suitable for estimating effects of environmental influences on a trait – in this case asthma – using discordant MZ twin pairs. In some instances, however, co-twin control studies benefit from including discordant DZ twin pairs as controls. This is the case if one wants examine whether the relationship between the trait and the risk factors studied is the result of underlying genetic and/or environmental factors shared between the trait and those risk factors. Comparison of the ORs for the risk factors in MZ twins with those of DZ twins carries this out. If the relationship between asthma and a risk factor – for example, hay fever – is due to underlying environmental factors shared between hay fever and asthma, the OR for hay fever in MZ twins will significantly exceed that of DZ twins. Conversely, if the relationship is due to shared genetic factors, one would expect a significantly higher OR in DZ twins compared with MZ twins. Combinations of those two situations can also be present, emphasizing the combined role of underlying genetic and environmental contributions to the observed relationship (19). Tests for homogeneity of ORs between MZ and DZ pairs were carried out using likelihood ratio tests. Data were analysed with the statistical package R, using the clogit function (20). The protocol was evaluated and approved by the Scientific Ethics Committee.

Results

The distribution of twin pairs in which asthma developed during the study period is outlined in Table 1. These comprised 26 concordant (both twins developed asthma) and 447 discordant pairs. The incidence rates of asthma from 1994 to 2002 in the entire population were 4.5 and 6.4/1000-person-years, respectively, among male and female subjects. For all ages, the probability of incident asthma was greater for female subjects (OR = 1.49, 95% CI: 1.24–1.78, *P* > 0.001) (21).

Table 1. Development of new asthma, between 1994 and 2002, in a sample of 6090 young adult twin pairs

Zygosity group	Unaffected (pairs in 1994)	Concordant affected (pairs in 2002)	Discordant affected (pairs in 2002)	Total*
MZ	2063	14	135	149 (4.0)
Males	837	6	49	55 (3.6)
Females	1226	8	86	94 (4.2)
DZ-ss	2226	7	169	176 (4.1)
Males	984	3	52	55 (2.9)
Females	1278	4	117	121 (4.9)
DZ-os	1801	5	143	148 (4.2)
Males [†]			56	61 (3.4)
Females [†]			87	92 (5.1)
All DZ	4027	12	312	324 (4.2)
Total	6090	26	447	473 (4.1)

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

*Number (percentages) of pairs with new asthma from 1994 to 2002.

[†]Males and females being the affected twin, respectively.

Table 2 shows the distribution of explanatory variables according to zygosity in twin pairs discordant for asthma. Table 3 shows the result from conditional logistic regression analysis. Because of missing information on one or several explanatory variables for 48 twin pairs, responses from a total of 399 discordant pairs; 126 MZ pairs and 273 DZ pairs, were analysed. In MZ twins, hay fever (OR = 3.16, 95% CI: 1.29–7.73, $P = 0.007$) and exercise (OR for inactivity = 0.35, 95% CI: 0.13–0.91, $P = 0.023$) were significantly associated with asthma, whereas in DZ twins, hay fever (OR = 2.44, 95% CI: 1.44–4.13, $P = 0.001$), eczema (OR = 1.96, 95% CI: 1.02–3.78, $P = 0.040$), female sex (OR between males and females = 0.54, 95% CI: 0.36–0.80, $P = 0.002$) and increasing levels of BMI (OR per unit = 1.11, 95% CI: 1.02–1.20, $P = 0.009$) were statistically significant predictors of asthma. We found no significant effects of smoking or having <10 years of schooling in either zygosity group. Comparison of the ORs in MZ twins with

Table 2. Distribution of risk factors for asthma in a sample of 399 young adult twin pairs discordant for asthma

Variable	Monozygotic twin pairs ($n = 126$)		Dizygotic twin pairs ($n = 273$)	
	Affected twins	Unaffected twins	Affected twins	Unaffected twins
Hay fever	30	18	74	45
Eczema	16	17	32	18
Male sex*	45	45	49	79
BMI (mean)	21.7	21.7	22.6	22.2
Ever smoking	41	43	128	125
Physical activity [†]	9	18	43	34
Schooling (≤ 10 years)	64	63	158	161

The figures in each column refer to the number of subjects having the risk factor [for body mass index (BMI), the figure is the mean value].

*For dizygotic twins the figures refer to opposite-sex pairs only.

[†]Reference category is <2 h per week of light leisure time exercise activities.

those of DZ twins for the different risk factors showed significant heterogeneity for physical activity ($P = 0.008$).

Discussion

We conducted a prospective co-twin control study nested within a comprehensive nationwide questionnaire survey, originating from the Danish Twin Registry. We found that hay fever and exercise in MZ twins and hay fever, eczema, female sex and increasing levels of BMI in DZ twins were risk factors for asthma. Our study is among a few that have employed this type of design in a longitudinal setting. Recently, however, Huovinen et al. examined several risk factors for asthma in a Finnish questionnaire study comprising 60 MZ and 179 DZ twin pairs discordant for asthma (22). Their analyses were based on questionnaire follow up of subjects 20–50 years of age, and allowed the opportunity to look at exposure and outcome, interspaced by a 17-year period. As opposed to our results, no statistically significant findings were reported for MZ twins, whereas analysis of DZ twins revealed allergic disease and sedentary lifestyle as predictive factors. Compared with our study, the definition of asthma in the Finnish study is very narrow, thus increasing specificity but at the expense of milder cases and number of accessible pairs.

In a co-twin control study from Australia airway responsiveness, total immunoglobulin E (IgE), and sensitization to aeroallergens were measured in a sample of 419 adult twin pairs with a mean age of 36 years (19). That study found a discriminative effect of sensitization to indoor allergens (house dust mite, cat and cockroach) both in MZ and DZ twin pairs discordant for asthma, whereas discordant DZ pairs also differed significantly in sensitization pattern to outdoor allergens, such as grass pollen. The mean intrapair differences in wheal sizes for specific allergens and levels of total IgE were compared for MZ and DZ twins, and for most determinants the DZ difference was greater. These findings indicate that pollen allergy in asthmatics tends to develop as a result of an underlying atopic predisposition shared with asthma, whereas indoor allergens are more likely the direct environmental causes of asthma (19).

We found a discriminative effect of hay fever both in MZ and DZ twin pairs, which underlines the close relationship between allergic upper and lower airways disease (23). Several previous studies have likewise found that hay fever significantly predicts development of asthma. Whether this constitutes a direct causal effect or merely is an indicator of the natural course of the disease, is however, less clear (24). We tested grossly this latter hypothesis when comparing the risk estimates for hay fever between MZ and DZ twin pairs. We did not find a significant difference between these estimates, which could be due to lack of statistical power. Irrespective of this, our finding of equal effect sizes for hay

Table 3. Risk factors for discordant development of asthma, from 1994 to 2002, in a sample of 399 young adult twin pairs

Variable	Monozygotic twin pairs (n = 126)			Dizygotic twin pairs (n = 273)			OR _{MZ} = OR _{DZ} *
	χ^2 (d.f.)	OR (95% CI)	P-value	χ^2 (d.f.)	OR (95% CI)	P-value	
Hay fever	7.32 (1)	3.16 (1.29–7.73)	0.007	11.94 (1)	2.44 (1.44–4.13)	0.001	0.620
Eczema	0.006 (1)	0.95 (0.26–3.49)	0.938	4.22 (1)	1.96 (1.02–3.78)	0.040	0.331
Male sex				9.93 (1)	0.54 (0.36–0.80)	0.002	
BMI (per unit)	0.10 (1)	0.97 (0.79–1.19)	0.749	6.88 (1)	1.11 (1.02–1.20)	0.009	0.224
Ever smoking	0.15 (1)	0.79 (0.23–2.71)	0.701	1.26 (1)	1.30 (0.82–2.07)	0.262	0.451
Physical activity†	5.17 (1)	0.35 (0.13–0.91)	0.023	1.83 (1)	1.48 (0.84–2.61)	0.176	0.008
Schooling (≤ 10 years)	0.74 (1)	1.59 (0.55–4.62)	0.390	0.12 (1)	0.92 (0.56–1.51)	0.734	0.357

CI, confidence interval; OR, odds ratio; BMI, body mass index; MZ, monozygotic; DZ, dizygotic.

*P-value for test of homogeneity of ORs between MZ and DZ pairs.

†Reference category is <2 h per week of light leisure time exercise activities.

fever in MZ and DZ twin pairs signals that hay fever is associated with asthma because of an underlying genetic and environmental vulnerability shared between the two traits. Furthermore, we conclude that because asthma do not develop in all subjects with a previous history of hay fever genetic and environmental factors may influence both asthma and hay fever, independently. This conclusion was also drawn in two previous studies, which have determined the magnitude of genetic and environmental sharing between the two traits (25, 26). In an Australian sample of 3808 adult twin pairs and in a Swedish population comprising 1480 pairs, 7–9 years of age, the correlations between genetic factors influencing both asthma and hay fever were on the order of 0.60 and 0.90, respectively. Furthermore, the environmental correlation was around 0.40 in the Australian sample but not significantly different from zero in the Swedish population.

We found a positive association between increasing levels of BMI and liability to asthma in DZ but not in MZ twin pairs. It is known from other studies that obesity is associated with development of asthma both in males and females and much speculation has arisen as to the mechanisms that cause these conditions 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 (27). We compared the risk estimate in MZ twins with that of DZ twins and found a greater, however not statistically significant, OR in DZ twins. This finding suggests some genetic covariation between BMI and asthma, which essentially means that the phenotypic expression of the two traits to some extent could be influenced by the same genetic factors (28).

We found a protective effect of sedentary lifestyle on the risk of asthma in MZ twin pairs, which in its broadest interpretation could suggest that excess amounts of exercise is a risk factor for asthma. Our definition of physical activity is, however, rather crude distinguishing only subjects doing < 2 h per week of light leisure time exercise activities from those doing more. Essentially, what this variable measures is therefore not exercise but inactivity.

On this behalf we suspect our finding to be false-positive because the direction of effect is reversed compared with findings from several previous studies linking physical inactivity to increased risk of asthma (22, 29).

We noted a strong female preponderance in liability to asthma. This agrees with results from other studies, which report greater incidence rates for females than for males in this age group (9, 30). In fact, results from an Australian study support that different genetic models can be derived for the two sexes and that the phenotypic expression of asthma in females is under simple additive genetic control, whereas genetic nonadditivity seems to be important among males also (26).

We rely solely on questionnaire responses and this might have affected the accuracy to detect the presence or absence of disease. It is possible that some subjects tend to confuse a true incidence of asthma with relapse of disease, forgetting that they developed the condition already in childhood. The extent, however, to which this affects the reliability of the estimates, is in other studies demonstrated to be of variable importance (18, 31).

This study is a longitudinal case-control study performed within a nationwide sampling frame, which increases robustness against ascertainment bias. With this design, we are able to indirectly control several known confounding factors such as genetic composition, sex and age, as well as an array of unmeasured exposures encountered in the rearing environment that potentially contribute to phenotypic dissimilarity. These advantages should be balanced against the reduced power provided by the often relatively low number of subjects that can enter into a co-twin control study. Furthermore, for many risk factors a lack of twin to co-twin variation makes it difficult to obtain clear results. This property should, however, not be seen as a weakness but rather be used, as in this study, to examine the genetic (pleiotropy) and environmental factors associating different traits. These challenges can be further faced by including the entire population of several thousand individuals enrolled in the large twin registries at the benefit of increased power to detect effects of risk factors, but at the expense of the explicit study design (4).

In conclusion, this study suggests that hay fever, eczema, female sex and increasing levels of BMI are risk factors for asthma in young adults. The different risk profile observed in MZ twins compared with DZ twins may reflect an underlying genetic vulnerability shared between those risk factors and asthma. Further studies of genetically informative samples are required to add insight into the nature of these relationships.

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