SHORT REPORT

Genes and environment in asthma: a study of 4 year old twins

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Abstract

***Background*—Although the genetic and environmental factors of asthma have been investigated in adolescence and adulthood, no previous studies have focused on the early development of asthma.**

***Aims*—To test, in a large sample of 4 year old twins, the hypotheses derived from the literature on adolescents and adults that genetic influences are substantial and shared environmental influences are modest.**

***Methods*—The sample consisted of 4910 twin pairs who were born in England and Wales in 1994 and 1995. Data on asthma status were obtained from the twins' parents by postal questionnaire.**

***Results*—Univariate parameter estimates derived from model fitting were 68% heritability, 13% shared environment, and 19% non-shared environment.**

***Conclusions*—Our findings suggest that asthma is highly heritable in 4 year olds, whereas shared environmental influences are not statistically significant.**

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Asthma is one of the most common health problems within industrialised societies, and incidence rates have risen considerably over the last few decades.[1–3] Prevalence rates for childhood asthma vary widely throughout the world, with the highest rates (17–30%) reported in the UK, Australia, and New Zealand.[2] Although the onset of asthma can occur at any age, over 80% of asthmatics experience their first episode by the age of 5.[4] Most cases of childhood asthma tend to become less severe over time and as many as half who developed asthma as children become asymptomatic by the time they reach adulthood.[5]

It is reasonable to expect that environmental exposures to allergens are of primary importance for the occurrence and the development of asthma. Such environmental exposures should be shared by children living within the same family and thus should contribute to sibling similarity in the occurrence of asthma. Such shared environmental exposures include parental smoking, air pollution, domestic animals, and dust mites, as well as number of siblings and factors associated with socioeconomic status.[3 6] The role of environmental exposures of allergens and their contribution to asthma has recently been reviewed.[7 8] The relation between asthma and parental smoking and air pollution remains controversial.[9 10]

Results from twin studies have consistently found evidence that genetic factors contribute importantly to asthma. Concordance rates in monozygotic twins are consistently higher than in dizygotic twins, suggesting the involvement of genetic factors.[11–15] Estimates of heritability range from 0.36[15] to 0.87.[11 16–19] Moreover, despite the reasonableness of shared environmental hypotheses about the origins of asthma, these twin studies consistently find little evidence for shared environmental influence. Twin studies estimate shared environmental influence as the resemblance of twin pairs that cannot be explained by genetic influence. Because genetic influence (heritability) is indexed by twice the difference between identical and fraternal twin correlations, shared environmental influence is indicated by the extent to which the identical twin correlation is greater than twice the difference between identical and fraternal twin correlations.

Most of these twin studies involved samples of a wide age range, typically from adolescence to adulthood, although one study[17] focused on middle childhood (ages 7 to 9). No previous twin studies have examined the development of asthma in preschool children. The Twins Early Development Study (TEDS) provides an opportunity to test in early childhood the hypotheses that heritability is substantial and shared environmental influences are modest, using a large representative sample of 4 year old twins.

Methods

The present results are based on all twins who were born in England and Wales in 1994 and 1995 who were enrolled in TEDS. The sample has been described in detail elsewhere.[20]

Data were obtained by postal questionnaires, which were sent to the families at about the time of the twins' fourth birthday. Written consent was obtained from the twins' parents who were informed that they could withdraw from the study at any time. Zygosity was ascertained by parent questionnaire ratings of twins' physical similarity.[21] An analysis of the zygosity

Table 1 Sample size, prevalence, concordance, and tetrachoric correlations for 4 year old twins

Group	Pairs (n)	Probands (n)	Prevalence of asthma (%)	Discordant pairs (n)	Concordant pairs (n)	Probandwise concordance rate (%)	Tetrachoric correlations	95% CI
Male MZ	780	313	20.1	113	100	64	0.79	0.71 to 0.85
Female MZ	878	302	17.2	104	99	66	0.84	0.77 to 0.88
All MZ	1658	630	19.0	217	199	65	0.81	0.77 to 0.85
Male DZss	847	317	18.7	175	71	45	0.54	0.43 to 0.64
Female DZss	804	272	16.9	180	46	34	0.39	0.25 to 0.51
All DZss	1651	589	17.8	355	117	40	0.47	0.39 to 0.55
Male DZos		342	21.4					
Female DZos		253	15.8					
All DZos	1601	595	18.6	391	102	34	0.35	0.26 to 0.44
All DZ	3252	1184	18.2	746	219	37	0.41	0.35 to 0.47
Total	4910	1814	18.4	963	418	46		

instrument used in TEDS found that zygosity was correctly assigned by parent ratings in 94.7% of the cases as validated against zygosity assigned by identity of polymorphic DNA markers.[22] The TEDS assessment included the following question to parents about asthma status in the twins: "Have either of your twins been prescribed any medication to control asthma?". Only twins with complete information on zygosity and asthma status were included in the analyses. The sample included a total of 4910 twin pairs: 1658 monozygotic (MZ), 1651 dizygotic same sex (DZss), and 1601 dizygotic opposite sex (DZos).

STATISTICAL METHODS

Twin similarity was assessed using probandwise concordance rates for asthma. Probandwise concordance rates are the ratio of twice the number of concordant pairs divided by twice the number of concordant pairs plus the number of discordant pairs.[23] Furthermore, tetrachoric correlations were also calculated from pairwise contingency tables. Tetrachoric correlations were used as an index of twin similarity and for genetic model fitting analyses. Tetrachoric correlations are based on the assumption of an underlying continuous distribution of liability to asthma despite the dichotomous measurement of asthma.

Twin concordances and correlations were interpreted on the basis of classic twin theory in respect to how the contribution of genes and environment can account for similarity and differences between MZ and DZ twins. MZ twins share all of their genetic make-up, whereas DZ twins share on average 50% of their segregating genes. Consequently, greater similarity for MZ twins than for DZ twins indicates genetic influence. Environmental factors can be shared or non-shared between members of a twin pair. Shared environmental influences are experienced by both members of a twin pair and thereby contribute to twin resemblance, regardless of zygosity. The importance of shared environmental effects is implicated to the extent that the MZ correlation exceeds heritability. Lastly, non-shared environmental factors are not shared by members of a twin pair and do not contribute to twin resemblance but only to within pair differences.

The tetrachoric correlations were used in structural equation modelling procedures (MX)[24] in order to estimate genetic and environmental components of variance. These techniques are commonly used within twin research and have been described in detail elsewhere.[23]

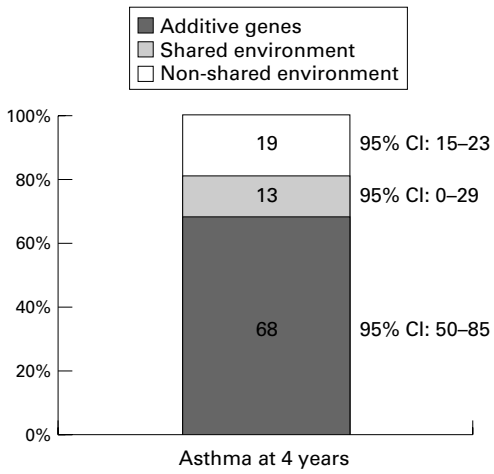

Figure 1 Maximum likelihood liability model estimates of heritability and environmental influences for asthma.

Results

Table 1 summarises sample size, prevalence, probandwise concordance rates, and tetrachoric correlations by zygosity and gender groups. The prevalence rates for asthma are somewhat higher for MZ than DZ twins and for boys than girls. For all twins as well as for same sex male and female pairs, concordances and tetrachoric correlations are substantially greater for MZ twins than for DZ twins, suggesting genetic influence. Shared environmental influence appears to be modest in that the MZ correlations only moderately exceed heritability, estimated by doubling the difference between the MZ and DZ correlations. Correlations for opposite sex DZ twins are lower than correlations for same sex DZ twins but not significantly so, warranting more research on possible gender differences in genetic and environmental influences.

Figure 1 shows maximum likelihood liability model fitting estimates of genetic and environmental influences on asthma for same sexed twins. The liability model fit the data well ($\chi^2_{(8)} = 12.41$, $p = 0.13$). Genetic influence is substantial (68%; 95% CI: 50–85%). Shared environmental influence is modest and non-significant (13%; 95% CI: 0–29%). Non-shared environmental influence was modest and significant (19%; 95% CI: 15–23%). A

subsequent comparison between males and females suggested higher heritability in girls (82%; 95% CI: 62–88%) than in boys (50%; 95% CI: 26–74%), although the difference is not statistically significant.

Discussion

The present findings indicate that asthma is highly heritable, even in preschool children exposed to the same environmental allergens in the home. Shared environmental factors such as rearing environment, family diet, and air pollutants seem to play a minor role. The present results are in line with but also extend those of studies of older twins that have found little or no shared environmental influence.[11 19] Nonetheless, genotype–environment interaction remains a possibility in the sense that some individuals might be more susceptible genetically to shared environmental exposures in the home.

A limitation of the study is that it relied on parental reports of medical treatment for asthma because this was deemed the most valid single item that could be asked of parents in relation to their children's asthma. Although we are not aware of studies of the validity of parental reports of asthma, asthma has been shown to be highly reliable.[13] Nonetheless, it would be useful in future research to include other respiratory symptoms, such as the occurrence of wheezing over the past 12 months. Because wheezing is quite common in young children, with incidences as high as 50%,[25 26] it is possible that our assessment of medical treatment for asthma included transient respiratory problems. It would also be useful to assess children's history of respiratory illness, because individuals who contract viral infections during infancy or early childhood are more likely to develop asthma.[27] It is possible that these early infections increase vulnerability to respiratory illnesses later on as well as increasing sensitivity to potential environmental triggers.

The genetic contribution to asthma is likely to be polygenic, with many distinct genes contributing to susceptibility. Genome screening studies have found markers on most chromosomes that may be associated with asthma.[28 29] In addition to identifying genes responsible for the substantial heritability of asthma, another direction for future research is to identify the non-shared environmental factors responsible for making children growing up in the same family discordant for asthma.

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