

ORIGINAL ARTICLE

Estimates of asthma heritability in a large twin sample

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Summary

Background Asthma is a complex disease characterized by symptoms of wheezing, shortness of breath, chest tightness, and cough.**Objective** To study the relative contribution of genetic and environmental factors in the liability to asthma in a large sample of twins.**Methods** Data on asthma in 21 135 twin pairs, 3–71 years of age, from the Danish Twin Registry were collected via a multidisciplinary questionnaire survey. Heritability estimates were calculated using variance components models.**Results** A monozygotic twin had an approximately sixfold increased risk of asthma whereas a dizygotic twin only had an approximately threefold increased risk relative to the general population if his or her co-twin was affected. The difference was more pronounced among males. Familial aggregation of asthma in children and adolescents was explained mainly by additive genetic factors, but common environment was also important. The heritability of asthma was also substantial in adults aged 20–49 years. In older adults (aged 50–71 years), additive genetic factors did not significantly influence the disease risk.**Conclusion** Genetic influences on asthma are substantial throughout the life span but the proportion of the disease liability explained by genetic factors is decreased in older adults.**Keywords** asthma, epidemiology, genetics, heritability, twin study*Submitted 1 September 2009; revised 19 March 2010; accepted 23 March 2010*

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Introduction

Asthma is a complex disease characterized by symptoms of wheezing, shortness of breath, chest tightness, and cough. It is part of the atopic triad also involving atopic dermatitis and hayfever. The prevalence and incidence of asthma differ markedly between different countries, and across age groups and sexes, suggestive of a substantial individual variation in the liability to the disease [1].

Previous twin studies have indicated that asthma is a highly heritable trait and that the individual variation in the liability to the disease can be ascribed both to genetic and environmental influences with heritability estimates ranging between 50% and 90% [2] (Table 1). Notably, a large number of polymorphisms in genes positioned throughout the genome have been implicated in asthma causation [3]. Moreover, a range of environmental exposures such as smoking, dietary factors, weight gain, allergens, respiratory infections, and occupational hazards have been incriminated as triggers or causative factors for asthma and atopic disease in general [4].

The classical twin design assumes that monozygotic (MZ) twins not only share all their genes, but also their upbringing and early environment, whereas dizygotic (DZ) twins share, besides their upbringing and early environment, on average half of their segregating genes. Hence, if MZ twins resemble each other more than DZ twins with respect to a disease, genetic factors are assumed to contribute to development of that disease [5]. In this study, we used the framework of the classical twin design on a large sample of Danish twins in order to provide estimates of the genetic and environmental contributions to the individual liability to asthma. Particularly, we studied genetic and environmental differences between the sexes and between age groups.

Methods

Population

The studied sample comprised twins born between 1931 and 2000 who were registered with the nationwide Danish

Table 1. Population-based studies of asthma in twins that report heritability estimates

Study (first author)	Country	Age group (years)	Number of pairs	Prevalence* (%)	C_P -MZ [†]	C_P -DZ [†]	rMZ [‡]	rDZ [‡]	$h^§$	Genetic model [¶]	Diagnostic method
Skadhaug [9]	Denmark	12–41	11 688	6.0/6.5	0.49/0.40	0.18/0.18	0.79/0.68	0.37/0.31	0.73	AE	Self-reported ever asthma
Edfors-Lubs [25]	Sweden	46–85	6996	3.5/4.0	0.19**	0.05**	0.65 ^{††}	0.25 ^{††}	0.63 ^{‡‡}	AE	Self-reported ever asthma
Lichtenstein [26]	Sweden	7–9	1480	8.0/4.0 and 18.0/10.0	0.62/0.41	0.26/0.18	0.79/0.64	0.25/0.27	0.76/0.62	AE/AE	Parent-reported physician diagnosed asthma and self-reported ever asthma
Harris [27]	Norway	18–25	2570	6.0/5.4	0.52/0.37	0.13/0.07	0.81/0.68	0.17/0.05	0.75	DE	Self-reported ever asthma
Nystad ^{§§} [28]	Norway	18–35	3334	8.1	0.45/0.44	0.15/0.11	0.73/0.70	0.28/0.09	0.71	DE	Self-reported ever asthma
Nieminen [18]	Finland	28–80	13 888	1.8/2.1	0.08/0.10	0.09/0.05	0.31/0.50	0.34/0.16	0/0.68 ^{¶¶}		Hospital discharge data, and reimbursed medications
Laitinen [29]	Finland	16	1713	4.7/3.1	0.55/0.25	0.27/0.11	0.84/0.61	0.54/0.30	0.79	AE	Self-reported ever physician diagnosed asthma
Van Beijsterveldt [15]	The Netherlands	5	8633	10.2/7.2			0.89/0.92	0.37/0.47	0.91	AE	Parent-reported ever physician diagnosed ever asthma
Willemsen [30]	The Netherlands	25	14 177	11.3/12.1			0.77/0.77	0.24/0.36	0.75	ADE	Self-reported ever physician diagnosed asthma
Koeppen-Schomerus [14]	England/Wales	4	4910	20.1/16.6	0.64/0.66	0.45/0.34	0.79/0.84	0.54/0.39	0.68	ACE	Ever had medication for asthma
Duffy [17]	Australia	18–88	3808	13.8/12.9	0.55/0.42	0.23/0.22	0.76/0.59	0.19/0.26	0.76/0.59	ADE/AE	Self-reported ever asthma or wheezing
Hallstrand [31]	United States	32	1384	11.1/15.8			0.51	0.34	0.53	AE	Self-reported ever physician diagnosed asthma
Fagnani [32]	Italy	8–17	392	8.6/7.8	0.67	0.35	0.92	0.55	0.92	AE	Parent-reported asthma

*Estimates separated by a '/' denote prevalence for males and females, respectively.

†Pro-bandwise concordance rate. Estimates separated by a '/' denote values for males and females, respectively.

‡Cross-twin (tetrachoric) correlation. Estimates separated by a '/' denote values for males and females, respectively.

§Heritability. Estimates separated by a '/' denote values for males and females, respectively.

¶Preferred model when variance components modelling was performed. Additive genetic (A), non-additive genetic (D), shared (C), and non-shared (E) environmental sources of variance. Models separated by a '/' denote models for males and females, respectively.

||Approximate value.

**Casewise concordance rate (number of concordant pairs divided by total number of pairs with at least one affected member).

†† Adopted from Los et al. [2].

‡‡ Estimated by Duffy [33].

§§ Same population studied by Harris et al. [27].

¶¶ Estimated from $h = 2(rMZ - rDZ)$ [5].

||| Mean age.

DZ, dizygotic; MZ, monozygotic.

Twin Registry. A detailed description of the ascertainment of the study population can be found in previous publications [6–8]. In brief, the population constituted three separate cohorts of twins all ascertained differently by the registry. The first cohort included twins born between 1931 and 1952. This cohort was identified and enrolled in the Danish twin registry in 1996 and corresponded to 69% of all twin pairs born in Denmark during these years. The second cohort included twins born between 1953 and 1982. This cohort was identified and enrolled in the Danish Twin Registry in 1991 and corresponded to 74% of all twin pairs born in Denmark between 1953 and 1967 and 97% of all twin pairs born in Denmark between 1968 (when the Danish Civil Registration System was established) and 1982. The cohort born 1953–1982 participated in a questionnaire study in 1994 and Skadhauge et al. [9] have reported previously results for this population with respect to asthma. The third cohort included twins born between 1983 and 2000. This cohort was identified and enrolled in the Danish Twin Registry in 2003 and corresponded to all live-born twin pairs in Denmark during these years.

The present study included questionnaire responses on asthma for all these three cohorts. Notably, the cohorts born 1931–1952 and 1953–1982 (50–71 and 20–49 years of age at examination, respectively) participated in a multidisciplinary questionnaire study concerning health and lifestyle in 2002 when a history of asthma was recorded. The response rate to the questionnaire was 75%. In 2003, subjects born between 1983 and 2000 (3–20 years of age at examination) responded to a two-page questionnaire concerning atopic diseases, diabetes, febrile and epileptic seizures, and mental health attributes. For twins born between 1988 and 2000 (3–15 years of age at examination), the questionnaire was answered by the parents of the twins. The response rate to the questionnaire was 68%.

In total, 54 726 subjects (54 530 twin individuals and 196 higher order multiples) participated in the questionnaire studies. Of these, a total of 13 649 twin individuals (4240 intact pairs with complete data on asthma) were from the cohort born 1931–1952, a total of 21 133 twin individuals (7201 intact pairs with complete data on asthma) were from the cohort born 1953–1982, and a total of 19 748 twin individuals (9694 intact pairs with complete data on asthma) were from the cohort born 1983–2000, resulting in a total of 21 135 intact twin pairs. For twins born 1931–1987, a history of asthma was defined as an affirmative response to the question 'Do you have, or have you ever had, asthma?' whereas for twins born 1988–2000 a history of asthma was defined as an affirmative response to the question 'Has your child ever had asthma?' Twin zygosity was determined using four questions of similarity and mistaken identity, which assign zygosity correctly in >96% of the cases [10]. The local scientific ethics committee approved the protocol.

Statistical analysis

First, pro-bandwise concordance rates for asthma were calculated for the different sex-by-zygosity groups. The pro-bandwise concordance rate denotes the probability that one twin is affected given that the co-twin is affected. Because we had complete ascertainment of cases, the concordance rate can be estimated as two times the number of concordant pairs (both twins are affected) divided by two times the number of concordant affected pairs plus the number of discordant pairs (one twin is affected) [11]. Recurrence risk ratios were calculated by dividing the pro-bandwise concordance rate with the prevalence rate and hence are measures of the increased risk of disease between siblings relative to the general population.

Second, tetrachoric correlations in liability to asthma were estimated under the assumptions of the multifactorial threshold model [5]. Tetrachoric correlations are measures of similarity for dichotomous variables that estimate what the correlation would be if the variables were measured on a continuous scale. Tetrachoric correlations thus represent the correlation between asthma in twin 1 and asthma in twin 2 within a twin pair.

Finally, latent factor models of genetic and environmental factors were fitted to the raw data. These are standard twin analyses, assuming that the variation in the liability to asthma can be partitioned into genetic and environmental sources of variance. Genetic variance was partitioned into additive genetic (loci contributing additively to disease risk, *A*) and non-additive genetic variance (interacting alleles, either from the same locus – genetic dominance – or from separate loci – epistasis, *D*). Environmental variance was partitioned into shared environmental (environmental factors that increase the resemblance between members of the same family, *C*) and non-shared – random – environmental variance (influences unique to individuals that result in differences between family members, *E*). The *E*-component also includes variance due to measurement error [5]. For most human traits, it is reasonable to assume that all four sources of variance (*A*, *D*, *C*, and *E*) act simultaneously. However, components *C* and *D* are not identified under the same model in studies that include only twins reared together [12]. Therefore, the likelihood of the data was determined under a saturated model that either included components *A*, *C*, and *E* whenever there was evidence that shared environment could influence the disease liability (MZ correlation below twice the DZ correlation), or *A*, *D*, and *E* whenever there was evidence that genetic non-additivity could influence the disease liability (MZ correlation above twice the DZ correlation). The resulting expected phenotypic variance is defined as the sum of these sources of variance, i.e. either $A+C+E$ or $A+D+E$. Because MZ twins are genetically identical, the expected

covariance for MZ twins equals $A+C$ or $A+D$, while the covariance between DZ twins, who share on average 50% of their genes, equals $0.5 \times A+C$ or $0.5 \times A+0.25 \times D$ [12]. The significance of the contribution of the individual parameters to the variance in disease liability was determined by a likelihood ratio test for the difference between the full ACE or ADE model and subsequently fitted nested models (AE, DE, and CE models). In cases when two models were equally plausible, the preferred model was the one with the smallest difference in χ^2 goodness-of-fit compared with the saturated model. We also considered the fit of models that included tests for quantitative and qualitative differences in genetic effects across sexes by comparing the additive genetic effects between same sex MZ and DZ twins, and the correlation between the additive genetic effects of same sex DZ and opposite sex DZ twins, respectively. In the cohort born 1983–2000 (age group 3–20 years), a covariate effect of whether the parents answered the questionnaire was incorporated into the threshold model, whereas in the cohorts born 1953–1982 and 1931–1952 (age groups 20–49 and 50–71 years), covariate effects of age and smoking were modelled on the thresholds. For all three cohorts, the variance–covariance structure was initially allowed to differ for males and females. The statistical package Mx was used for the analyses [13].

Results

Descriptive statistics

The prevalence of asthma was not statistically significantly different in MZ and DZ twins within all three age groups. Males were more often affected than females in the age group 3–20 years, whereas females were more often affected in the older age groups. Smoking was a significant predictor for asthma in the age group 50–71 years but only among females (Table 2).

Measures of twin similarity

Concordances for asthma were consistently larger in MZ than in DZ twins, particularly for the younger ages whereas the MZ to DZ concordance rate ratio approached 1 for older adults, not least among males (Table 3). An MZ twin had an approximately sixfold increased risk of asthma relative to the general population if his or her co-twin was affected whereas a DZ twin had an approximately threefold increased risk if the co-twin was affected. The difference was most pronounced among males.

Variance components analysis

Familial aggregation of asthma in 3–20-year-old subjects was explained mainly by additive genetic factors, but

Table 2. Characteristics of subjects with and without asthma among Danish twins, 3–71 years of age

	Asthma		Odds ratio (95% confidence intervals)	P-value
Measure	Yes	No		
3–20 years (<i>n</i> = 9694)				
Sex				
Males	13.0	87.0	1.00	
Females	9.3	90.7	0.69 (0.63–0.75)	<0.001
Age				
Males	9.4	9.3	1.03 (0.91–1.17)	0.606
Females	9.9	9.5	1.19 (1.03–1.37)	0.018
Zygoty				
MZ	11.8	88.2	1.00	
DZ	11.1	88.9	0.93 (0.82–1.05)	0.243
20–49 years (<i>n</i> = 7201)				
Sex				
Males	8.2	91.8	1.00	
Females	10.1	89.9	1.26 (1.14–1.38)	<0.001
Age				
Males	33.1	33.6	0.92 (0.83–1.03)	0.145
Females	33.0	33.5	0.89 (0.82–0.97)	0.011
Zygoty				
MZ	9.2	90.8	1.00	
DZ	9.0	91.0	0.97 (0.87–1.09)	0.634
Smoking				
Males	8.1	8.2	0.99 (0.85–1.14)	0.850
Females	10.6	9.6	1.12 (0.99–1.26)	0.073
50–71 years (<i>n</i> = 4240)				
Sex				
Males	6.7	93.3	1.00	
Females	9.0	91.0	1.37 (1.21–1.56)	<0.001
Age				
Males	58.3	56.8	1.35 (1.19–1.54)	<0.001
Females	57.3	57.0	1.07 (0.96–1.19)	0.243
Zygoty				
MZ	6.9	93.1	1.00	
DZ	7.8	92.2	1.14 (0.96–1.37)	0.143
Smoking				
Males	7.0	5.7	1.24 (0.98–1.57)	0.074
Females	10.6	6.7	1.66 (1.39–1.99)	<0.001

Numbers are proportions (%) except age (mean). Proportions are calculated from all available data (not only from complete twin pairs) for the individual variables.

Odds ratio for sex is the risk of asthma in females relative to males; odds ratio for age is per 10 years; odds ratio for zygoty is the risk of asthma in DZ relative to MZ twins; odds ratio for smoking is the risk of asthma in smokers relative to non-smokers stratified by sex. *P*-values are not adjusted for dependency between twins.

MZ, monozygotic twins; DZ, dizygotic twins; Smoking, ever smoking.

common environment was also of importance. The heritability of asthma was also substantial in the age group 20–49 years. In older adults (aged 50–71 years), additive genetic factors did not significantly influence the disease risk (Table 4).

Table 3. Prevalence and resemblance for asthma in 21 135 Danish twin pairs, 3–71 years of age

Age group	Pairs (n)	Asthma (n)	Prevalence (%)	Discordant pairs (n)	Concordant pairs (n)	C _P	Tetrachoric correlation	RRR
3–20 years	9694	2155	11.1 (10.7–11.6)	1177	489			
All MZ	1728	409	11.8 (10.8–13.0)	97	156	0.76 (0.72–0.80)	0.94 (0.91–0.96)	6.63 (5.55–7.93)
All DZ	7323	1604	11.0 (10.5–11.5)	1018	293	0.37 (0.34–0.39)	0.55 (0.50–0.59)	3.34 (3.00–3.72)
MZM	867	248	14.3 (12.7–16.0)	56	96	0.77 (0.72–0.82)	0.94 (0.90–0.96)	5.41 (4.30–6.82)
MZF	861	161	9.3 (8.1–10.8)	41	60	0.75 (0.67–0.81)	0.94 (0.89–0.97)	7.97 (5.99–10.61)
DZM	2039	498	12.2 (11.2–13.3)	292	103	0.41 (0.37–0.46)	0.59 (0.52–0.66)	3.39 (2.81–4.08)
DZF	1989	395	9.9 (9.0–10.9)	227	84	0.43 (0.38–0.47)	0.65 (0.57–0.72)	4.28 (3.48–5.27)
DOS	3295	711	10.8 (10.1–11.6)	499	106	0.30 (0.27–0.33)	0.44 (0.36–0.51)	2.76 (2.33–3.28)
UZ	643	142	11.0 (9.4–12.9)	62	40	0.56 (0.48–0.65)	0.65 (0.57–0.72)	5.10 (3.69–7.05)
20–49 years	7201	1328	9.2 (8.8–9.7)	1004	162			
All MZ	2351	418	8.9 (8.1–9.7)	258	80	0.38 (0.34–0.43)	0.61 (0.53–0.68)	4.31 (3.50–5.30)
All DZ	4671	874	9.4 (8.8–10.0)	726	74	0.17 (0.15–0.20)	0.21 (0.13–0.29)	1.81 (1.50–2.18)
MZM	945	163	8.6 (7.4–9.9)	89	37	0.45 (0.38–0.53)	0.70 (0.59–0.80)	5.26 (3.83–7.23)
MZF	1406	255	9.1 (8.0–10.2)	169	43	0.34 (0.28–0.40)	0.54 (0.43–0.64)	3.72 (2.82–4.90)
DZM	1065	155	7.3 (6.2–8.5)	129	13	0.17 (0.11–0.24)	0.28 (0.09–0.44)	2.31 (1.48–3.59)
DZF	1488	308	10.3 (9.3–11.5)	236	36	0.23 (0.19–0.29)	0.32 (0.20–0.44)	2.26 (1.71–2.99)
DOS	2118	411	9.7 (8.8–10.6)	361	25	0.12 (0.09–0.16)	0.08 (0.00–0.20)	1.25 (0.92–1.71)
UZ	179	36	10.1 (6.9–13.2)	20	8	0.44 (0.28–0.61)	0.67 (0.38–0.86)	4.42 (2.26–8.68)
50–71 years	4240	614	7.2 (6.7–7.8)	482	66			
All MZ	1005	134	6.7 (5.6–7.9)	92	21	0.31 (0.24–0.40)	0.55 (0.39–0.68)	4.70 (3.19–6.92)
All DZ	3120	462	7.4 (6.8–8.1)	376	43	0.19 (0.15–0.22)	0.31 (0.21–0.41)	2.51 (1.96–3.22)
MZM	442	43	4.9 (3.5–6.5)	31	6	0.28 (0.15–0.44)	0.56 (0.28–0.77)	5.74 (2.86–11.55)
MZF	563	91	8.1 (6.6–9.8)	61	15	0.33 (0.23–0.44)	0.55 (0.36–0.71)	4.08 (2.57–6.48)
DZM	714	92	6.4 (5.2–7.8)	68	12	0.26 (0.17–0.36)	0.48 (0.28–0.66)	4.05 (2.48–6.63)
DZF	913	146	8.0 (6.8–9.3)	114	16	0.22 (0.16–0.30)	0.36 (0.18–0.52)	2.74 (1.81–4.16)
DOS	1493	224	7.5 (6.6–8.5)	194	15	0.13 (0.09–0.19)	0.18 (0.02–0.37)	1.79 (1.19–2.67)
UZ	115	18	7.8 (4.4–11.3)	14	2	0.22 (0.06–0.48)	0.37 (0.00–0.76)	2.84 (0.92–8.91)
Total	21135	4097	9.7 (9.4–10.0)	2663	717			
All MZ	5084	961	9.5 (8.9–10.0)	447	257	0.53 (0.50–0.57)	0.78 (0.74–0.81)	5.66 (4.99–6.42)
All DZ	15114	2940	9.7 (9.4–10.1)	2120	410	0.28 (0.26–0.30)	0.43 (0.39–0.47)	2.87 (2.63–3.13)
MZM	2254	454	10.1 (9.2–11.0)	176	139	0.61 (0.57–0.66)	0.84 (0.80–0.88)	6.08 (5.09–7.26)
MZF	2830	507	9.0 (8.2–9.7)	271	118	0.47 (0.42–0.51)	0.71 (0.65–0.77)	5.20 (4.35–6.22)
DZM	3818	745	9.8 (9.1–10.4)	489	128	0.34 (0.31–0.38)	0.54 (0.47–0.60)	3.52 (3.00–4.14)
DZF	4390	849	9.7 (9.1–10.3)	577	136	0.32 (0.29–0.35)	0.50 (0.44–0.56)	3.31 (2.84–3.86)
DOS	6906	1346	9.7 (9.3–10.2)	1054	146	0.22 (0.20–0.24)	0.31 (0.25–0.37)	2.23 (1.94–2.56)
UZ	937	196	10.5 (9.1–11.9)	96	50	0.51 (0.44–0.58)	0.77 (0.64–0.82)	4.88 (3.68–6.47)

Asthma is self-reported lifetime prevalence of asthma.

Numbers in parentheses are 95% confidence intervals.

MZM, monozygotic male twins; MZF, monozygotic female twins; DZM, dizygotic male twins; DZF, dizygotic female twins; DOS, dizygotic opposite sex twins; UZ, same sex twins of unknown zygosity; C_P, pro-bandwise concordance rate; RRR, recurrence risk ratio (C_P divided by the prevalence).

Table 4. Variance components analysis of asthma in 21 135 Danish twin pairs, 3–71 years of age

Model	Variance components*				Fit statistics		
	A	D	C	E	$\Delta-2 \log Q$	Δdf	P-value
3–20 years							
Males							
ACE	0.66 (0.51–0.83)	–	0.27 (0.11–0.41)	0.07 (0.04–0.11)			
AE	0.94 (0.91–0.96)	–	–	0.06 (0.04–0.09)	10.349	1	0.001
CE	–	–	0.74 (0.69–0.78)	0.26 (0.22–0.31)	62.117	1	0.000
Females							
ACE	0.59 (0.42–0.76)	–	0.35 (0.19–0.49)	0.06 (0.05–0.11)			
AE	0.95 (0.91–0.97)	–	–	0.05 (0.03–0.09)	16.130	1	0.000
CE	–	–	0.75 (0.70–0.80)	0.25 (0.20–0.30)	41.246	1	0.000
20–49 years							
Males							
ADE	0.39 (0.00–0.77)	0.31 (0.00–0.78)	–	0.30 (0.21–0.41)			
AE	0.69 (0.58–0.78)	–	–	0.31 (0.22–0.42)	0.656	1	0.418
DE	–	0.71 (0.60–0.80)	–	0.29 (0.20–0.40)	1.591	1	0.207
Females							
ACE	0.47 (0.14–0.65)	–	0.09 (0.00–0.35)	0.44 (0.35–0.56)			
AE	0.57 (0.47–0.66)	–	–	0.43 (0.34–0.53)	0.402	1	0.526
CE	–	–	0.43 (0.35–0.51)	0.57 (0.49–0.65)	7.983	1	0.005
50–71 years							
Males							
ACE	0.30 (0.00–0.83)	–	0.36 (0.00–0.66)	0.34 (0.16–0.57)			
AE	0.73 (0.53–0.87)	–	–	0.27 (0.13–0.47)	2.192	1	0.139
CE	–	–	0.56 (0.39–0.69)	0.44 (0.31–0.61)	1.976	1	0.160
Females							
ACE	0.27 (0.00–0.70)	–	0.28 (0.00–0.55)	0.45 (0.29–0.63)			
AE	0.59 (0.43–0.73)	–	–	0.41 (0.27–0.57)	1.749	1	0.178
CE	–	–	0.46 (0.33–0.59)	0.54 (0.41–0.67)	2.477	1	0.116

*Standardized adjusted parameter estimates (95% confidence intervals) of additive genetic factors (A), non-additive genetic factors (D), shared environmental factors (C), and non-shared environmental factors (E).

$\Delta-2 \log Q$, difference in model fit (log-likelihood) between saturated model and nested model.

Δdf , difference in degrees of freedom between saturated model and nested model.

Preferred models are shown in bold.

Further analyses, however, showed that the variance decomposition was not significantly different for males and females in the age groups 3–20 and 20–49 years, respectively, and therefore that common models could be derived for the two sexes for these age groups. These models showed that the variation in the liability to asthma in the age group 3–20 years was for 63% (52–75%) attributable to additive genetic factors, for 30% (19–41%) to common environmental factors, and for 7% (5–9%) to non-shared environmental factors; and that in the age group 20–49 years, additive genetic factors explained 61% (53–68%) of the variation in the liability to asthma and non-shared environmental factors explained 39% (32–47%).

We performed additional model fitting comparing the correlation between the additive genetic effects in same-sex and opposite-sex DZ twin pairs for the age groups 3–20 and 20–49 years. This analysis showed that the correlation between the additive genetic effects in same-sex and opposite-sex DZ twin pairs was significantly

different, indicating that different genes are expressed in males and females (3–20 years; correlation = 0.26, *P*-value for deviation from 0.50 = 0.006 and 20–49 years; correlation = 0.09, *P*-value for deviation from 0.50 < 0.001).

Discussion

This study showed that: (1) The relative importance of hereditary factors on asthma susceptibility decreases over the life span, particularly in old adulthood. This effect was mirrored by an increasing importance of non-shared environmental factors for asthma susceptibility from childhood through old adulthood. Furthermore, shared (household) environmental factors were also of importance for the liability to asthma in childhood and old adulthood but were less important in middle adulthood. (2) Different genes influence the liability to asthma in males and females among children and young adults but the proportion of the liability to asthma explained by

genetic factors was the same in males and females in these two age groups.

Our results expand upon findings from previous twin studies of asthma. Particularly, this is the largest population study of asthma heritability to date, which increases the precision of our estimates. Notably, most studies report a heritability of asthma around 70% based on a model that includes only additive genetic and non-shared environmental variance irrespective of the diagnostic criteria, country, age group, and sample size. We found that a model based both on additive genetic, shared, and non-shared environmental variance fitted our data best for childhood asthma, consistent with a study by Koepfen-Schomerus et al. [14] of 4-year-old British twins, but contradictory to a Dutch study of 5-year-old twins by Van Beijsterveldt and Boomsma [15] that did not find evidence of shared environment. Our significant estimate of shared environment may, however, reflect a different age of the studied twins, a larger sample size, [16] and/or synchronized responses between the twins due to the fact that the parents of the youngest twins answered the questionnaire. Both of these two factors will increase the likelihood of attaining common environmental influences in the model. We found a considerably higher similarity in MZ twins compared with DZ twins for asthma among males of young adulthood indicating non-additive genetic influences on the disease liability. This finding is in line with a study of Australian twins by Duffy et al. [17] and reflects a substantial heritable component for asthma in this age group. However, further model fitting did not show this, in that a common model for males and females suggested that familial aggregation of asthma in middle adulthood was ascribable only to additive genetic effects. In contrast, we found that genetic factors explained a much smaller proportion of the disease liability in older adults, not least in males consistent with a low heritability for asthma among older males in a study of Finnish adults [18]. It is possible that these findings reflect recall bias and diagnostic mix-up with chronic obstructive pulmonary disease, not least exemplified by our observation that smoking was a risk factor for female asthma in older but not in younger adults. However, an alternative possibility is that this reflects a true effect, in that environmental changes over the years have increased the expression of genes, leading to a higher influence of heritability in the younger cohorts.

We found a prevalence of asthma that is in agreement with previous studies. Generally, the prevalence of asthma is higher in studies of children compared with adults and in older females compared with older males. Moreover, the prevalence of asthma is higher in British studies, in studies of newer date, and in studies when the diagnosis of asthma is self-reported compared with studies that use a doctor's diagnosis of asthma and/or medication use.

Our study relies mainly on recollection of past episodes of disease, and therefore prevalence estimates can be biased downwards [19]. This could be the case if the disease episodes lie primarily in early childhood or if episodes are mild. In studies of relatives, these may consult each other before answering, which can be helpful, but may also alter subject-to-subject variation [20]. In studies of children, parents assist in answering questions. This may prevent dropout but can lead both to false positives and false negatives [20, 21]. Asthma was diagnosed by the question 'Do you have, or have you ever had asthma?' This method has been shown previously to have a high validity in the diagnosis of asthma [22]. Furthermore, we validated the asthma diagnosis in a subset of 575 clinically examined twins from the cohort born 1953–1982, who either themselves, and/or their co-twin reported a history of asthma at the questionnaire [23]. Of these, a total of 89% with questionnaire-asthma were subsequently diagnosed with asthma based on the findings at the clinical examination. Likewise, only 12% of those who denied a history of asthma at the questionnaire survey were diagnosed with asthma at the clinical examination [24]. We conclude that genetic influences on asthma are substantial throughout the life span but that the proportion of the disease liability explained by genetic factors is decreased in older adults.

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