UNIVERSITEIT
AMSTERDAM

# VU Research Portal

**Heritability of self-reported asthma and allergy: A study in adult Dutch twins, siblings and parents.**

Willemsen, G.; van Beijsterveldt, C.E.M.; van Baal, G.C.M.; Postma, D.; Boomsma, D.I.

**document version**
Publisher's PDF, also known as Version of record

**Link to publication in VU Research Portal**

# Heritability of Self-Reported Asthma and Allergy: A Study in Adult Dutch Twins, Siblings and Parents

Gonneke Willemsen,[1] Toos C. E. M. van Beijsterveldt,[1] Caroline G. C. M. van Baal,[2] Dirkje Postma,[3] and Dorret I. Boomsma[1]

[1] Department of Biological Psychology, VU University Amsterdam, Amsterdam, the Netherlands

[2] Department of Neurosciences, University Medical Center Utrecht, Utrecht, the Netherlands

[3] Department of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

The present study assessed the prevalence of asthma and allergy, and estimated the importance of genetic and environmental influences on asthma and allergy liability and their association. Longitudinal data on self-reported, doctor-diagnosed asthma and allergy were collected in over 14,000 individuals registered with the Netherlands Twin Register. Structural equation modeling was used for univariate and bivariate genetic analyses on data from twins, their siblings, and parents. Results showed no sex, age, and minimal birth cohort effects for asthma prevalence (11.8%). For allergy, prevalence was higher in women (19.8%) than in men (13.9%). Allergy prevalence at ages 22, 23, and 24 years increased from the 1970 to the 1980 birth cohort. The prevalence of allergy, but not of asthma, was higher in nontwin siblings than in twins. No assortative mating was observed. High (broad-sense) heritabilities were found for asthma (75%) and allergy (66%), with evidence for nonadditive genetic effects in asthma. The association between asthma and allergy (correlation = .65) was largely due to common genes (70%). No sex differences in genetic architecture were found. In conclusion, the prevalence of allergy but not of asthma increased in recent years. Individual differences in the liability to asthma, allergy and their co-occurrence are for a large part accounted for by differences in genetic background. Nonadditive gene action is important, which may have consequences for gene hunting strategies.

Asthma, a respiratory disease characterized by airway hyperresponsiveness, reversible airflow obstruction and bronchial hyperresponsiveness, is highly prevalent in Western societies. In the Netherlands 9.1% of the population in 2006 received asthma medication on doctor's prescription, while 7.6% reported to have suffered from asthma in the last year (Statistics Netherlands, www.cbs.nl). Yearly, asthma costs society more than 140 million Euros in medical care (Hoogendoorn et al., 2004) and though the death rate as a result of asthma is low in the Netherlands (76 persons in 2003, Netherlands Bureau of Statistics), these figures clearly demonstrate the burden of asthma on both individuals and society. The precise cause of asthma is still unknown, but the disorder is most likely a combination of environmental factors, such as air pollution and tobacco smoke exposure, and genetic factors (London, 2007; Ober & Hoffjan, 2006; Vercelli, 2004). Twin studies have shown heritability estimates for asthma to be high, ranging from 60% to 90% (e.g., Duffy et al., 1990; Harris et al., 1997; Koeppen-Schomerus et al., 2001; Laitinen et al., 1998; Skadhauge et al., 1999; van Beijsterveldt & Boomsma, 2007). Significant gene–environment interactions are likely to be present, probably representing the genetic regulation of immune responses to environmental factors and allergens and the tissue-repair processes which ultimately lead to asthma (Ober & Thompson, 2005; Yang et al., 2007).

Liability to asthma has a genetic component and multiple efforts have been made to identify the genes involved in asthma related processes. Association and linkage studies have implicated more than 100 genes in asthma, but few of these genes have consistently been replicated and the search for the asthma genes still continues (Bosse & Hudson, 2007; Ober & Hoffjan, 2006). This is a difficult and time-consuming undertaking, as asthma represents a complex genetic disease, with possibly many genes exerting small effects, interacting with other genes and with the environment (Finkelman & Vercelli, 2007). Gene finding may benefit from a better understanding of the underlying genetic architecture of asthma and its association with other disorders.

Asthma has been shown to be highly comorbid with allergy, a chronic inflammation that occurs when the immune system recognizes ubiquitous harmless substances as allergens and initiates complex immune defenses. In fact, asthma itself may result from immunological reactions, generally as the result of the production of IgE antibodies in response to low doses of allergens. In the case of IgE-mediated asthma, this is sometimes referred to as atopic asthma, as atopy generally indicates the genetic predisposition to become IgE-sensitized to allergens (Johansson et al., 2004). The terms allergy and atopy have been used somewhat inconsistently in the literature. In the present paper, when we refer to allergy, we refer to a hypersensitivity reaction which is initiated by an immunological mechanism, either IgE-mediated or non-IgE-mediated, that does not result in asthma. Like asthma, allergy is very prevalent in Western societies. Over the last two decades, the prevalence of asthma and allergy in both men and women has shown a steep increase, with figures recently becoming more stable. This increase is thought to reflect changes in environmental factors (Platts-Mills et al., 2006). Allergy has also been shown to be genetically influenced, with heritability estimates ranging from 35% to 90% (Duffy et al., 1990; Edfors-Lubs, 1971; Lichtenstein & Svartengren, 1997; Rasanen et al., 1998; Thomsen et al., 2006b; van Beijsterveld & Boomsma, 2007). Gene finding studies have implicated several genes in the development of allergy, in particular genes in the immunoglobulin pathways (Finkelman & Vecelli, 2007). The association between asthma and allergy may point to a common etiology, especially considering the fact that high sensitivity to specific allergens, such as the house dust mite, has also been found to be associated with asthma (Platts-Mills, 2002). This common etiology may represent the expression of shared genes, increasing both the risk of allergy and asthma. Twin studies addressing this possibility estimated that common genes explained 70 to 85% of the association between asthma and allergy (Lichtenstein & Svaertengren, 1997; Thomsen et al., 2006a; van Beijsterveldt & Boomsma, 2007). In the present study we will seek replication of these research findings in a sample of Dutch adults, including not only twins, but also their family members, and explore whether nonadditive (dominant) genetic effects are present. To this aim we use data on self-reported asthma and allergy collected in twins, their siblings, and their parents registered with the Netherlands Twin Register (NTR). The inclusion of siblings and parents increases the power to detect possible dominant genetic effects, while it also allows for the testing of prevalence differences between twins and nontwins and the presence of assortative mating (Boomsma et al., 2002a).

Since data on asthma and allergy were collected longitudinally over a period of 11 years, this provided the opportunity to examine possible effects over time and sex and age differences. The aim of the present study was therefore twofold, to (1) assess the prevalence of asthma and allergy as a function of sex, age and birth cohort, and (2) determine the importance of genetic and environmental influences on the liability for asthma and allergy, and the association between them.

## Methods

### Participants

This study is part of an ongoing longitudinal survey study on health, lifestyle and personality (for a detailed description, see Boomsma et al., 2002b, 2006). Every 2 to 3 years twins and their family members who are registered with the NTR receive a questionnaire booklet. Surveys were sent in 1991, 1993, 1995, 1997, 2000, 2002, and 2004. For this study we concentrate on the data collected in the first six questionnaires, from 1991 to 2002, spanning an 11-year time period. Twins were included in every wave of the data collection, parents of the twins received the first three and the last survey, and siblings received the last four surveys. A total of 19,002 subjects consisting of monozygotic (MZ) and dizygotic (DZ) twin pairs, their parents, their siblings and their spouses participated at least once in the survey study (see Table 1). We discarded the data of triplets, half-siblings, spouses of twins, second twin pairs in the family, third or higher order (nontwin) siblings in the family, nonbiological parents, and subjects with unknown sex or birth date. There were 725 MZM pairs (+ 76 single twins), 1277 MZF pairs (+ 121 single twins), 528

**Table 1**

Number of Participants that Filled Out 1 to 6 Questionnaires

| N questionnaires | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Twins | 2760 | 2146 | 1463 | 1131 | 829 | 409 |
| Siblings | 1057 | 842 | 601 | 304 | 0 | 0 |
| Fathers | 920 | 665 | 730 | 389 | 0 | 0 |
| Mothers | 1024 | 722 | 787 | 444 | 0 | 0 |
| Spouses | 1457 | 282 | 0 | 0 | 0 | 0 |
| Other* | 24 | 10 | 1 | 0 | 1 | 0 |

Note: *Other = triplets, half-siblings, nonbiological parents

Parents were asked to participate in questionnaires 1, 2, 3 and 6

Siblings were asked to participate in questionnaires 3 to 6, spouses in 5 and 6

Gonneke Willemsen, Toos C. E. M. van Beijsterveldt, Caroline G. C. M. van Baal, Dirkje Postma, and Dorret I. Boomsma

**Table 2**

Overview of the Questionnaires Used to Establish Asthma and Allergy Status at Ages 22, 23 and 24 Years

| Age | 1970 | 1971 | 1972 | 1973 | 1974 | 1975 | 1976 | 1977 | 1978 | 1979 | 1980 |
|-----|------|------|------|------|------|------|------|------|------|------|------|
| 22 |  | 1993 |  | 1995 |  | 1997 |  |  | 2000 |  | 2002 |
| 23 | 1993 |  | 1995 |  | 1997 |  |  | 2000 |  | 2002 |  |
| 24 |  | 1995 |  | 1997 |  |  | 2000 |  | 2002 |  |  |

DZM pairs (+ 50 single twins), 750 DZF pairs (+86 single twins) and 1133 DOS pairs (+ 47 male and 122 female single twins). The sample further contained 995 nontwin brothers and 1108 nontwin sisters, 2196 fathers, and 2854 mothers. The total number of subjects in the present study was 16,481, 42.2% being male. The mean (SD) age of the fathers was 50.5 (6.1) years, and of the mothers 48.1 (6.1) years. Twins and siblings showed a rather skewed distribution with ages ranging from 8 to 91 years old, but the majority (83.2%) was born between 1960 and 1980. Mean age of the twins was 25.3 years, (SD = 11.19), mean age of siblings was 28.6 years (SD = 10.79).

**Zygosity**

Twin zygosity was determined from DNA or blood polymorphisms (in 29% of the same-sex twin pairs), or from survey questions. Every survey asked each of the twins whether they were alike in eye, hair, and face color and facial shape. Twins also indicated whether they were as a child mistaken for each other by their parents, other family members, and strangers. Parents were also asked these questions. Based on the answers, twin zygosity was determined for every occasion. Next, all individual judgments were combined into one measure of twin zygosity. When there was inconsistency over time and persons, the majority of the judgments determined the final outcome. The correspondence between questionnaire zygosity and DNA zygosity for the same-sex pairs was 99% in this sample.

**Asthma and Allergy Assessment**

In all six questionnaires, participants received the same questions on asthma and allergy: 'Has a doctor ever concluded that you suffer from asthma or bronchitis' and: 'Has a doctor ever concluded that you suffer from allergy or hay fever?' Subjects could answer yes or no to these questions.

A diagnosis for asthma and for allergy was obtained by combining the answers to these two questions across the possible one to six questionnaires. This score was based on consensus in the answers: if all answers were the same, the composite score was that answer. If participants answered 'Yes' in some questionnaires, but 'No' in others, then the composite score was the answer that was given most often, but only if this was done two times more than the other answer. Therefore, 3 × Yes and 1 × No resulted in Yes, but 3 × Yes and 2 × No or 2 × Yes and 1 × No resulted in a missing value. Using this approach, data on

asthma were obtained for 14,177 participants, and on allergy for 13,823 participants.

The longitudinal survey data were used to assess asthma and allergy status at ages 22, 23, and 24 years for participants born between 1970 and 1980. Surveys were filled out in 1991, 1993, 1995, 1997, 2000, and 2002. Therefore, asthma and allergy status at age 23 for someone born in 1970 was obtained from the 1993 questionnaire, whereas asthma status at the same age for someone born in 1977 was obtained from the 2000 questionnaire. These data were used to investigate a possible increase in prevalence of asthma and allergy in recent years. Because six questionnaires have been sent out, we could have a maximum of six different birth cohorts to assess asthma and allergy status at a particular age. We could only use data of birth cohorts 1970 to 1980, because these birth cohorts had a substantial number of participants (over 400 for each cohort). This resulted in five prevalence estimates for asthma and allergy at ages 22 and 23, and four at age 24 years (see Table 2).

**Statistical Analyses**

Kruskal-Wallis tests (SPSS) were used to test whether prevalences differed between men and women, between three different age cohorts (born before 1954, born between 1954 and 1974 and born after 1974), and between twins and nontwin siblings.

For participants born between 1970 and 1980, the Kruskal-Wallis test was used to assess whether asthma or allergy prevalence at ages 22, 23, or 24 years differed between the four or five birth cohorts that provided data on those prevalences.

**Univariate Genetic Analyses of Asthma and Allergy**

Threshold models for dichotomous data were used to obtain correlations between family members for asthma and for allergy liability. These tetrachoric correlations give the correlation between relatives on the underlying liability distribution (means = 0, SDs = 1). The threshold which divides the participants into 'affected' and 'unaffected' is based on the sample prevalences. The pattern of answers in a family (e.g., the 2 × 2 contingency tables for a twin pair) provides the information to estimate the correlations between the liabilities of family members. These correlations, combined with the biological and environmental associations between family members, can then be used to estimate the proportion of vari-
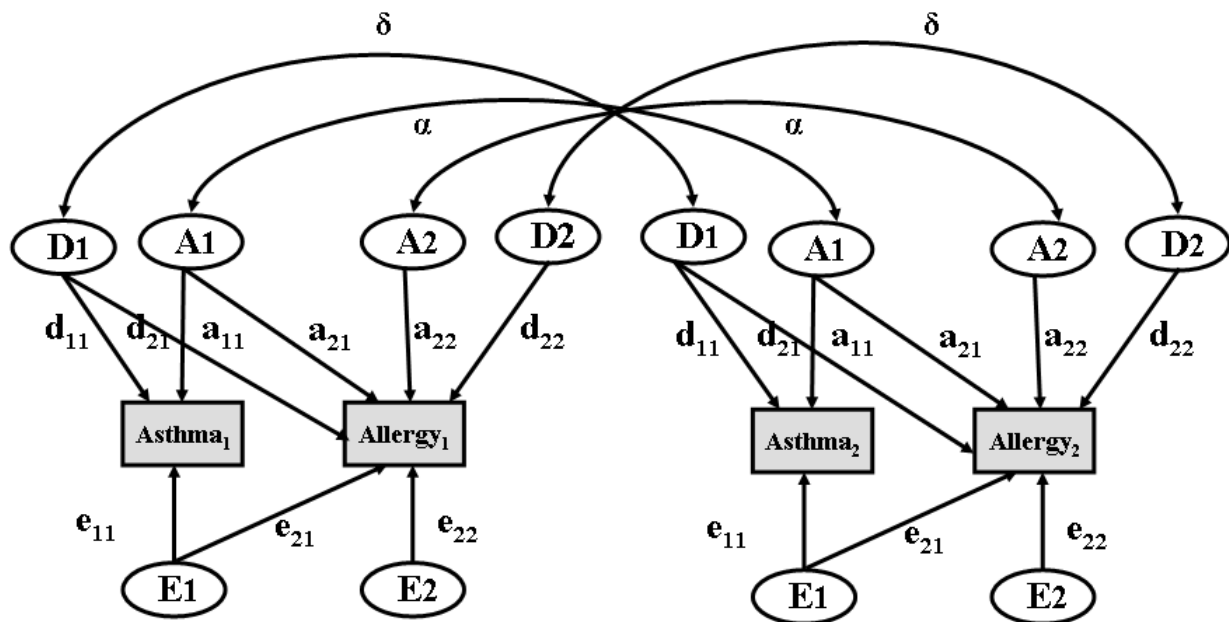
**Figure 1**

Bivariate ADE model for 2 family members. A, D, and E are latent factors (with unit variance). A1, D1, and E1 influence asthma and allergy, while A2, D2, and E2 influence allergy only. Latent factors are correlated in family members depending on their relatedness ($\delta$ = 1 for MZ twins, $\delta$ = .25 for DZ twins/siblings and $\delta$ = 0 for parents-offspring; $\alpha$ = 1 for MZ twins and $\alpha$ = .5 for all other first degree relatives).

ance in the liability distribution that can be attributed to different genetic and environmental sources (Falconer & Mackay, 1996).

The pattern of familial correlations, with MZ correlations being more than twice the DZ, sibling and parent-offspring correlations, suggests that common environment does not play a role in asthma and allergy, while dominant genetic factors may be present. Components of variance in liability, which were tested in this study therefore included additive genetic, nonadditive (dominant) genetic and unique environmental components. The correlations between spouses (parents of twins) were estimated separately and constrained at zero in the genetic models. The covariance between parents and offspring was modeled to be half the additive genetic variance ($0.5*a^2$). The covariance between DZ twins and other siblings (including twin-sibling pairs) was half the additive genetic variance plus a quarter of the dominant genetic variance ($0.5*a^2 + 0.25*d^2$). The covariance between MZ twins was modeled as additive plus dominant genetic variance ($a^2 + d^2$; Falconer & Mackay, 1996). Because the variance of the liability distribution was constrained at one, the covariances equal the correlations in family members. Parameters $a^2$ and $d^2$ were estimated and $e^2$ was obtained as $1 - (a^2 + d^2)$.

### Bivariate Genetic Analyses of Asthma and Allergy

In a similar way, bivariate analyses to assess the etiology of the association between asthma and allergy

liabilities were carried out. This was done by a Cholesky decomposition, as shown in Figure 1. In this model, for every source of variance (A, D, and E) one factor which accounts for covariation between asthma and allergy was defined, and one factor which accounted for allergy specific influences. The cross-trait cross-subject correlations (e.g., correlation between asthma in family member 1 with allergy in family member 2) provide the critical information for the decomposition of the phenotypic correlation between asthma and allergy into the three different sources. As with twin correlations, if MZ cross correlations are approximately twice the DZ cross correlations, then the association between asthma and allergy will be due to a common additive genetic factor. Using this approach it could be assessed whether covariation between the two liability distributions existed, and to which source of variance (A, D, E) it could be attributed. We first tested if parameter d21 could be omitted, and at subsequent models whether d21 and d11 could be omitted, and finally whether a21 could be omitted.

Parameter estimates were obtained with maximum likelihood estimation for ordinal data, using the software package Mx (Neale et al., 2003).

### Results

#### Prevalences

Table 3 shows the asthma prevalence and allergy prevalence for males and females, and for participants in three age cohorts (born before 1954, born between 1954 and 1974, and born after 1974).

Gonneke Willemsen, Toos C. E. M. van Beijsterveldt, Caroline G. C. M. van Baal, Dirkje Postma, and Dorret I. Boomsma

**Table 3**

Prevalence (%) of Asthma and Allergy in Men, Women and the Total Sample as a Function of Birth Cohort

| | Asthma | | | | | | Allergy | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Both | | Men | | Women | | Both | |
| Age cohort | % | N | % | N | % | N | % | N | % | N | % | N |
| Before 1954 | 9.9 | 2102 | 12.7 | 2602 | 11.5 | 4704 | 9.0 | 2090 | 16.3 | 2558 | 13.0 | 4648 |
| 1954–1974 | 11.8 | 1873 | 11.8 | 2897 | 11.8 | 4770 | 16.9 | 1818 | 23.6 | 2805 | 21.0 | 4623 |
| After 1974 | 12.3 | 2064 | 11.9 | 2639 | 12.0 | 4703 | 16.3 | 2027 | 19.0 | 2525 | 17.8 | 4552 |
| All age cohorts | 11.3 | 6039 | 12.1 | 8138 | 11.8 | 14177 | 13.9 | 5935 | 19.8 | 7888 | 17.2 | 13823 |

The prevalences of asthma were not significantly different for males and females, $\chi^2(1) = 2.234$, $p = .135$, or for different age cohorts, $\chi^2(2) = 0.711$, $p = .701$. Females had more frequently allergy, $\chi^2(1) = 80.762$, $p < .0001$, as did participants in the middle age cohort, $\chi^2(1) = 104.351$, $p < .0001$. This latter outcome may be a result of a combination of age of onset and birth cohort effect: prevalence of allergy may have increased in the last decades, resulting in higher prevalences for younger participants. The youngest age cohort though may have a lower prevalence because these participants may not have reached their age of onset for allergy yet.

To disentangle these effects, we assessed the prevalence of asthma and allergy at age 22, 23, and 24 years for participants of different birth cohorts (data assessed in different questionnaires, as described in the method section). Figure 2 shows the prevalences for the 11 birth cohorts. We found a significant increase across the years for allergy at ages 22 years, $\chi^2(4) = 9.720$, $p = .045$, 23 years, $\chi^2(4) = 10.167$, $p = .038$, and 24 years, $\chi^2(3) = 8.693$, $p = .034$, which is visualized as a linear effect in the figure (solid lines). For asthma, the increase in prevalences across the years was significant at age 23 years, $\chi^2(4) = 11.248$, $p = .024$, but not at ages 22, $\chi^2(4) = 4.031$, $p = .402$, or 24 years, $\chi^2(3) = 7.168$, $p = .067$.

Differences in prevalences between twins and nontwin siblings were not significant for asthma, $\chi^2(1) = 1.632$, $p = .201$, but nontwin siblings showed a higher prevalence of allergy (23.3%) than twins, 18.2%; $\chi^2(1) = 27.163$, $p < .0001$, $N(\text{sibs}) = 2046$, $N(\text{twins}) = 7506$.
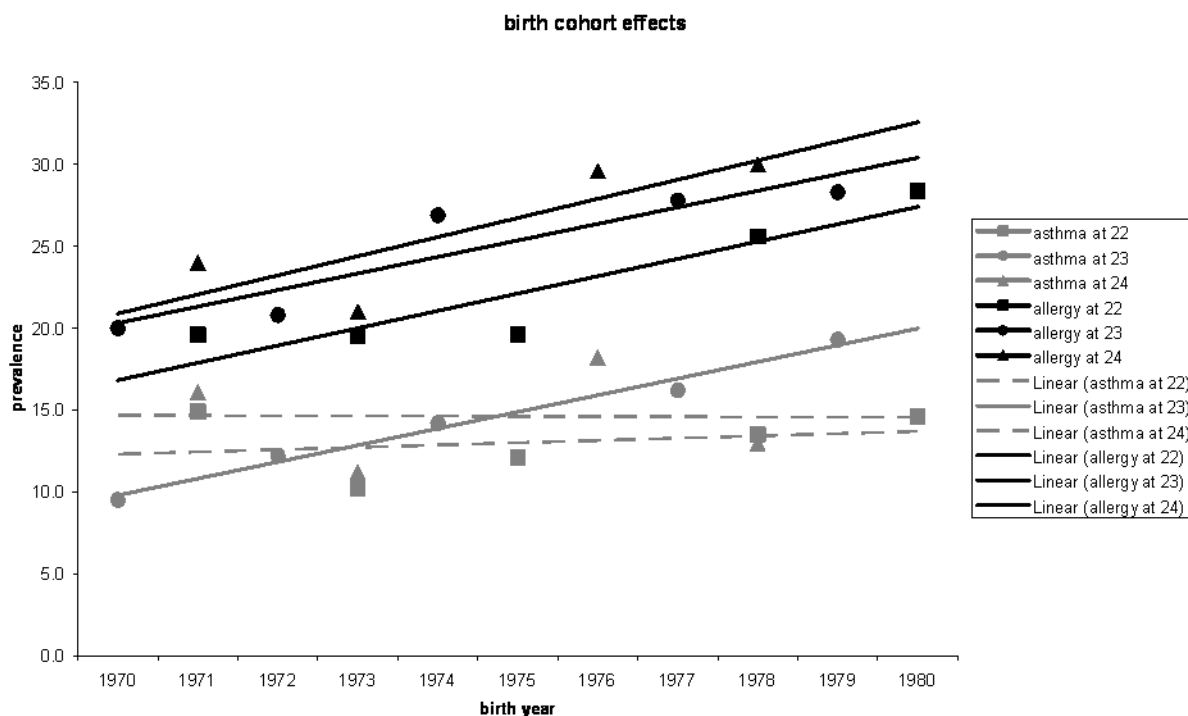


**birth cohort effects**

**Figure 2**

Prevalence of asthma (grey) and allergy (black) at ages 22, 23, and 24 years for 11 birth cohorts (1970 to 1980). Lines indicate a significant increase of prevalence due to birth cohorts (Kruskal Wallis test, $p < .05$), dotted lines are not significant.

**Table 4**

Family Structure for Families Included in the Within-Family Correlations and Genetic Modeling

| | Asthma | | | Allergy | | | Astma and allergy | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2 twins, 1 sib | 2 twins, no sib | 1 twin, 1 sib | 2 twins, 1 sib | 2 twins, no sib | 1 twin, 1 sib | 2 twins, 1 sib | 2 twins, no sib | 1 twin, 1 sib |
| MZM | 222 | 322 | 49 | 208 | 313 | 51 | 178 | 298 | 63 |
| MZF | 360 | 597 | 78 | 315 | 571 | 94 | 270 | 528 | 108 |
| DZM | 178 | 222 | 34 | 157 | 217 | 49 | 138 | 206 | 57 |
| DZF | 209 | 351 | 49 | 207 | 319 | 49 | 172 | 304 | 58 |
| DOS | 351 | 441 | 89 | 308 | 419 | 118 | 265 | 389 | 133 |
| 2 Parents | 707 | 542 | 112 | 605 | 516 | 153 | 462 | 412 | 159 |
| Father | 844 | 682 | 139 | 744 | 650 | 192 | 603 | 569 | 213 |
| Mother | 915 | 1005 | 161 | 792 | 967 | 216 | 642 | 849 | 235 |

Note: *N* in the table indicates the number of families

**Table 5**

Familial Correlations for Asthma and Allergy and the Familial Cross Correlations

| | Asthma | Allergy | Asthma and Allergy |
|---|---|---|---|
| Parents | .06 (−.07 to .02) | .05 (−.09 to .18) | .07 (−.03 to .17) |
| MZ twins | .76 (.75 to .81) | .66 (.60 to .67) | .43 (.40 to .48) |
| MZM | .77 (.65 to .86) | .69 (.55 to .80) | .46 (.33 to .56) |
| MZF | .77 (.68 to .84) | .67 (.57 to .74) | .41 (.32 to .45) |
| DZ twins | .22 (.19 to .31) | .19 (.14 to .28) | .15 (.10 to .23) |
| DZM | .24 (.01 to .46) | .16 (−.07 to .38) | .21 (.05 to .29) |
| DZF | .36 (.15 to .54) | .12 (−.06 to .19) | .18 (.03 to .31) |
| DOS | .14 (−.05 to .32) | .24 (.09 to .38) | .11 (−.01 to .22) |
| Siblings | .15 (.11 to .18) | .26 (.18 to .33) | .15 (.08 to .17) |
| Brothers | −.11 (−.36 to .15) | .22 (.05 to .38) | .15 (.01 to .29) |
| Sisters | .25 (.09 to .40) | .35 (.23 to .46) | .18 (.08 to .29) |
| Opposite sex | .02 (−.12 to .16) | .24 (.14 to .33) | .11 (.03 to .20) |
| Parent–offspring | .23 (.17 to .29) | .30 (.25 to .35) | .16 (.12 to .20) |
| Father–son | .20 (.11 to .30) | .30 (.22 to .38) | .19 (.13 to .26) |
| Father–daughter | .18 (.08 to .28) | .26 (.17 to .34) | .18 (.11 to .25) |
| Mother–son | .26 (.18 to .34) | .30 (.24 to .37) | .17 (.11 to .23) |
| Mother–daughter | .26 (.17 to .34) | .33 (.26 to .39) | .17 (.11 to .23) |

Note: Familial cross correlations are for those with asthma in one family member and allergy in the other family member

### Genetic Analyses

The number of twin pairs with sibs and parents with data for the genetic analyses are presented in Table 4. We calculated parent-offspring, sibling and twin correlations as presented in Table 5. The spousal correlations, calculated between the father and mother of the twin, were very low for asthma and allergy and not significantly different from 0, indicating an absence of assortative mating. MZ correlations were the same for males and females, and were more than twice the DZ correlations, indicating a substantial influence of genetic factors, which most likely are partly nonadditive (dominance). Sibling correlations substantiated this effect for asthma because they were lower than half the MZ correlations. However, parent-offspring correlations were rather high, and are accounted for only by additive genetic factors, which would argue against a large contribution of genetic dominance. For allergy, the influence of nonadditive genetic influences was not supported by sibling or parent-offspring correlations, but the importance of genetic influences remained obvious. The overall phenotypic correlation between asthma and allergy was .65, and as can been from the correlations in Table 5, MZ correlations on the presence of both asthma and allergy were more than twice as high as correlations between dizygotic twin pairs, twin-sibling, and parent-offspring pairs, again suggesting dominant genetic effects may underlie this association.

Gonneke Willemsen, Toos C. E. M. van Beijsterveldt, Caroline G. C. M. van Baal, Dirkje Postma, and Dorret I. Boomsma

**Table 6**

Univariate Model–Fitting Results and Parameter Estimates (Proportion of Variance explained by A, D and E)

| Asthma model | $a^2$ | $d^2$ | $e^2$ | −2 LL | df | $\varnothing\chi^2$ | $\varnothing df$ | p |
|---|---|---|---|---|---|---|---|---|
| ADE | 41% | 34% | 25% | 9284.681 | 13,356 | | | |
| AE | 63% | — | 37% | 9309.564 | 13,357 | 24.883 | 1 | .000 |
| E | — | — | 100% | 9583.580 | 13,358 | 274.016 | 1 | .000 |
| Allergy model | $a^2$ | $d^2$ | $e^2$ | −2 LL | df | $\varnothing\chi^2$ | $\varnothing df$ | p |
| ADE | .56 | .09 | .35 | 11,288.440 | 13,028 | | | |
| AE | .62 | — | .38 | 11,290.910 | 13,029 | 2.469 | 1 | .116 |
| E | — | — | 1.00 | 11,658.480 | 13,030 | 367.571 | 1 | .000 |

Note: $a^2$ = proportion of variance explained by additive genetic factors

$d^2$ = proportion of variance explained by dominant genetic factors

$e^2$ = proportion of variance explained by unique environmental factors

−2 LL = −2 loglikelihood

$\varnothing\chi^2$ = differences in the chi square −2 loglikelihood

$\varnothing df$ = difference in the degrees of freedom.

Table 6 summarizes the univariate analyses of asthma and allergy. Genetic influences were always significant. For asthma, the inclusion of a nonadditive genetic factor (D) in the model improved the fit significantly, resulting in a broad heritability estimate of 75% (41% additive, 34% nonadditive). For allergy, estimates of the full ADE model showed some nonadditive genetic influences (9%), but these were not significant at the .05 significance level. Broad heritability was 62% in the best fitting model (65% in the full model).

Asthma and allergy may partly be influenced by the same underlying influences. A bivariate analysis was carried out to assess the correlations (phenotypic, additive, and nonadditive genetic and environmental) between the two phenotypes. In addition, in a bivariate design the power to detect nonadditive genetic influences on allergy is improved.

**Table 7**

Bivariate Model-Fitting Results (A) and Parameter Estimates (B, Proportion of Variance Explained by A, D and E)

| A | | | $r^a$ | $r^d$ | $r^e$ | −2 LL | df | Compared to model | $\varnothing\chi^2$ | $\varnothing df$ | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Full model | AcAsDcDsEcEs | .69 | .63 | .65 | 19,508.790 | 26,431 | | | | |
| 2 | No specific D | AcAsDc——EcEs | .65 | 1 | .62 | 19,510.781 | 26,432 | 1 | 1.991 | 1 | .158 |
| 3 | No D on allergy | AcAsDast——EcEs | .76 | — | .74 | 19,517.505 | 26,433 | 2 | 6.724 | 1 | .010 |
| 4 | No D at all | AcAs————EcEs | .64 | — | .64 | 19,540.902 | 26,434 | 3 | 23.397 | 1 | .000 |
| 5 | No specific genetic influences | Ac——Dc——EcEs | 1.00 | 1.00 | .67 | 19,529.344 | 26,433 | 2 | 18.563 | 1 | .000 |

| B | | | Var (asthma) | | | Var (allergy) | | | Covar (asthma, allergy) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | $a^2$ | $d^2$ | $e^2$ | $a^2$ | $d^2$ | $e^2$ | $a^2$ | $d^2$ | $e^2$ |
| 1 | Full model | AcAsDcDsEcEs | 38% | 36% | 26% | 52% | 13% | 35% | 48% | 21% | 31% |
| 2 | No specific D | AcAsDc——EcEs | 38% | 36% | 26% | 56% | 6% | 38% | 47% | 23% | 30% |
| 3 | No D on allergy | AcAsDast——EcEs | 42% | 28% | 29% | 59% | 0% | 41% | 60% | 0% | 40% |
| 4 | No D at all | AcAs————EcEs | 60% | 0% | 40% | 59% | 0% | 41% | 60% | 0% | 40% |
| 5 | No specific genetic influences | Ac——Dc——EcEs | 23% | 51% | 26% | 58% | 1% | 41% | 57% | 9% | 34% |

Note: A — $r^a$ = correlation between additive genetic effects

$r^d$ = correlation between dominant genetic effects

$r^e$ = correlation between unique environmental effects

−2 LL = −2 loglikelihood

$\varnothing\chi^2$ = differences in the chi square −2 loglikelihood

$\varnothing df$ = difference in the degrees of freedom

B — $a^2$ = proportion of variance explained by additive genetic factors

$d^2$ = proportion of variance explained by dominant genetic factors

$e^2$ = proportion of variance explained by unique environmental factors.

Results of the bivariate analyses are shown in Table 7A and B, with a representation of the full model tested in Figure 1. The only reduction allowed was to omit the specific dominant genetic influences on allergy (Model 2 vs. Model 1). The same dominance factor influenced asthma and allergy, accounting for 36% of the variance in asthma and 6% of the variance in allergy. It was not allowed to omit all genetic dominance influences for allergy in this bivariate model, as opposed to the univariate model, which reflects the higher statistical power to detect it. Specific additive genetic influences existed, which indicated that asthma and allergy are not one disease at a genetic level. The additive genetic correlation was .65 in the best fitting model (Model 2). Seventy per cent of the covariance between asthma and allergy was genetic (47% additive, 23% nonadditive). The remaining covariance was due to unique environmental factors.

## Discussion

The first aim of the present study was to assess the prevalence of asthma and allergy as a function of sex, age, and birth cohort. The prevalence of asthma did not vary with age and sex and occurred in 11.8% of this Dutch population-based twin-family sample. This is somewhat higher than the figures reported by Statistics Netherlands. Several reasons may account for this difference. In our study, we present data on cases, who report that they received a doctor's diagnosis of asthma, independently of medication use, which will therefore result in a higher prevalence of asthma. Furthermore, self-report measures are generally higher than the prevalence indicated by physicians reports (Mohangoo et al., 2006), though we did specifically indicate that a physician needed to have made the diagnosis. In addition, we asked for lifetime diagnosis of asthma, while the population statistics reflect the number of individuals that experienced asthma in the previous year.

Still, one may argue that twins have an increased risk of developing asthma, since they are more often born premature, and prematurity itself constitutes a risk for asthma (Halvorsen et al., 2004). However, we did not find any differences between twins and their nontwin siblings, which argues against a specific twin-increased risk for asthma.

We also did not find any sex or age differences in asthma prevalence. The increase in prevalence across the years was significant, but only at age 23 years and not at age 22 or 24. It is hard to interpret this result, as it seems unlikely that societal changes would only influence such a narrow age band.

Allergy was overall more prevalent in females than in males (19.8 of the females vs. 13.9% of the males in the total sample). Though this is higher than the 5.8% of the Dutch population that use medication for allergy in 2006 (Statistics Netherlands, www.cbs.nl), the same arguments uphold as for asthma. That is, we used self-reported lifetime history of allergy, not medication use, and the difference between having an allergy diagnosis and using medication for allergy will be relatively large. Moreover, within the Dutch population the percentage of medication use is higher among the age groups that were most represented among our sample. In 2006 13.9% of the 15- to 24-year-olds and 9.8% of the 25- to 44-year-olds used medication for allergy, with women reporting more frequently that they used medication than men, though the sex difference was not as prominent as in our sample (Statistics Netherlands, www.cbs.nl). In addition, Van de Ven (2006) reported a lifetime prevalence of allergy of 52.6% among Dutch adolescents, indicating the wide range of reported prevalence of allergy in the Netherlands. Allergy prevalence was higher in the birth cohort 1954–1974, especially in women. For the 1970–1980 birth cohort, allergy prevalence increased across the years by 15%, reflecting the general trend in Dutch society.

Interestingly, nontwin siblings more often reported allergy than twins. Since the majority of the nontwin siblings was older than the twins (76%), this finding may be taken as support for the hypothesis that that the presence of older siblings is protective and decreases the risk of hypersensitivity to allergens due to exposure to infections in early life (McKeever et al., 2001).

Spousal correlations for asthma and allergy were small and not significant, which suggests that there is no assortative mating for asthma and allergy.

Our second aim was to determine the importance of genetic and environmental influences on the liability for asthma and allergy, and the association between them. The parent-offspring correlations for asthma, allergy, and their co-existence ranged from .13 to .33, with somewhat higher correlations for allergy than for asthma and asthma-allergy. There were no significant differences between father–offspring and mother–offspring, though there was a trend for mother–offspring correlations to be higher than father–offspring correlations for asthma.

There was a trend for same-sex DZ twin correlations to be higher than sibling correlations. This could point to influences of age on the resemblance, but then parent–offspring correlations would have been expected to be even lower. It may also indicate some other twin-specific common environmental influence, which is likely to be sex specific, since the twin-sibling difference is not seen in the opposite-sex correlations. Opposite-sex correlations in twins and in siblings did differ significantly from those in same-sex twins and siblings and are rather low, which could be interpreted as sex-specific gene expression. However, this pattern does not repeat itself in the parent offspring correlations, and is therefore hard to interpret. Because the differences in the correlations were not significant according to the confidence intervals, these effects were not taken into account in the models.

Gonneke Willemsen, Toos C. E. M. van Beijsterveldt, Caroline G. C. M. van Baal, Dirkje Postma, and Dorret I. Boomsma

Both asthma and allergy were found to be highly heritable. Broad heritability for asthma was 75% and dominant genetic effects were found to be important, explaining 34% of the individual differences in asthma prevalence. For allergy, heritability was somewhat lower than for asthma, with a broad heritability estimate of 62%. Dominant genetic effects were suggested for allergy in the univariate analyses, but these were not significant. However, in the bivariate analyses of asthma and allergy, which have an increased power to detect dominance, dominant effects for allergy were significant, though small (6%). These broad heritability estimates are in line with those reported by other studies, but the present data further confirm the presence of dominant genetic effects in these disorders. Including gene–gene interactions in gene finding strategies may enhance the possibility of finding the relevant genes. Millstein et al. (2006) incorporated gene–gene interaction into a testing strategy for case-control studies and identified three genes in the oxidative stress pathway relevant for asthma and allergy. It is likely that the incorporation of such gene–gene interactions may further help determine the pathways leading to asthma and allergy.

One of the main questions we wanted to answer was whether the association between asthma and allergy in adults was due to common genes. We found evidence for high comorbidity of asthma and allergy as their phenotypic correlation was .65. The higher MZ correlations compared to correlations within the DZ twin and sibling pairs and parent-offspring pairs, suggest that there is a large genetic component to this association, and further indicate the likelihood of dominance. In accordance with other research findings (Duffy et al., 1990; Lichtenstein & Svaertengren, 1997; Nystad et al., 2005; van Beijsterveldt & Boomsma, 2007), our results confirm that the co-existence of allergy and asthma is for the largest part due to an overlap in genes. Our study results further indicate that these genes interact as dominant genetic effects, accounting for 23% of the overlap between asthma and allergy. When trying to locate the genes responsible for these processes that characterize both asthma and allergy, one needs to take gene-gene interaction into account. However, the fact that unique genetic and environmental effects were also present for both asthma and allergy indicates that, although their genetic etiology is partly the same, they are still two distinct diseases.

Some limitations of the present study should be noted. First, we used self-reported diagnoses for asthma and allergy, which may have resulted in a number of false positives. We could have restricted asthma and allergy diagnoses to only those who used medication, but this would mean only severe cases would receive a diagnosis. Especially for allergy, this would have meant a significant reduction in prevalence, resulting in a large number of false negatives (individuals who suffer from allergy but do not take medication). Second, the sample was restricted in age range and birth cohort, encompassing only individuals aged 22 to 24 born between 1970 and 1980, and these results therefore may not readily be generalized to older populations, who grew up under different environmental circumstances. This may be particularly relevant considering the fact that gene–environment interaction is thought to play a role in asthma and allergy (Yang et al., 2007). Third, we used lifetime prevalence of asthma and allergy, which does not take age of onset into account. We therefore do not distinguish between individuals who are still suffering from asthma or allergy, and those who suffered from asthma or allergy in the past as a child, but have not had any recurrence of the disease since childhood. Last, the results of our study show that asthma and allergy share part of their etiology, but to understand the precise nature of this common genetic pathway, we need to further study the underlying mechanisms. For instance, Ferreira et al. (2006) studied the genetic overlap between different asthma phenotypes, and such a study could be extended to include additional phenotypes related to and overlapping with allergy.

In conclusion, asthma and allergy are two highly prevalent and heritable disorders. The co-occurrence of the two disorders is due in large part to shared genes. These genes are likely to interact in a nonadditive manner, which will have implications for gene finding strategies.

## References

Boomsma, D., Busjahn, A., & Peltonen, L. (2002a). The classical twin study and beyond. *Nature Reviews. Genetics, 3,* 872–882.

Boomsma, D. I., de Geus, E. J., Vink, J. M., Stubbe, J. H., Distel, M. A., Hottenga, J. J., Posthuma, D., van Beijsterveldt, T. C., Hudziak, J. J., Bartels, M., & Willemsen, G. (2006). Netherlands Twin Register: From twins to twin families. *Twin Research and Human Genetics, 9,* 849–857.

Boomsma, D. I., Vink, J. M., van Beijsterveldt, T. C., de Geus, E. J., Beem, A. L., Mulder, E. J., Derks, E. M., Riese, H., Willemsen, G. A., Bartels, M., van den Berg, M., Kupper, N. H., Polderman, T. J., Posthuma, D., Rietveld, M. J., Stubbe, J. H., Knol, L. I., Stroet, T., & van Baal, G. C. (2002b). Netherlands Twin Register: A focus on longitudinal research. *Twin Research, 5,* 401–406.

Bosse, Y., & Hudson, T. J. (2007). Toward a comprehensive set of asthma susceptibility genes. *Annual Review of Medicine, 58,* 171–184.

Duffy, D., Martin, N., Battistutta, D., Hopper, J., & Mathews, J. (1990). Genetics of asthma and hay fever in Australian twins. *American Review of Respiratory Disease, 142,* 1351–1358.

Edfors-Lubs, M. L. (1971). Allergy in 7000 twin pairs. *Acta Allergologica, 26,* 249–285.

Falconer, D. S., & Mackay, T. F. C. (1996). *Introduction to quantitative genetics* (4th ed.). Harlow, Essex: Longmans Green.

Ferreira, M. A. R., O'Gorman, L. O., Le Souëf, P., Burton, P. R., Toelle, B. G., Robertson, C. F., Martin, N. G., & Duffy, D. L. (2006). Variance components analyses of multiple asthma traits in a large sample of Australian families ascertained through a twin proband. *Allergy, 61,* 245–253.

Finkelman, F. D., & Vercelli, D. (2007). Advances in asthma, allergy mechanisms, and genetics in 2006. *Journal of Allergy and Clinical Immunology, 120,* 544–550.

Halvorsen, T., Skadberg, B. T., Eide, G.E., Røksund, O.D., Carlsen, K. H., & Bakke, P. (2004). Pulmonary outcome in adolescents of extreme preterm birth: A regional cohort study. *Acta Paediatrica, 93,* 1294–1300.

Harris, J., Magnus, P., Samuelsen, S., & Tambs, K. (1997). No evidence for effects of family environment on asthma. A retrospective study of Norwegian twins. *American Journal of Respiratory and Critical Care Medicine, 156,* 43–49.

Hoogendoorn, E. J. I., Feenstra, T. L., & Rutten-van Mölken, M. P. M. H. (2004). *Inventarisatie van het gebruik en de kosten van zorg voor astma en COPD in Nederland* [Resource use and costs of care for treating asthma and COPD in the Netherlands]. RIVM rapport 260604001/2004.

Johansson, S. G., Bieber, T., Dahl, R., Friedmann, P. S., Lanier, B. Q., Lockey, R. F., Motala, C., Ortega Martell, J. A., Platts-Mills, T. A., Ring, J., Thien, F., Van Cauwenberge, P., & Williams, H. C. (2004). Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *Journal of Allergy and Clinical Immunology, 113,* 832–836.

Koeppen-Schomerus, G., Stevenson, J., & Plomin, R. (2001). Genes and environment in asthma: A study of 4-year-old twins. *Archives of Disease in Childhood, 85,* 398–400.

Laitinen, T., Rasanen, M., Kaprio, J., Koskenvuo, M., & Laitinen, L. (1998). Importance of genetic factors in adolescent asthma: A population-based twin-family study. *American Journal of Respiratory and Critical Care Medicine, 157,* 1073–1078.

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

London, S. J. (2007). Gene-air pollution interactions in asthma. *Proceedings of the American Thoracic Society, 4,* 217–220.

McKeever, T. M., Lewis, S. A., Smith, C., Collins, J., Heatlie, H., Frischer, M., & Hubbard, R. (2001). Siblings, multiple births, and the incidence of allergic disease: A birth cohort study using the West Midlands general practice research database. *Thorax, 56,* 758–762.

Millstein, J., Conti, D. V., Gilliland, F. D., & Gauderman, W. J. (2006). A testing framework for identifying susceptibility genes in the presence of epistasis. *American Journal of Human Genetics, 78,* 15–27.

Mohangoo, A., van der Linden, M., Schellevis, F., & Raat, H. (2006). Prevalence estimates of asthma or COPD from a health interview survey and from general practitioner registration: What's the difference? *European Journal of Public Health, 16,* 101–105.

Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2003) *Mx: Statistical modeling* (6th ed.). Richmond, VA: Department of Psychiatry.

Nystad, W., Røysamb, E., Magnus, P., Tambs, K., & Harris, R. (2005). 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. *International Journal of Epidemiology, 34,* 1–8.

Ober, C., & Hoffjan, S. (2006). Asthma genetics 2006: The long and winding road to gene discovery. *Genes and Immunity, 7,* 95–100.

Ober, C., & Thompson, E. E. (2005). Rethinking genetic models of asthma: The role of environmental modifiers. *Current Opinion in Immunology, 17,* 670–678.

Platts-Mills, T. A. (2002). The role of allergens in the induction of asthma. *Current Allergy and Asthma Reports, 2,* 175–180.

Platts-Mills, T. A., Erwin, E. A., Woodfolk, J. A., & Heymann, P. W. (2006). Environmental factors influencing allergy and asthma. *Chemical Immunology and Allergy, 91,* 3–15.

Rasanen, M., Laitinen, T., Kaprio, J., Koskenvuo, M., & Laitinen, L. (1998). Hay fever: A Finnish nationwide study of adolescent twins and their parents. *Allergy, 53,* 885–890.

Skadhauge, L., Christensen, K., Kyvik, K., & Sigsgaard, T. (1999). Genetic and environmental influence on asthma: A population-based study of 11,688 Danish twin pairs. *The European Respiratory Journal, 13,* 8–14.

Thomsen, S. F., Ulrik, C. S., Kyvik, K. O., Skadhauge, L. R., Steffensen, I., & Backer, V. (2006a). Findings on the atopic triad from a Danish twin registry. *The International Journal of Tuberculosis and Lung Disease, 10,* 1268–1272.

Thomsen, S. F., Ulrik, C. S., Kyvik, K. O., von Bornemann Hjelmborg, J., Skadhauge, L. R., Steffensen, I., & Backer, V. (2006b). Genetic and environmental contributions to hay fever among young adult twins. *Respiratory Medicine, 100,* 2177–2182.

van Beijsterveldt, C. E. M., & Boomsma, D. I. (2007). Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. *European Respiratory Journal, 29,* 516–521.

van de Ven, M. O., van den Eijnden, R. J., & Engels, R. C. (2006). Atopic diseases and related risk factors among Dutch adolescents. *European Journal of Public Health, 16,* 549–558.

Vercelli, D. (2004). Genetics, epigenetics, and the environment: Switching, buffering, releasing. *Journal of Allergy and Clinical Immunology, 113,* 381–386.

Yang, I. A., Savarimuthu, S., Kim, S. T., Holloway, J. W., Bell, S. C., & Fong, K. M. (2007). Gene-environmental interaction in asthma. *Current Opinion in Allergy and Clinical Immunology, 7,* 75–82.