

GENETIC EPIDEMIOLOGY

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

Wenche Nystad,* Espen Røysamb, Per Magnus, Kristian Tambs and Jennifer R Harris

Accepted 1 March 2005

Background We compared patterns of genetic and environmental influences on variation in liability for asthma, hay fever and eczema with those for symptoms of the same diseases, and determined how common sets of genes and environmental factors contribute to the relationship between diseases and symptoms among Norwegian twins.

Methods Analyses were based on self-reported asthma, hay fever and eczema and symptoms of the same diseases among 3334 pairs of Norwegian twins aged 18–35 years. Structural equation modelling was conducted to estimate the genetic and environmental variance structures.

Results For all diseases the concordances and the twin correlations were higher among monozygotic than among dizygotic twins. The results of the modelling confirmed that genetic effects were substantial for the diseases, and were more moderate for symptoms. The phenotypic correlation between disease and symptom was 0.67 for asthma and wheeze (a/w), 0.64 for hay fever and sneeze (hf/s), and 0.54 for eczema and itch (e/i). Decomposition of these correlations into genetic (G) and environmental (E) pathways revealed that $G = 0.48$ and $E = 0.19$ for a/w, $G = 0.40$ and $E = 0.24$ for hf/s, and $G = 0.34$ and $E = 0.20$ for e/i. For the diseases, the specific sources of genetic variance accounted for more variation than the specific environmental variance. Variance decomposition revealed that specific sources of variance were primarily explained by genetic effects for diseases and by environmental influences for symptoms.

Conclusions Genetic effects account for greater variation in reported diseases than symptoms. Co-occurrence of diseases and symptoms is mainly explained by genetic effects common to both phenotypes, but non-shared environment is also important.

Keywords Genes, environment, atopic diseases, symptoms

Atopic diseases such as asthma, hay fever and eczema are among the most common chronic diseases in children and adolescents. Formulating hypotheses about the links between possible aetiological factors and these diseases requires unambiguous disease definitions. However, clinical manifestation fluctuates in severity over time, and these disorders may not always present

in a way that is sufficiently distinct from the normal state or from other conditions. Furthermore, aetiology may be heterogeneous reflecting multiple pathophysiological mechanisms. These factors contribute to the difficulties in establishing precise definitions, classifications and terminology. Consequently, most epidemiological research has been based upon a cluster of atopy related phenotypes for which the clinical and aetiological boundaries are unclear.

The majority of prevalence studies have relied on questionnaires using self or parental reports of a disease diagnosis or of symptoms as the outcomes.^{1–3} The International

Division of Epidemiology, Norwegian Institute of Public Health, Nydalen, Oslo, Norway.

* Corresponding author. Division of Epidemiology, Norwegian Institute of Public Health, PO Box 4404 Nydalen, N-0403 Oslo, Norway.
E-mail: wenche.nystad@fhi.no

Study of Asthma and Allergies in Childhood (ISAAC) and the European Community Respiratory Health Survey (ECRHS) was founded to maximize the value of epidemiological research of asthma and allergic disease by establishing a standardized methodology and facilitating international collaboration.^{2,3} The developers of these questionnaires recognized the importance of including items to assess symptomatology.³⁻⁵

The chief symptoms used to assess asthma in such questionnaires are wheezing and whistling in the chest. However, using symptoms as an outcome for asthma in ISAAC consistently yielded a higher prevalence of wheeze in all countries when compared with parental- or self-reports of asthma in the same studies.^{6,7} Furthermore, the interpretation of a question of wheezing may differ between centres.⁸ The results of the ECRHS study also report a higher prevalence of self-reported wheezing compared with asthma.⁹ These results question the extent to which discrepancies reflect individual differences in reporting symptoms vs diseases and also underscore the importance of determining whether reported symptoms and disease reflect the same underlying disorder with the same aetiological factors. Using self-report of asthma vs wheeze as an outcome in epidemiological studies subsequently led to different results, and such differences should be considered when interpreting results.

A valuable approach to the question of differential diagnosis is to study whether the same sources of individual variation underlie liability to disease and symptoms. Twin studies are widely used to estimate genetic and environmental contribution to disease liability and provide a powerful design to explore differential aetiology. Results of several studies indicate the importance of genetic influences on variation in asthma liability, and environmental influences appear to contribute to at least 25% of the total variance.¹⁰ Furthermore, the heritability and concordance results from these population-based twin studies of asthma are strikingly similar using reported asthma as the outcome.¹¹⁻¹⁴ Similar comparisons of other allergic diseases have been less commonly reported. Few twin studies contain data that permit testing for differences in the pattern of genetic and environmental influences for atopic diseases assessed by symptomatology vs self-reported disease. To our knowledge there are no previous twin studies that included self-reports of symptoms and diseases enabling comparisons of asthma, hay fever and eczema and their respective symptoms of wheeze, sneeze and itch. The methodology of ISAAC offers such an opportunity.³ We conducted a twin study that included the standardized ISAAC questionnaire on wheezing, rhinitis and eczema.

The objective of this study is to compare patterns of genetic and environmental influences on variation in liability for self-reported asthma, hay fever and eczema with those for symptoms of the same diseases. Furthermore, we investigate genetic and environmental sources of covariation between the diseases and their respective symptoms.

Methods

Sample

The data are from a population-based sample of Norwegian twins participating in a study on health and development at the Norwegian Institute of Public Health (NIPH) in Oslo. All twins born from 1967 to 1979 were identified through the Medical

Birth Registry ($n = 15\,370$). Pairs in which both twins were alive and residing in Norway were recruited into the NIPH programme of research. Two questionnaire studies have been conducted so far, in 1992 (cohorts born 1967-1974) and in 1998 (cohorts born 1967-1979). A total of 12 700 twins were sent the questionnaire in 1998.¹⁵ The individual response rate was 63% and included 3334 pairs. Zygosity classification is described elsewhere¹⁶ and was based upon questionnaire methodology using seven items that have been shown to correctly classify 97% of the pairs when compared with serological markers.¹⁷ The distribution of pairs by zygosity and sex is provided in Table 1.

Diseases and symptoms

The questionnaire included an illness checklist with items inquiring if they had asthma, hay fever or eczema. The checklist was prefaced with 'have you now or have you ever had, any of the following illnesses' where asthma, hay fever and atopic eczema were items on the list. The symptoms were measured by the standardized ISAAC core questionnaire on wheezing, rhinitis and eczema.³ The questions analysed related to: wheezing—'Have you had wheezing or whistling in the chest in the past 12 months?'; Sneezing—'In the past 12 months, have you had a problem with sneezing, or a runny or blocked nose when you did not have a cold or a flu?'; Itch (required a positive response to the following two questions)—'Have you ever had an itchy rash which was coming and going for at least six months?', 'Have you had this itchy rash at any time in the past 12 months?'.

Analyses

The prevalence of asthma, wheezing, hay fever, sneezing, eczema and itch were estimated in the total sample and in groups based on zygosity and sex. Twin resemblance was measured by co-twin correlations in groups stratified by zygosity and sex. In these calculations each pair is treated as a class, and the correlations represent the proportion of total variance (between and within) accounted for by between-pair variance. Tetrachoric correlations, calculated in PRELIS.¹⁸ The tetrachoric correlation is used as a measure of the intraclass correlation between two normally distributed measures, which are both expressed as a dichotomy.¹⁹ It is estimated as the Pearson correlation between the corresponding continuous latent trait variables assumed to underlie the outcomes. So in this case it represents the correlation between the normally distributed liability for the diseases and symptoms. Interpretation of the intraclass correlations is based on biometric models specifying how genes and environment contribute to twin similarity or differences in identical [monozygotic (MZ)] and fraternal [dizygotic (DZ)] pairs. Structural equation modelling procedures using Mx were used to estimate the genetic and environmental components of variance for asthma, hay fever, eczema and for symptoms for the same diseases.²⁰ These models are widely used with twin data and applications are detailed elsewhere.^{12,21}

We estimated additive (A) and non-additive (D) genetic effects, plus shared (C) and non-shared (E) environmental influences. A refers to the additive effects of the alleles at a locus, D refers to intralocus gene interactions, C contributes to twin resemblance regardless of zygosity, whereas (E) are unique

effects contributing only to within-pair differences for a trait. Broad-sense heritability refers to the percent of the phenotypic variation that is accounted for by all genetic effects (additive and non-additive), and narrow sense heritability is the percent of phenotypic variation explained by additive genetic effects. In order to resolve the variance components model biometrical expectations are specified that reflect the degree of genetic similarity and shared sources of environmental influence between the twins in different zygosity classes. MZ twins share all of their genes in common and thereby are perfectly correlated for the additive and dominant genetic effects. DZ twins share, on average, 50% of their segregating genes. This translates to a correlation of 0.5 between additive genetic influences and 0.25 for dominant genetic influences between members of DZ pairs. Common environment is perfectly correlated between twins in both zygosity groups whereas non-shared environment only contributes to differences between twins. Based upon this parameterization, the equations for the expected variances and twin-covariances are as follows:

$$VP = a^2 + d^2 + c^2 + e^2 = A + D + C + E \quad (1)$$

$$rMZ = a^2 + d^2 + c^2 \quad (2)$$

$$rDZ = 0.5a^2 + 0.25d^2 + c^2 \quad (3)$$

where VP is variance of the phenotype, a is the effect of additive genetic factors, d the effect of non-additive genetic factors, c the effect of common environment, and e the effect of non-shared environment. The squares of these effects yield total variance accounted for by each factor, typically denoted A , D , C and E . Thus, Equation 1 shows that the variance of a given phenotype is the sum of the squared effects of the four basic factors. As shown in Equation 2, the expected twin-co-twin correlation for MZ twins is the sum of the squared a , d and c effects. Equation 3 shows the expected twin-co-twin correlation for DZ twins.

These models were fit to the data by means of asymptotic weighted least squares estimation using Mx statistical program. The modelling procedure tests the expected variance-covariance matrices generated from the biometric models against the observed data pattern. First, the full ADE model was analysed and then nested submodels, AE and DE, were tested. The chi-square (χ^2) statistic is given by $N-1$ times the minimum value of the fit function for the specified model, thus reflecting the discrepancy between the model and the observed data. The degree of freedom (df) indicates the total number of observed statistics minus the number of free parameters to be estimated. Two alternative models can be formally tested against each other using the chi-square difference test ($\Delta\chi^2$, with Δdf), when the two models are nested (i.e. one model is a restricted version of the other).²¹ Model fit was also evaluated by using the Akaike's Information Criteria (AIC).²² AIC equals χ^2 minus twice the number of degrees of freedom, and reflects both goodness of fit and parsimony of the models. A lower value of AIC is a better fit model, and a difference of 2 is generally regarded as significant. Profile likelihood tests were conducted to test whether the genetic effects were significantly stronger for diseases compared with symptoms. This procedure constrains the heritability of one phenotype (e.g. disease) to be equal to the estimated heritability of another phenotype (e.g. the corresponding symptom), and this model is then compared with a relaxed model that allows the heritability to be freely estimated. The χ^2 difference between

the models on 1 df tests whether the unconstrained model provides a significantly better fit.

Extension of the univariate model to a bivariate analysis also allows the covariances between the phenotypes to be partitioned into genetic and environmental components. A bivariate model was used to investigate whether the underlying genetic and environmental contributions are common for the disease and symptom.²¹ The phenotypic correlation is decomposed into component genetic and environmental pathways linking the two phenotypes. For instance, the additive genetic pathway is the product $h_1 \times r_G \times h_2$, where h_1 is the square root of the heritability for the disease and h_2 represents the square root of the heritability for the symptom, and r_G is the correlation between genetic effects for these two phenotypes. Similar pathways are calculated for shared and non-shared environmental effects. Independent factor models were tested, which constrained the effects of the common factors to be equal for both phenotypes, while the unique effects of genes and environmental factors were freely estimated. This model allows for total variation in liability to disease or symptoms to be parsed into genetic and environmental sources common to both measures and unique to each measure.

Results

Prevalence

Prevalence rates were greater for the symptoms than for the diseases, and were 8.1% (537/6668) for asthma, 15.8% (1052/6668) for wheezing, 13.9% (925/6668) for hay fever, 31.8% (2122/6668) for sneezing, 6.0% (402/6668) for atopic eczema and 14.9% (992/6668) for itch. There was no evidence of significant prevalence difference across zygosity for any of these measures.

Twin similarity

Tables 1 (asthma and wheezing), 2 (hay fever and sneezing) and 3 (eczema and itch) contain the number of discordant and concordant affected pairs, probandwise concordance, and tetrachoric correlations for the five groups defined by zygosity and sex groups. For all disease categories (asthma, hay fever and eczema), the concordances and the correlations were consistently higher among MZ than among DZ twins. This indicates that the genetic effects were important in the pathogenesis of asthma, hay fever and eczema. A similar pattern was found for each of the reported symptoms. However, the differences between the MZ and DZ correlations were not as great as was found for the diseases.

Model fitting: univariate results

Univariate model fitting results are presented in Table 4 (asthma and wheezing), (hay fever and sneezing) and (eczema and itch). These results confirmed the pattern of effects indicated by the tetrachoric correlations. Among the models tested, a model including genetic dominance and non-shared environment effects (DE model) provided the best overall fit according to the AIC. However, genetic dominance in the absence of genetic additivity is rare, and this study may have too little statistical power to distinguish between these two effects. The results of the modelling indicate that genetic effects were substantial for the atopic diseases (asthma, hay fever and eczema), and were

Table 1 Probandwise concordance rates and intraclass correlations for asthma and wheeze

Group	Pairs (<i>n</i>)	Cases (<i>n</i>)	Discordant pairs (<i>n</i>)	Concordant pairs (<i>n</i>)	Probandwise concordance	Tetrachoric intraclass correlations
Asthma						
MZm	526	75	41	17	0.45	0.729
DZm	397	52	44	4	0.15	0.281
MZf	777	131	73	29	0.44	0.695
DZf	655	109	97	6	0.11	0.089
DZu	979	170	140	15	0.18	0.251
Wheeze						
MZm	526	125	79	23	0.37	0.532
DZm	397	106	84	11	0.21	0.192
MZf	777	246	142	52	0.42	0.552
DZf	655	255	189	33	0.26	0.157
DZu	979	320	252	34	0.21	0.124

Cases = number of persons with asthma and wheeze.

Table 2 Probandwise concordance rates and intraclass correlations for hay fever and sneeze

Group	pairs (<i>n</i>)	Cases (<i>n</i>)	Discordant pairs (<i>n</i>)	Concordant pairs (<i>n</i>)	Probandwise concordance	Tetrachoric intraclass correlations
Hay fever						
MZm	526	159	81	39	0.49	0.659
DZm	397	121	95	13	0.21	0.161
MZf	777	205	103	51	0.50	0.696
DZf	655	178	136	21	0.24	0.253
DZu	979	262	210	26	0.20	0.171
Sneeze						
MZm	526	320	166	77	0.48	0.410
DZm	397	233	157	38	0.33	0.080
MZf	777	482	224	129	0.54	0.510
DZf	655	478	278	100	0.42	0.138
DZu	979	609	407	101	0.33	0.053

Cases = number of persons with respectively hay fever and sneeze.

Table 3 Probandwise concordance rates and intraclass correlations for eczema and itch

Group	Pairs (<i>n</i>)	Cases (<i>n</i>)	Discordant pairs (<i>n</i>)	Concordant pairs (<i>n</i>)	Probandwise concordance	Tetrachoric intraclass correlations
Eczema						
MZm	526	51	29	11	0.43	0.748
DZm	397	35	33	1	0.06	0.063
MZf	777	127	71	28	0.44	0.700
DZf	655	84	76	4	0.10	0.1187
DZu	979	105	95	5	0.10	0.218
Itch						
MZm	526	144	106	19	0.26	0.332
DZm	397	93	79	7	0.15	0.135
MZf	777	234	156	39	0.33	0.414
DZf	655	221	183	19	0.17	0.009
DZu	979	300	238	31	0.21	0.155

Cases = number of persons with respectively eczema and itch.

Table 4 Genetic and environmental variance estimates and model fit statistics for asthma and wheeze, hay fever and sneeze and eczema and itch

Model	A	D	E	χ^2	df	P	AIC
Asthma							
ADE	0.13	0.58	0.29	1.54	3	0.67	-4.46
AE	0.68		0.32	5.95	4	0.20	-2.06
DE		0.71	0.29	1.78	4	0.78	-6.22
Wheeze							
ADE	0.04	0.50	0.45	0.32	3	0.96	-5.68
AE	0.49		0.51	5.91	4	0.21	-2.09
DE		0.55	0.45	0.37	4	0.99	-7.63
Hay fever							
ADE	0.10	0.58	0.32	0.85	3	0.84	-5.15
AE	0.64		0.36	7.94	4	0.09	-0.06
DE		0.69	0.31	1.11	4	0.89	-6.89
Sneeze							
ADE	–	0.47	0.53	3.18	3	0.37	-2.82
AE	0.41		0.59	15.06	4	0.005	7.06
DE		0.47	0.53	3.18	4	0.53	-4.82
Eczema							
ADE	–	0.72	0.28	0.77	3	0.86	-5.23
AE	0.69		0.31	5.71	4	0.22	-2.29
DE		0.72	0.28	0.77	4	0.94	-7.23
Itch							
ADE	0.02	0.36	0.62	2.41	3	0.49	-3.59
AE	0.34		0.66	4.79	4	0.31	-3.21
DE		0.38	0.62	2.43	4	0.66	-5.58

A, additive genetic effects; D, non-additive genetic effects; C, shared environmental influences; E, non-shared environmental influences; χ^2 , model fit, Chi-square statistics; df, degrees of freedom; AIC, the Akaike's Information Criteria.

more moderate for the symptoms. The heritability estimates were 0.71 (95% confidence interval (CI) 0.62–0.80) for asthma, 0.69 (0.61–0.76) for hay fever and 0.72 (0.62–0.81) for eczema. In contrast, the heritability estimates were 0.55 (0.46–0.64) for wheezing, 0.47 (0.39–0.54) for sneezing and 0.38 (0.28–0.49) for itch. The 95% CIs indicate that the genetic effects were significantly stronger, and the environmental effects were weaker for diseases than for symptoms. The environmental effects were 0.29 (0.19–0.38) for asthma, 0.31 (0.23–0.40) for hay fever and 0.28 (0.18–0.39) for eczema, whereas the effects were 0.45 (0.36–0.55) for wheezing, 0.53 (0.45–0.62) for sneezing, and 0.62 (0.51–0.73) for itch. Shared environmental influences were not important for any of the phenotypes. In summary, genetic effects are greater for the diseases than the symptom outcomes, and environmental influences are more important for the symptom outcomes. The significance of these findings was also confirmed by formal testing using the profile likelihood test ($P < 0.001$, for all tests).

Model fitting: bivariate results

The next step in the analysis was to investigate the nature of the association between the diseases and their respective symptoms.

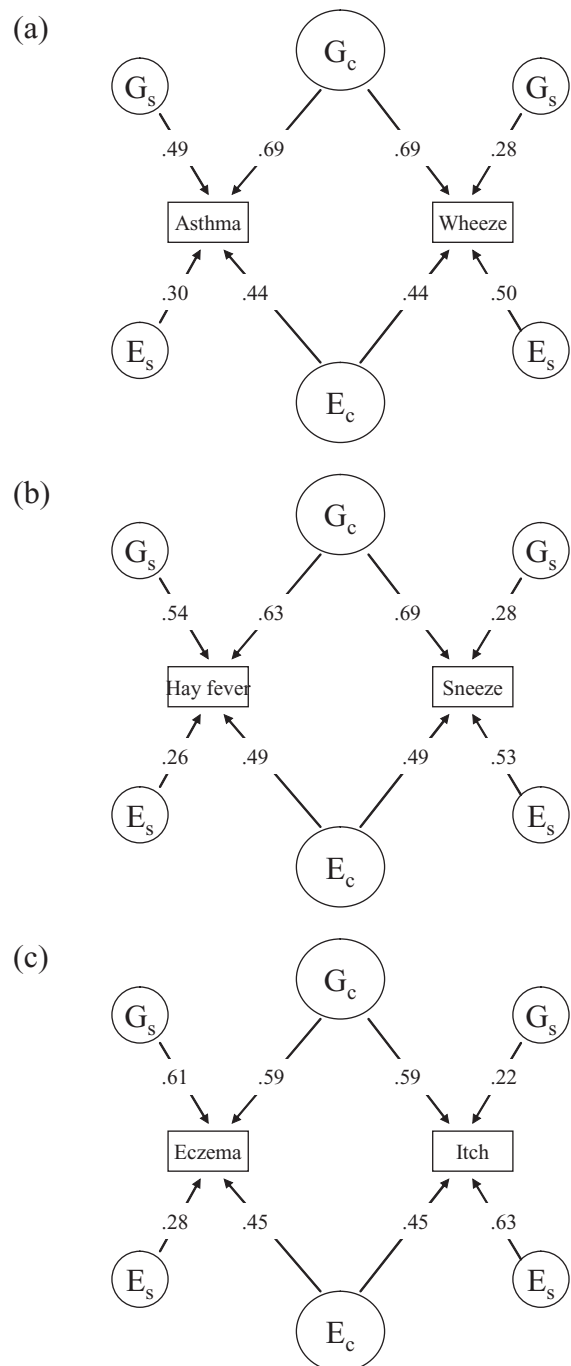


Figure 1 The effects of genetic factors common (G_c) to the two phenotypes (asthma and wheeze (a), genetic effects specific for each phenotype (G_s), environmental factors common to the phenotypes (E_c), and environmental factors specific for the phenotypes (E_s). Effects are shown as standardized coefficients. Squared effects yield explained variance (e.g. total genetic variance in Asthma is $0.49^2 + 0.69^2 = 0.71$). The same effects are shown for hay fever and sneeze (b) and eczema and itch (c)

The estimates in Figure 1 describe the degree to which the total variance in liability for the phenotypes are attributable to genetic and environmental influences that are either common or unique to each phenotype. In general, more than half of the

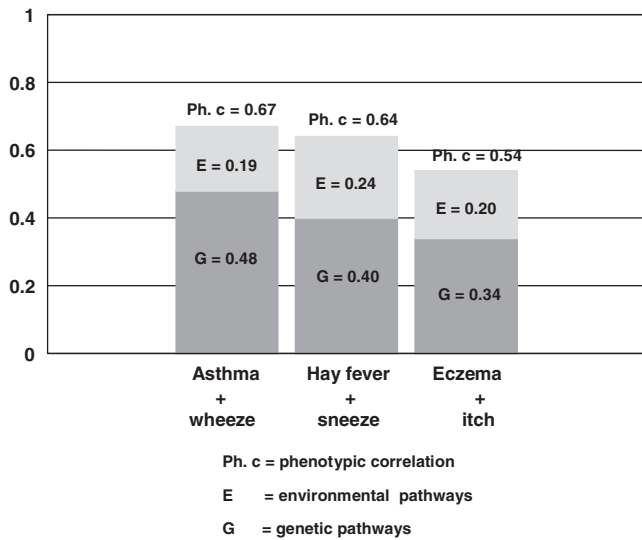


Figure 2 Bivariate analyses. The height of the bars in the figure corresponds to the magnitude of the tetrachoric correlations measuring the phenotypic relationship between disease and symptom. The bars are partitioned into components reflecting portions of the phenotypic correlation that are accounted for by genetic (G), which is A and D combined, and environmental (E) pathways

variance is due to common sources of genetic and environmental influence for diseases and symptoms. Differences emerge between diseases and symptoms in the factors that explain the specific sources of variation. Among the diseases, genetic effects account for most of the specific sources of variation, whereas for symptoms non-shared environment accounts for most of the specific sources of variation.

Figure 2 presents the results that decompose the phenotypic correlation into common genetic and environmental pathways. The height of the bars in the figure corresponds to the magnitude of the tetrachoric correlations measuring the phenotypic relationship between disease and symptom. The bars are partitioned into components reflecting portions of the phenotypic correlation that are accounted for by genetic (G), which is A and D combined, and environmental (E) pathways. Decomposition of the phenotypic correlation between asthma and wheezing (0.67) revealed that the genetic pathway is 0.48 and the environmental pathway is 0.19. This translates into 72% of the phenotypic correlation being mediated through genes and the rest is explained by non-shared environment. For the phenotypic correlation between hay fever and sneezing (0.64), common genes contribute with 0.40, and the environmental pathway is 0.24. Only 62% of the phenotypic correlation is mediated through genes and the rest is explained by non-shared environment. For eczema and itch, which had the lowest phenotypic correlation (0.54), the contribution of genes was 0.34 and the environmental pathway is 0.20, 63% of the phenotypic correlation is mediated through genes and the rest is explained by non-shared environment.

Discussion

This is the first twin study of asthma and allergy to estimate genetic and environmental influences on variation in liability

for self-reports of atopic diseases vs symptoms of the same diseases. The main finding is that the genetic and environmental variance structures vary for atopic diseases that have been differentially assessed by self-reported disease vs symptomatology. The results suggest that there might be differential aetiology for symptoms and disease.

Several previous twin studies report that genetic factors contribute importantly to atopic diseases. Heritability estimates are wide and ranged from 0.33 for hay fever among boys aged 7–9 years to 0.79 for asthma among twins aged 27–41 years.^{11–13,23} Most other twin studies report heritability results for asthma consistent with ours of about 0.75.¹⁰ But few twin studies also include hay fever and eczema.^{12,23,24} No previous studies addressed our question concerning differences in heritability between diseases and respective symptomatology. A specific focus of this paper was to explore whether common underlying genetic and environmental effects contributed to self-reports of symptoms vs disease.

In their study of female twins using wheezing as an outcome, Strachan *et al.* found no zygosity differences in probandwise concordance rates.²⁴ Duffy *et al.* reported estimates of heritability for asthma or wheezing of ~60% in women and 75% in men.¹² Those results may be affected due to the shift in the diagnostic threshold that was used, which included asthma or wheezing. A lower heritability of asthma (including asthma or wheeze) among women may indicate sex differences, or may signal sex differences in reporting asthma and wheeze. If women are more likely to report wheeze than asthma, the genetic effects will be weaker among women compared with men.

It is important to assess symptomatology. In clinical practice, a diagnosis of asthma, for example, usually arises from a history of recurrent exacerbation often provoked by exogenous factors such as allergens, irritants, exercise, and virus infections, and may thus be influenced by the doctor's readiness to diagnose wheezing illness as asthma. Thus, standardized questionnaires including several items of symptoms were developed and facilitate international collaboration. However, it is likely that questions regarding symptoms are ambiguous. The results of several studies using the ISAAC questionnaire showed that the prevalence of reported symptoms compared with reports of the illness varied both within and between countries.^{6–8} A recent report indicated also that a written question of wheezing was interpreted differently from the audio-visual presentation of the symptom in ISAAC.⁸ Another complicating factor is that the characteristics of wheeze, its relation with asthma, and its risk factors change with age.²⁵ These findings suggest that reported symptoms and disease may reflect two different phenotypes with differential aetiology.

An alternative interpretation is that our finding of substantially different heritabilities for the diseases and the corresponding symptoms might be due to different degrees of reliability for the two sets of measures. If symptom reporting is more prone to error then this would lead to an inflation of environmental factors. This follows from the notion that random error contributes only to variances but not to the twin covariances. Thus, twin similarity is explained by systematic variance, whereas twin differences can be due to both systematic and random variance. If this interpretation is valid the disease and symptom measures might be indicators of the same underlying phenomenon, but the symptom measures are

characterized by a higher degree of random error. In that case it still seems fair to conclude that the single item symptom measures are not optimal indicators of the phenotype, though common genes contributed to most of the correlation between the disease and symptom. Non-shared environment was also important. Further research is thus needed to determine whether our differential findings for symptoms vs diseases are accounted for by differences in random measurement and to validate symptom reports as reliable measurements of atopic diseases.

Typically, in biometric modelling measurement error will be estimated as part of the non-shared environment (E). Genetic studies using the twin-design are based upon a few major assumptions. First, twins are representative of the general population for the outcomes being studied. This assumption is valid supposing that representative or complete samples are taken from the population. We found no evidence of zygosity differences in the prevalence of diseases and symptoms. Comparisons with prevalence rates from non-twin population-based Norwegian data suggest that the twin data are representative of the general population.^{11,26–28} Our previous study of Norwegian twins aged 18–25 years reported a lifetime prevalence of asthma of 5.7%.¹¹ The prevalence of wheeze in the past 12 months using the ISAAC questionnaire ranged from 13.6 to 8.5% among Norwegian school children aged 6–16 years, whereas the prevalence of hay fever varied from 7.8 to 9.4% and eczema from 15.5 to 17.1% in the same study.^{27,28} A second assumption is that of equal environments among MZ and DZ twins. Under this assumption, greater MZ than DZ similarity reflects genetic effects. However, shared environment can be 'hidden' in shared genetic effects, because environmental effects shared by MZ co-twins may be greater than environmental effects shared by DZ co-twin pairs.²⁹ We cannot dismiss the possibility of such bias. However, for the purpose of comparison between results for diseases and for symptoms of the same diseases, this source of bias, if present, would hardly affect our results. It is unlikely that a violation of this equal environment assumption should differentially affect self-reports of disease compared with symptoms of the same diseases. A limitation of the present study is that we use self-reported asthma, hay fever and eczema, rather than a report of physician diagnosis. However, Norwegian studies of asthma have shown that the prevalence of asthma varies <1% using self-report compared with a doctor diagnosis of asthma.³⁰ It has also been previously reported that people who claim to have a certain lung disease nearly always seem to have asthma.¹

In conclusion, genetic effects account for greater variation in reported diseases than symptoms. The correlation between disease and symptoms is mainly explained by genetic effects common to both phenotypes, but non-shared environment is also important. If self-reports of symptoms are less reliable than self-reports of diseases then this could contribute to our findings.

Although epidemiological studies often rely on symptom reports to study disease, we find that reported disease and symptom of the same disease may not reflect the same underlying disorder with the same aetiological factors. Therefore, the results of such studies must be interpreted with caution. Further research is needed to understand the nature of disease-symptom relationship.

Acknowledgements

The Norwegian Institute of Public Health programme of twin research is supported by grants from The Norwegian Research Council, The Norwegian Foundation for Health and Rehabilitation, and the European Commission under the programme, 'Quality of Life and Management of the Living Resources' of 5th Framework Programme (no. QL2-CT-2002-01254). We thank the twins for their participation.

References

- 1 Burney P, Laitinen LA, Perdrizet S *et al.* Validity and repeatability of the IUATLD (1984). Bronchial symptoms questionnaire: an international comparison. *Eur Respir J* 1989;**2**:940–45.
- 2 Burney PG, Luczynska C, Chinn S, Jarvis D, for the European Community Respiratory Health Survey. The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7**:954–60.
- 3 Asher MI, Keil U, Anderson HR *et al.* International study of asthma and allergies in childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483–91.
- 4 Medical Research Council. *Questionnaire on Respiratory Symptoms*. London: Medical Research Council, 1976.
- 5 British Medical Research Council. *Recommended Respiratory Disease Questionnaires for Use with Adults and Children in Epidemiological Research*. London: British Medical Research Council, 1978, pp. 7–55.
- 6 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998;**351**:1225–32.
- 7 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J* 1998;**12**:315–40.
- 8 Crane J, Mallol J, Beasley R, Stewart A, Asher I, on behalf of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase I Study group. Agreement between written and video questions for comparing asthma symptoms in ISAAC. *Eur Respir J* 2003;**21**:455–61.
- 9 European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;**9**:687–95.
- 10 Los H, Postmus PE, Boomsma DI. Asthma genetics and intermediate phenotypes: a review from twin studies. *Twin Res* 2001;**4**:81–93.
- 11 Harris JR, Magnus P, Samuelsen SO, Tambs K. No evidence for effects of family environment on asthma. *Am J Respir Crit Care Med* 1997;**156**:43–49.
- 12 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**:1351–58.
- 13 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.
- 14 Spain WC, Cooke RA. Studies in specific hypersensitiveness. XI. The familial occurrence of hayfever and bronchial asthma. *J Immunol* 1924;**9**:521–69.
- 15 Harris JR, Magnus P, Tambs K. The Norwegian Institute of Public Health Twin Panel: a description of the sample and program of research. *Twin Res* 2002;**5**:415–23.
- 16 Harris JR, Tambs K, Magnus P. Sex-specific effects for body mass index in the Norwegian twin panel. *Genetic Epidemiol* 1995;**12**:251–65.
- 17 Magnus P, Berg K, Nance WE. Predicting zygosity in Norwegian twin pairs born 1915–1960. *Clin Genet* 1983;**24**:103–12.

- ¹⁸ Joreskog KG, Sorbom D. *PRELIS 1. User's Manual Version 1*. Chicago: Scientific Software Inc., 1988.
- ¹⁹ Harris B. Tetrachoric correlation coefficient. In: Kotz L, Johnson NL (eds). *Encyclopedia of Statistical Sciences*. New York: Wiley, 1988, pp. 223–25.
- ²⁰ Neale MC. *Mx: Statistical Modelling*. 2nd edn. Richmond, VA: Department of Psychiatry, MCV, 1994.
- ²¹ Neale M, Cardon L (eds). *Methodology for Genetic Studies of Twins and Families*. Dordrecht, The Netherlands: Kluwer Academic Publisher, 1992.
- ²² Akaike H. A new look at statistical identification. *IEEE Trans Autom Control* 1974;**19**:716–22.
- ²³ Lichtenstein PSM. Genes, environments, and sex: factors of importance in atopic diseases in 7–9-year-old Swedish twins. *Allergy* 1997;**52**:1079–86.
- ²⁴ Strachan DP, Wong HJ, Spector TD. Concordance and interrelationship of atopic diseases and markers of allergic sensitization among adult female twins. *J Allergy Clin Immunol* 2001;**108**:901–07.
- ²⁵ Wright AL. Epidemiology of asthma and recurrent wheeze in childhood. *Clin Rev Allergy Immunol* 2002;**22**:33–44.
- ²⁶ Skarpaas IJK, Gulsvik A. Prevalence of bronchial asthma and respiratory symptoms in schoolchildren in Oslo. *Allergy* 1985;**40**:295–99.
- ²⁷ Nystad W, Magnus P, Gulsvik A, Skarpaas I, Carlsen KH. Changing prevalence of asthma in school children. Evidence for diagnostic changes in asthma in two surveys 13 years apart. *Eur Respir J* 1997;**10**: 1046–51.
- ²⁸ Nystad W, Magnus P, Røksund O, Svidal B, Hetlevik Ø. The prevalence of respiratory symptoms and asthma among school children in three different areas of Norway. *Pediatr Allergy Immunol* 1997;**8**:35–40.
- ²⁹ Hopper JL. Why common environmental effects are so uncommon in the literature. In: Spector TD, Snieder H, Mac Gregor AJ (eds). *Advances in Twin and Sib-Pair Analysis*. Oxford: Oxford University Press, 2000, pp. 151–65.
- ³⁰ Nystad W, Søyseth V, Magnus P. The prevalence of asthma among school children in Norway in 1985–94. *Tidsskr Nor Lægeforen* 1997;**117**:644–47.