ERJ Express. Published on January 10, 2007 as doi: 10.1183/09031936.00065706

Genetics of parental-reported asthma, eczema, and rhinitis in 5-year-old Dutch twins

C.E.M. van Beijsterveldt & D.I. Boomsma

Department of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands

Running title: genetics of parental-reported asthma in 5-year-old twins

Word count text: 3433

Word count abstract: 191

Please address correspondence to: CEM van Beijsterveldt,

Department of Biological Psychology, Vrije Universiteit,

Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands

E-mail: toos@psy.vu.nl, Fax. +31 20 598-8832

ABSTRACT

The aim of this study was to examine the genetic and environmental contributions to the individual differences in susceptibility to asthma, eczema, and rhinitis in childhood and their role in the association among these conditions.

Information on asthma, eczema, and rhinitis was obtained by parental-report. Parents were asked whether a physician ever diagnosed the condition. Complete data were available for 8633 5-year-old twin pairs born between 1986 and 1998.

The frequency of parental-reported asthma, eczema, and rhinitis was 8.7%, 16.8% and 4.4%, respectively, and was higher in boys than girls. Genetic factors accounted for about 90% of the variance in the susceptibility to asthma, eczema, and rhinitis. The magnitude of genetic factors did not differ between boys and girls. The remaining part of the variance was explained by environmental factors not shared by family members. The phenotypic correlations between parental-reported asthma, eczema, and rhinitis were moderate and mainly mediated by the same genetic factors.

The high heritability and the limited influence of shared environmental factors may point to gene x environment interactions. Future research should focus on this type of interaction processes.

Key words: asthma, rhinitis, childhood, eczema, heritability, twins

INTRODUCTION

Over the recent decades the prevalence of asthma and allergic diseases has increased substantially [1]. These diseases often start in childhood, have a chronic character and can have a considerable impact on the quality of life and the well-being of children [2]. Although many twin studies showed that genetic factors play an important role in the development of asthma [3], several issues remain worth of study. Firstly, most studies reported on the genetics of asthma, but the genetics of eczema and rhinitis are less well studied. Secondly, most twin studies were done in adolescents and adults. And thirdly, the etiology of the association among asthma, eczema, and rhinitis in very young children has not been studied before.

To derive the genetic and environmental contribution to complex diseases the twin design is a powerful design [4]. The general result from twin studies is that asthma is a highly heritable trait. About 70% of the variance in liability to asthma is explained by genetic factors [5-11]. If there were sex differences in genetic factors, then the influence of genetic factors was usually lower for females than males. Another consistent finding from twin studies is that the environment shared by family members does not contribute to the variation in susceptibility to asthma. Only environmental influences not shared by family members play a role. In the light of the increasing rate of asthma in the last decades, the minor role of environmental factors seems remarkable, as the time period of 2 decades is simply too short for changes in allele frequencies in genes which could account for the increasing rate of asthma.

In contrast to asthma, the heritability of hay fever and eczema has not been studied often. In a sample of Norwegian twins aged 18-35 years genetic factors accounted for about 72% and 68% of the variance in liability to eczema and hay fever, respectively [10]. In a Finish sample of adolescent twins genetic factors accounted for 74-82% of the variance in liability to hay fever [12]. In children aged 7 to 9 years, the heritability for hay fever was 0.33

for boys and 0.70 for girls and the heritability for eczema was around 70% for both boys and girls [9].

Several studies provided evidence that asthma and related diseases tend to cluster within families and that overlapping genes may play a major role in this clustering of diseases [5, 9, 13, 14]. However, only a few studies have used structural equation modelling to estimate the extent to which the same genes contribute to association between asthma and related diseases [5, 9].

In the present study susceptibility to asthma, eczema, and rhinitis was assessed by parental report in a large sample of 5-year-old Dutch twin pairs. The first aim was to examine the genetic and environmental contributions to variance in susceptibility to parental-reported asthma, eczema, and rhinitis. The second aim was to estimate the extent that shared genes and/or environments contribute to the comorbidity of asthma, eczema and rhinitis.

METHOD

Participants and measures

The data presented in this paper come from a longitudinal study, which examines the genetic and environmental influences on the development of behavioral and emotional problems in twins from birth onwards. The twin families are volunteer members of the Netherlands Twin Register (NTR), established by the Department of Biological Psychology at the Free University in Amsterdam [15]. From 1987 onwards the NTR recruits families with twins a few weeks or months after birth. Currently 40-50% of all multiple births are registered by the NTR. For this study, we included data that were obtained by questionnaires mailed to parents of 5-year-old twin pairs born between 1986 and 1997.

Parents were asked to report (yes/no) whether a physician ever diagnosed the following conditions: asthma, eczema, hay fever, and rhinitis. We defined a child as affected

for one of the specific conditions when the item was positively answered. Children with hay fever or allergic rhinitis were considered as cases for 'rhinitis'.

For 1218 same sex twin pairs zygosity was based on blood (N = 407) or DNA (N = 811) group polymorphisms. For the remaining twins, zygosity was determined by questionnaire items about physical similarity and frequency of confusion of the twins by family and strangers [16]. If zygosity was missing, the zygosity status was determined by items from surveys sent on other ages. This left 16 twin pairs without information on zygosity. Complete data were available for 1349 monozygotic male twin pairs (MZM), 1461 dizygotic male twin pairs (DZM), 1592 MZ female twin pairs (MZF), 1387 DZ female twin pairs (DZF); 2844 opposite sex (OS) twin pairs.

Data analysis

Prevalence

Prevalence rates were estimated using Mx [17], a structural equation modelling package, in order to obtain unbiased estimates for data assessed in family members. Likelihood-ratio χ^2-tests were to examine the significance of sex and zygosity on differences in prevalence.

Genetic analysis

The relative contribution of genetic and environmental factors to variance in susceptability to complex diseases, such as asthma, can be inferred with data from genetically related subjects such as MZ and DZ twins. The twin method compares the resemblance for a certain trait in MZ twin pairs, who are genetically identical, with resemblance in DZ pairs, who share on average 50% of their segregating genes. The twin method assumes that MZ and DZ twin pairs share their family environment to the same extent. If the MZ resemblance, often expressed in correlations, is twice as large as the DZ resemblance, the trait is influenced by

genetic factors, because the only difference between the two zygosity groups is in genetic relatedness. If the DZ correlation is the same or larger than half the MZ correlation, then a trait is influenced by shared environmental factors. Shared environmental factors include experiences due to growing up in the same family (e.g. exposure to the same smoking behaviour of parents), but also due to in utero experiences. Any true differences, free from measurement error, between MZ twins are attributable to their non-shared environment. Non-shared environmental influences denote to experiences that affect only one of the twin.

For dichotomous variables, tetrachoric correlations can be used to index twin similarity. This is the correlation between twins for an underlying, continuously distributed trait that is often called the "liability" or "susceptibility" to disease. It is assumed that many genes and environmental influences affect susceptibility, resulting in its normal distribution. A threshold on the susceptibility distribution divides the population into affected and unaffected subjects. [17, 18]. The threshold, expressed as a z-value of the normal distribution, is inferred from the prevalence of the disease in the sample.

With structural equation modelling, the influence of additive genetic effects (A), dominant genetic factors (D), shared or common environment effects (C), and non-shared environment (E) factors [4] on variation in susceptibility can be estimated. The modelling procedure starts with a model with A, C, and E factors (ACE full model) or A, D, and E factors (ADE full model). The significane of A, D, C, or E can be tested by omitting them from the model. A significant decrease in goodness-of-fit implies that the omission is not allowed and the factor contributed significantly to the variance of the trait. Sex differences in genetic architecture were tested by constraining the parameters that represent the influence of A, D, C or E to be equal across sex. Again, if the goodness-of-fit deteriorates significantly then the constraint is not allowed and there are significant sex differences in genetic and/or environmental influences. Goodness-of-fit statistics obtained for the different models were

compared with likelihood-ratio χ^2-tests. Mx jobs for the genetic analyses were obtained from the Mx-library [20].

To estimate the genetic and environmental influences on the association of asthma, eczema, and rhinitis cross-twin, cross-trait correlations (e.g. asthma in one twin and allergy in the other twin) in MZ and DZ twin pairs are used. If there is an overlap of genes for asthma and eczema, it is expected that the cross-trait cross-twin MZ correlation will be higher than the cross-trait cross-twin DZ correlation. Shared environmental influences to the co-occurrence of diseases are suggested if the DZ correlation is larger than half the MZ correlation. To estimate the genetic and environment influences on the association between asthma, eczema, and rhinitis, a bivariate genetic model was applied to the data [19]. The model provides estimates of the extent to which shared genetic factors and/or environmental factors contribute to the phenotypic correlation. If the genetic correlation ($r_{(g)}$) is 1, then the same genes influence both diseases. A correlation of 0 indicates that each disease is affected by a different set of genes. To estimate what proportion of the phenotypic correlation between asthma, eczema, and rhinitis, is due to genetic factors, the genetic correlation is weighted by the square roots of the heritabilities of the traits and divided by the phenotypic correlation.

RESULTS

Prevalence

Table 1 provides a summary of the characteristics of the sample according sex and birth cohort. The prevalence of astma, eczema, and rhinitis was higher for boys than girls (asthma: $\Delta\chi^2 = 49.62$, $\Delta df = 1$, $p<0.001$; eczema: $\Delta\chi^2 = 12.97$ $\Delta df = 1$, $p<0.001$; allergy: $\Delta\chi^2 = 32.90$, $\Delta df = 1$, $p<0.001$). Within each sex, the frequency of asthma, eczema, and rhinitis wasnot different MZ and DZ twins (asthma: $\chi^2 = 1.90$, $\Delta df = 2$, $p = 0.39$; eczema: $\chi^2 = 3.79$, $\Delta df = 2$, $p = 0.15$; Allergy: $\chi^2 = 0.07$, $\Delta df = 2$, $p = 0.96$).

Table 1 about here

Genetic analysis

We explored first whether the twin correlations for asthma, eczema and rhinitis were different among full-term born twins (>= 37 weeks), preterm born twins pairs (>=32 weeks and <37 weeks) and very preterm born twins (< 32 weeks). As we observed prevalence differences for asthma between very preterm twins (15.5%) and full-term twins (7.2%), it is possible that the etiology, explaining the variance in susceptibility to asthma, differ across these groups. A different pattern of MZ and DZ correlations may point to a different underlying etiology. As shown in Table 2, the difference between MZ and DZ twin correlations of asthma and rhinitis in the very preterm group was smaller than the difference between the MZ and DZ correlations in the preterm and full-terms twins. Constraining the DZ correlation to be equal in the very preterm to that of the twins born after 32 weeks resulted in a significant deterioration of the fit for asthma ($\Delta\chi^2 = 3.94$; $\Delta df = 1$; $p = 0.047$) but not for rhinitis ($\Delta\chi^2 = 1.93$; $\Delta df = 1$; $p = 0.165$). These results could indicate that for the very preterm twins both C and A factors contribute to variance in susceptibility to asthma, while for twins born after 32 weeks only genetic influences are suggested. However, structural equating modelling did not demonstrate the significance of C in the very preterm group. The detection of C in the classical twin design requires large samples and it is likely that the number of twins was too small to draw any firm conclusion about C. Since our study is ongoing, we hope that we can extend its sample size in the future, which may lead to a decisive answer to the question whether the genetic and environmental contribution to asthma and rhinitis is different in very preterm born children. For present analyses the very preterm born twins were excluded (N = 363) from further genetic analyses.

Table 2 about here

Table 3 gives the phenotypic correlations between asthma, eczema, and rhinitis, the twin correlations, and the cross-twin cross-trait correlations. For all 3 conditions the MZ correlations were higher than the DZ correlations, suggesting genetic influences. The results of the univariate genetic analyses are presented in Table 4. The analyses revealed no sex differences in genetic influences for asthma, eczema, and rhinitis. Additive genetic factors accounted for the most part of the variance in liability to asthma (h^2 = 95%) and to rhinitis (h^2 = 91%), and that the remaining part of the variance was explained by non-shared environmental factors. For eczema, an ADE model was the best fitting model which indicate that a large part of the variance in susceptibility of eczema could be explained by genetic factors (84%), but that both additive (35%) and dominant (49%) genetic factors were important.

Table 3 about here

Based on the univariate results, suggesting no sex differences in heritability and no evidence for shared environmental effects, the bivariate analyses were performed without sex differences in estimates for A and E and shared environmental factors were not included in the analyses. For eczema, a genetic dominance factor was included in the model. The phenotypic correlation of the first born twin (between the brackets the correlation for the second born twin) between asthma and eczema 0.348 (0.357), between asthma and rhinitis was 0.517 (0.475), and between eczema and rhinitis 0.375 (0.391). The structural equation modelling revealed that both genetic and environmental factors contributed to the phenotypic correlations of asthma, eczema, and rhinitis. The extent to which the same genes contribute to

phenotypic correlation was estimated at 0.55 for asthma and eczema, at 0.47 for asthma and rhinitis, and at 0.62 for eczema and rhinitis. These correlations, also underscored the importance of unique genetic factors for each condition. The extent to which the same environmental factors overlap was estimated at 0.18 for asthma and eczema, at 0.73 for asthma and rhinitis, and at 0.39 for eczema and rhinitis. The last 2 rows of Table 4 show the proportion of the phenotypic correlation that is due to same genetic and same environmental factors. It shows that the phenotypic correlation between asthma-eczema, asthma-rhinitis, and eczema-rhinitis was mainly mediated by genetic factors.

Table 4 about here

DISCUSSION

In this study we have explored the genetic effects of parental-reported asthma, eczema, and rhinitis in a large group of 5-year-old children covering birth cohorts from 1986 to 1998. The prevalence of asthma, eczema, and rhinitis was respectively 10.2%, 17.7%, and 5.6% for boys and 7.2%, 15.9%, and 3.8% for girls. Genetic factors accounted for a large part of the variance in susceptibility to asthma, eczema, and rhinitis and the influence of these factors were of same magnitude for boys and girls. The influence of environmental factors was small (they range from 6% to 14%) and were non-shared between twins. The phenotypic correlations among the 3 diseases were moderate and the overlap between the diseases was mainly due to overlapping genes. Before we further interpret our findings, it should be mentioned that in this study we rely on the parent report of asthma and related conditions and not on a clinical assessment. Our findings should be seen in the light of this limitation.

The parental-reported frequency of asthma (10.2 % for boys and 7.2 % for girls) was higher than the prevalence of asthma obtained by registration of the general practitioners in

Holland (6% for boys and 4.2% for girls) [21]. In the light of this findings, it could be questioned whether the twins are representative for the general population. However, several explanations are possible to account for these prevalence differences. In our study the frequency of asthma, eczema, and rhinitis was based on parental-report, in which the question was: 'did the child have doctor diagnosed asthma ever since birth?' So, the question involved a larger time span than the one single year in which the registration by the physician is based. In addition, it seems a consistent finding that the prevalence of asthma and related conditions obtained by self-report is higher than the prevalence reported by the physicians [24]. Our pervalences of asthma and eczema are comparable to studies based on parental-reports of asthma in 4-6 years-old Dutch children [22] and with the prevalence of 17.7% for skin rash ever in life reported for Dutch children of 7 to 12 years [23]. Nevertheless, we can not exclude that twins may form a special population. The percentage of preterm births is higher in twin than in singleton births. In addition, it is known that babies who are born prematurely, may have an increased risk for lung damage, which in turn may increase the sensitivity of developing asthma [25]. On the other hand, there also is evidence that the prevalence rate of asthma may just be lower in twins than in singletons because growing up with a co-twin increases the chance for exposure to infections in early life, which in turn protects against the development of allergic diseases [26, 27].

In this study we obtained a heritability of about 90% for parental-reported asthma, eczema, and rhinitis. The high heritability corresponds with the general finding of large genetic influences for asthma, but the heritability is somewhat higher than the general finding of 70%. The fact that most research of asthma is done in adolescents and adults may explain this difference. Adolescents and adults may be exposed to a wider range of environments than young twins and as a result the relative environmental influences may be larger in adolescents. A high heritability could also be the results of violation of the assumption of

equal environment for MZ and DZ twins. If MZ twins experience more equal environments than DZ twins do, then the influence of genetic factors could be overestimated. It seems unlikely that the exposition to risk factors is more similar for MZ than for DZ twins in 5 year old twin pairs who grow up in the same home. The influence of genetic factors may be overestimated as a result of parents' expectations regarding the MZ twin's resemblance. If this expectancy effect plays a role then it is expected that the twin correlations will be different between twins who were correctly classified as MZ twins and who where misclassified. Our findings do not suggest any parental bias. In a group of 214 MZ twin pairs misclassified by their parents the twin correlations for asthma, eczema, and rhinitis were also very high (0.86, 0.77 and 0.92 for respectively asthma, eczema, and rhinitis).

In agreement with other twin studies of asthma, our results do not provide evidence for influence of shared environmental factors. Thus, the fact that twins grow up in the same house and experience the same environmental risk factors, seems not to contribute to the variance in susceptibility to asthma. These findings seem to be in conflict with studies that suggested environmental risk factors, such as parental smoking, number of siblings, and air pollution, for the increase of asthma during the last decades.

The lack of evidence for shared environmental factors could be explained by gene-environmental interactions. It is likely that environmental risk factors trigger asthma only in persons with larger genetic susceptibility for allergic and asthmatic diseases [28]. In a twin design it is not possible to distinguish an interaction between genotype and shared environmental factors from genetic effects. There is some evidence for the possibility of gene-environment interactions for asthma and related diseases [29, 30]. These studies reported that the linkage results depended on the kind of environment to which the patient was exposed as a child. Evidence for linkage between certain chromosomes and asthma were only found for persons who where exposed to cigarette smoke in early childhood. Thus, certain genes may

come to expression only when the person is exposed to certain risk factors. These results show clearly the need for inclusion of the environmental information in genetic studies of asthma and related diseases.

An important question of this study was to what extent the same genes play a role in asthma, eczema, and rhinitis. The genetic correlations ranged from 0.47 (asthma-rhinitis) to 0.62 (rhinitis-eczema), meaning that to some common genes play a role in more than one disease. It has to be mentioned that the genetic correlations were less than 1, thus there were also genetic influences unique to each disease. Our results agree with those of Lichtenstein & Svartengren [9], who examined asthma, eczema and hay fever in 7-9-year-old twins. In their study the genetic correlation between asthma and hay fever was 0.90, between asthma and eczema was 0.35 and between hay fever and eczema was 0.73. Although the sizes of the genetic correlations differ from our correlations, in both studies it was found that the phenotypic correlations were mainly genetically mediated.

In conclusion, the present study showed that additive genetic factors contributed to the variance of susceptibility to asthma, eczema, and allergy. The lack of shared environmental influences on the variability of asthma and allergic diseases may point to importance of gene-environment interactions. Therefore, future studies should focus on the importance of the interplay between genetic and environmental factors.

ACKNOWLEDGMENTS

This work was supported by NWO Grant numbers 575-25-006, 575-25-012 and 904-57-94 (Boomsma, P.I.) and by the Centre for Neurogenomics and Cognition Research (CNCR) of the Vrije Universiteit, Amsterdam.

REFERENCES

1. ISAAC, steering, committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitus, and atopic eczema: ISAAC. *Lancet* 1998: 351: 1225-1232.

2. Crane J, Wickens K, Beasley R, Fitzharris P. Asthma and allergy: a worldwide problem of meanings and management? *Allergy* 2002: 57: 663-672.

3. Los H, Postmus P, Boomsma D. Asthma genetics and intermediate phenotypes: A review from twin studies. *Twin Res* 2001: 4: 81-93.

4. Boomsma D, Busjahn A, Peltonen L. The classical twin study and beyond. *Nat Genet Rev* 2002:3:872-882.

5. Duffy D, Martin N, Battistutta D, Hopper J, Mathews J. Genetics of asthma and hay fever in Australian twins. *Am Rev Respir Dis* 1990: 142: 1351-1358.

6. Harris J, Magnus P, Samuelsen S, Tambs K. No evidence for effects of family environment on asthma. A retrospective study of Norwegian twins. *Am J Respir Crit Care Med* 1997: 156: 43-49.

7. Koeppen-Schomerus G, Stevenson J, Plomin R. Genes and environment in asthma: a study of 4 year old twins. *Arch Dis Child* 2001 : 85:398-400.

8. Laitinen T, Rasanen M, Kaprio J, Koskenvuo M, Laitinen L. Importance of genetic factors in adolescent asthma: a population-based twin-family study. *Am J Respir Crit Care Med* 1998: 157: 1073-1078.

9. Lichtenstein P, Svaertengren M. Genes, environments, and sex: factors of importance in atopic diseases in 7-9-year-old Swedish twins. *Allergy* 1997: 52: 1079-1086.

10. Nystad W, Røysamb E, Magnus P, Tambs K, Harris R. A comparison of genetic and environmental variance structures for asthma, hay fever and eczema with symptoms of the same diseases: a study of Norwegian twins. *Int J Epidemiol* 2005: 34: 1-8.

11. Skadhauge L, Christensen K, Kyvik K, Sigsgaard T. Genetic and environmental influence on asthma: a population-based study of 11,688 Danish twin pairs. *Eur Respir J* 1999: 13: 8-14.

12. Rasanen M, Laitinen T, Kaprio J, Koskenvuo M, Laitinen L. Hay fever--a Finnish nationwide study of adolescent twins and their parents. *Allergy* 1998: 53: 885-890.

13. Clarke J, Jenkins M, Hopper J, Carlin J, Mayne C, Clayton D, et al. Evidence for genetic associations between asthma, atopy, and bronchial hyperresonsiveness. *Am J Res Crit Care Med* 2000: 162: 2188-2193.

14. Hopper J, Murray C, Macaskill G, Mathews J. Twin concordance for a binary trait: III. A bivariate analysis of hay fever and asthma. *Genet Epidemiol* 1990: 7: 277-289.

15. Boomsma D, Vink J, Van Beijsterveldt C, de Geus E, Beem A, Mulder E, et al. Netherlands Twin Register: A focus on longitudinal research. *Twin Res* 2002: 5: 1-6.

16. Rietveld M, Van der Valk J, Bongers I, Stroet T, Slagboom P, Boomsma D. Zygosity diagnosis in young twins by parental report. *Twin Res* 2000: 3: 134-141.

17. Neale M, Boker S, Xie G, Maes H. *Mx: Statistical Modeling*. 5th ed: VCU Box 900126, Richmond, VA 23298: Department of Psychiatry, 1999.

18. Falconer DS, Mackay TFC. *Introcution to Quantitative Genetics*. 4th ed. London: Longman, 1996.

19. Neale MC, Cardon LR. *Methodology for Genetic Studies of Twins and Families*. Dordrecht, The Netherlands: Kluwer Academic Publishers BV, 1992.

20. Posthuma D, Boomsma D. Mx Scripts Library: Structural equation modeling scripts for twin and family data. *Behav Genet* 2005: 35: 499-505.

21. Poos MJR, Gijsen RR. Prevalentie, incidentie en sterfte naar leeftijd en geslacht. In: Volksgezondheid Toekomst Verkenning NKVBR, <http://www.nationaalkompas.nl>

Gezondheid en ziekte\ Ziekten en aandoeningen\ Ademhalingswegen\ Astma en COPD, editor.

22. Hirasing R, Aardoom H, van den Heuvel E, Sanavro F, Leeuwenburg J. Prevalentie van door ouders gerapporteerde chronische aandoeningen bij schoolkinderen. *Nederlands Tijdschrift Geneeskunde* 1995:139:934-938.

23. Meerwaldt R, Rodink R, Landaeta R, Aarts F, Brunekreef B, Gerritsen J, et al. A lower prevalence of atopy symptoms in children with type 1 diabetes mellitus. *Clin Exp Allergy* 2002: 32: 254-255.

24. Mohangoo A, van der Linden, M., Schellevis, F., & Raat, H. Prevalence estimates of asthmaor COPD from a health interview survey and from general practitioner registration: what's the difference? *Eur J Public Health* 2006: 16: 101-105.

25. Halvorsen T, Skadberg B, Eide G, Roksund O, Carlsen K, Bakke P. Pulmonary outcome in adolescents of extreme preterm birth: a regional cohort study. *Acta Paediatr* 2004: 93: 1294-1300.

26. McKeever T, Lewis S, Smith C, Collins J, Heatlie H, Frischer M, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. *Thorax* 2001: 56: 758-762.

27. Strachan D, Moran S, McInneny K, Smalls M. Reduced risk of hospital admission for childhood asthma among Scottish twins: record linkage study. *Brit Med J* 2000: 321: 732-733.

28. Boomsma D, Martin N. Gene-environment interactions. In: D'haenen H, Boer JAd, Willner P, editors. *Biological Psychiatry*. West Sussex: John Wiley & Sons, 2002: 181-187.

29. Colilla S, Nicolae D, Pluzhnikov A, Blumenthal M, Beaty T, Bleecker E, et al. Collaborative Study for the Genetics of Asthma. Evidence for gene-environment

interactions in a linkage study of asthma and smoking exposure. *J Allergy Clin Immun* 2003:111:840-846.

30. Meyers DA, Postma D, Stine OC, Koppelman GH, Ampleford EJ, Jongepier J, et al. Genome screen for asthma and bronchial hyperresponsiveness: interactions with passive smoke exposure. *J Allergy Clin Immun* 2005: 115: 1169-1175.

Table 1: Distribution (%) of asthma, eczema, and rhinitis across boys and girls and across birth cohort.

	Asthma		Eczema		Rhinitis	
	Boys	Girls	Boys	Girls	Boys	Girls
Cohort:	N = 8807	N = 9135	N = 8781	N = 9152	N = 8665	N = 9035
1986-1989	6.5%	4.0%	16.4%	14.8%	6.6%	4.5%
1990-1992	8.9%	7.3%	17.1%	16.7%	5.3%	3.4%
1993-1995	12.9%	8.0%	18.6%	15.4%	5.9%	3.6%
1996-1998	11.7%	9.0%	18.5%	16.6%	4.5%	3.7%
Total	10.2%	7.2%	17.7%	15.9%	5.6%	3.8%

Table 2: Twin correlations separately for very preterm, preterm and full-term pregnancies.

	MZ	DZ
Very preterm (<32 weeks)	N = 146	N = 217
Asthma	0.92	0.65
Eczema	0.88	0.36
Rhinitis	0.97	0.74
Preterm (>=32 weeks and <37 weeks)	N = 1089	N = 1806
Asthma	0.91	0.36
Eczema	0.86	0.21
Rhinitis	0.97	0.52
Full-term (>=37 weeks)	N = 1706	N = 3669
Asthma	0.91	0.43
Eczema	0.83	0.33
Rhinitis	0.93	0.53

Table 3: Twin correlations, cross trait correlations and cross trait cross twin correlations for asthma, eczema, and rhinitis across zygosity and sex groups.

	MZM	DZM	MZF	DZF	OS-mf	OS-fm
	N = 1286	N = 1394	N = 1509	N = 1343	N = 1392	N = 1346
			Twin correlations			
Asthma	0.89	0.37	0.92	0.47	0.40	0.44
Eczema	0.83	0.27	0.85	0.32	0.24	0.36
Rhinitis	0.93	0.55	0.97	0.37	0.61	0.54
			Within twin cross trait correlations			
Asthma-Eczema	0.45	0.34	0.37	0.33	0.35	0.28
Asthma-Rhinitis	0.48	0.48	0.49	0.52	0.44	0.52
Eczema-Rhinitis	0.38	0.43	0.37	0.35	0.32	0.41
			Cross trait cross twin correlations			
Asthma-Eczema	0.43	0.05	0.34	0.18	0.09	0.06
Asthma-Rhinitis	0.38	0.21	0.43	0.28	0.19	0.18
Eczema-Rhinitis	0.35	0.17	0.35	0.15	0.25	0.15

Note: OS refers to Opposite Sex twin pairs, mf refers to male as first born and female as second born, fm refers to female as first born and male as second born.

Table 4: Model fitting results of genetic analyses.

Univariate		Asthma	Eczema	Rhinitis
Full model		ACE	ADE	ADE
Comparisons to the full model				
	ΔDf	ΔX^2	ΔX^2	ΔX^2
No sex differences	2	1.386	0.408	0.905
Drop C (D)	1	0	18.627	0
Parameter estimates (95% CI)				
a^2		91 (82-93)	35 (13 – 57)	95 (78 – 97)
d^2		-	49 (26 – 72)	-
e^2		9 (6 – 13)	16 (13 – 20)	5 (3 – 8)
Bivariate		Asthma & eczema	Asthma & rhinitis	Eczema & rhinitis
r_g		0.55	0.47	0.62
r_e		0.18	0.73	0.38
% of phenotypic correlation explained by genetic and environmental factors				
Genetic		82%	88%	96%
Environmental		18%	12%	4%