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Increase in the heritability of asthma from 1994 to 2003 among adolescent twins

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KEYWORDS

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Summary

Background: Over the past decades the prevalence of asthma has increased in most parts of the world, and widespread changes in lifestyle and environment have been postulated as the primary cause for this. We examined whether the extent to which genetic and environmental factors influence susceptibility to asthma has changed between 1994 and 2003.

Methods: Two different cohorts of twins ($n = 3393$ and $n = 2813$ pairs), both 12–20 years of age, from the Danish Twin Registry, participated in questionnaire studies nine years apart. Prevalence of asthma and resemblance between twins for asthma was compared between the two cohorts.

Results: The prevalence of asthma increased from 7.1% in 1994 to 10.8% in 2003, $p < 0.001$. The change was significant both in males (7.7 vs. 12.4%, $p < 0.001$); and females (6.6 vs. 9.2%, $p < 0.001$). The best-fitting model, which included additive genetic and non-shared environmental effects, showed that the heritability of asthma increased significantly from 79% in 1994 to 91% in 2003, $p = 0.005$.

Conclusions: This result could indicate that environmental changes over the past years have increased the expression of genes and thus have lead to a higher heritability in the succeeding cohort. This is consistent with the hypothesis that changes in the environment, particular in childhood, are the cause of the increase in the prevalence of asthma over the past decades.

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Introduction

The prevalence of asthma has increased dramatically in most parts of the world during the second half of the last century, and widespread changes in our lifestyle and environment have been postulated as the primary cause for this.¹ Particularly, secular trends in asthma prevalence have been coupled to 'westernisation', and such factors as changes in diet, infectious load, and housing conditions have been speculated to play a causative role.² Asthma is still increasing in many parts of the world notably in developing countries, whereas some reports from westernised societies have indicated that the prevalence has now plateaued, or in some instances has even declined. A recent systematic review of studies of asthma epidemiology, however, found no evidence whatsoever that the prevalence of asthma is currently declining,³ which stresses the importance of continuing research aimed at studying the etiological factors for the disease and its current increase in prevalence.

We put forward the hypothesis that if environmental change is the primary cause for the increase in the prevalence of asthma then this will result in a change in the relative importance of hereditary and environmental factors on the susceptibility to asthma. Such a change could then be detected in a genetically informative population such as for example twins. Notably, if environmental changes have caused an increase in the prevalence of asthma, then several observations are possible. First, the relative influence of shared environmental and/or non-shared environmental factors may have increased over time, and therefore the relative influence of genetic factors may have decreased. Second, the relative and/or absolute influence of genetic factors may have increased as a result of the environmental changes, in which case one would speak of genotype by environment interaction. That is, the extent to which genetic influences affect asthma has increased as a reaction to the environmental changes. A third possibility would be that the factors that have led to an increase in the prevalence in asthma are completely independent from the factors that cause a change in the relative importance of genes and environment, in which case one would observe an increase in prevalence but not a consequential change in the heritability or environmentability of asthma. We performed a serial cross-sectional study of two different populations of adolescent twins (aged 12–20 years), and examined whether the prevalence of asthma, and the influence of genetic and environmental factors on asthma, has changed between 1994 and 2003.

Methods

Study population

Two separate cohorts of twins, both 12–20 years of age, from the Danish Twin Registry, participated in cross-sectional questionnaire studies in 1994 and 2003, respectively. The first cohort included twins born between 1974 and 1982 and corresponded to 97% of all twin pairs born in Denmark during this period.⁴ The second cohort included

twins born between 1983 and 1991 and corresponded to all live-born twin pairs in Denmark during these years.⁵ After 1974, when the Danish Medical Birth Registry was established, the registry has tracked all twins automatically.

The present study is based on questionnaire responses on asthma for these two cohorts. Specifically, the cohort born in 1974–1982 participated in a multidisciplinary questionnaire study concerning health and lifestyle in 1994, in which a history of asthma was recorded. The response rate to the questionnaire was 86%. In this study also twin pairs born between 1953 and 1973 participated and Skadhauge et al have previously reported results for this population as a whole with respect to asthma.⁶ In 2003, the cohort born between 1983 and 1991 participated in a questionnaire study. The response rate to the questionnaire was 68%. This study also included twin pairs born between 1992 and 2000, and we have previously reported on the heredity of asthma for this cohort altogether.⁷

For the purpose of the present investigation, complete data on asthma were available for a total of 3393 intact pairs, 12–20 years of age, from the 1994-survey, and 2813 intact pairs, 12–20 years of age, from the 2003-survey.

For the entire 1994-population and the 16–20 year old twins from the 2003-population a history of asthma was defined as an affirmative response to the question 'Do you have, or have you ever had, asthma?', whereas for the twins 12–15 years of age from the 2003-population a history of asthma was defined as an affirmative response to the question 'Has your child ever had asthma?' answered by the parents of the twins. Twin zygosity was determined using four questions of similarity and mistaken identity, which assigns zygosity correctly in more than 96% of the cases.⁸ The local scientific ethics committee approved the protocol.

Statistical analysis

The prevalence and concordance rate for asthma was calculated for the different sex-by-zygosity groups. The concordance rate denotes the probability that one twin is affected given that the cotwin is affected. Since we have complete ascertainment of twins the concordance rate was 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).⁹

Latent factor models of genetic and environmental factors were fitted to the raw data following the methods described by Neale & Cardon.¹⁰ These are customary twin analyses assuming that the variation in the susceptibility to asthma can be partitioned into genetic and environmental sources of variance.¹¹ For both cohorts, the variance decomposition was initially allowed to differ between males and females, but since the variance components were not significantly different in males and females (see [Results](#) section) only sex and age effects on the thresholds (prevalences) were retained in the final model. 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.¹⁰ 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.¹¹ 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 shares an average 50% of their genes, equals $0.5 \cdot A + C$ or $0.5 \cdot A + 0.25 \cdot D$.¹¹ 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-, CE- and E-models). The statistical package Mx was used for the analyses.¹²

Results

The proportion of females was 50.8% in 1994 and 51.4% in 2003, $p = 0.460$, whereas the mean age was 16.08 in 1994 and 15.35 in 2003, $p < 0.0001$ (Table 1). The prevalence of asthma was the same across the different sex-by-zygosity groups in 1994 and 2003, respectively.

The prevalence of asthma increased from 7.1% in 1994 to 10.8% in 2003, $p < 0.001$. The change was significant both in males (7.7 vs. 12.4%), $p < 0.001$; and females (6.6 vs. 9.2%), $p < 0.001$. The significance levels for these comparisons were conserved when adjusting for age.

Table 2 shows the resemblance between twins for asthma. Both in 1994 and in 2003, the concordance rate for asthma was higher in MZ twins than in DZ twins, but the

ratio between the concordance rates for asthma in MZ and DZ twins was higher in 2003 compared to 1994 ($0.73/0.29$ vs. $0.50/0.24 = 2.52$ vs. 2.08 , respectively), suggesting a higher heritability of asthma in 2003 compared to 1994. The effect was most pronounced among females.

Table 3 shows the variance decomposition of asthma. The heritability of asthma was not significantly different in males compared to females in the 1994- and 2003-surveys, $p = 0.56$ and $p = 0.55$, respectively, and we therefore combined the data for the sexes and performed sex- and age-adjusted heritability analysis stratified by year of examination. The best-fitting model included additive genetic and non-shared environmental effects, while shared environmental effects, i.e., familial environmental effects that render members of the same family more alike, and dominance genetic effects were not significant. The heritability of asthma increased from 79% in 1994 to 91% in 2003, $p = 0.005$. Additional model-fitting restricted to twin pairs aged 16–20 years ($n = 1928$ pairs in 1994 and $n = 1234$ pairs in 2003) showed that the heritability in this age group increased from 72% in 1994 to 89% in 2003, $p = 0.020$. In this age group the prevalence of asthma increased from 7.5 to 9.2%.

Discussion

This study showed a significant increase in the prevalence of asthma from 1994 to 2003 among adolescent twins. This increase in prevalence was mirrored by an increase in the genetic propensity to asthma over the same period. Notably, the heritability of asthma increased with 12%; from 79% to 91%, between 1994 and 2003. This result could indicate that environmental changes over the past years have increased the expression of genes and thus have lead to a higher influence of heritability in the succeeding cohort, consistent with the hypothesis that changes in the environment, particular in childhood, have caused the increased prevalence of asthma over the past decades.

The heritability is a mathematical concept that describes the genetic susceptibility to a disease in a specific population with that population's particular environmental circumstances.¹³ It estimates the proportion of phenotypic variability of a trait accounted by genetic variability between the individuals of the population.¹⁴ The heritability is a latent construct that encapsulates all unmeasured

Table 1 Population characteristics of two cohorts of adolescent Danish twins.

	1994 $N = 3393$ pairs	2003 $N = 2813$ pairs	<i>P</i> -value
Males	3342 (49.2)	2733 (48.6)	
Age (years)	16.00 (2.56)	15.33 (2.47)	0.000
Asthma	258 (7.7)	340 (12.4)	0.000
Females	3444 (50.8)	2893 (51.4)	
Age (years)	16.15 (2.56)	15.36 (2.52)	0.000
Asthma	227 (6.6)	266 (9.2)	0.000
Total			
Age (years)	16.08 (2.56)	15.35 (2.50)	0.000
Asthma	485 (7.1)	606 (10.8)	0.000

Males, females and asthma are numbers (%). Age is mean.

Table 2 Resemblance between adolescent Danish twins for asthma in 1994 and 2003.

Zygosity group	Pairs (n)	Asthma (%)	Discordant pairs (n)	Concordant Pairs (n)	Concordance rate
1994					
MZ	1273	168 (6.6)	84	42	0.50
Males	601	85 (7.1)	43	21	0.49
Females	672	83 (6.2)	41	21	0.51
DZ-ss	1192	169 (7.1)	119	25	0.30
Males	606	88 (7.3)	66	11	0.25
Females	586	81 (6.9)	53	14	0.35
DZ-os	928	148 (8.0)	122	13	0.18
All DZ	2120	317 (7.5)	241	38	0.24
2003					
MZ	662	151 (11.4)	41	55	0.73
Males	325	79 (12.2)	19	30	0.76
Females	337	72 (10.7)	22	25	0.69
DZ-ss	1248	263 (10.5)	169	47	0.36
Males	590	138 (11.7)	90	24	0.35
Females	658	125 (9.5)	79	23	0.37
DZ-os	903	192 (10.6)	152	20	0.51
All DZ	2151	455 (10.6)	321	67	0.29

MZ, monozygotic; DZ-ss, dizygotic same sex; DZ-os, dizygotic opposite sex.

genetic effects and also genetic interaction with the environment. As such the heritability is not informative in regards to what specific genes that cause the observed variation in the susceptibility to a disease. We acknowledge that the heritability estimate is too simple a measure to account in detail for the intricate interplay between the environment of the population and its genetic make-up, and therefore our results remain tentative in regards to the dynamics of secular change in asthma. Furthermore, the heritability is influenced by several uncontrolled factors alluding both to the design of the study and to the population within which it is calculated.¹⁵ Nevertheless, this

study offers advantages over what have previously been reported on asthma heritability, since we are able to measure this statistic at two time-points, which has not been done before.

There is an abundant literature on secular trends in asthma, mainly from affluent countries but also to some extent from developing countries. Our finding of an increase in the prevalence of asthma is in keeping with these reports. However, the major part of the change in prevalence of asthma in Western societies mainly took place between the 1960s and 1990s, and less so during the time period from the 1990s to the 2000s, where our study

Table 3 Variance components analysis of asthma in adolescent Danish twins in 1994 and 2003.

Model	Variance components ^a			Fit statistics		
	A	C/D	E	$\Delta-2 \log Q$	Δdf	P-value
1994						
ACE	0.75 (0.48–0.86)	0.04 (0.00–0.26)	0.21 (0.14–0.30)			
AE	0.79 (0.71–0.86)	—	0.21 (0.14–0.29)	0.11	1	0.738
CE	—	0.57 (0.50–0.64)	0.43 (0.36–0.50)	27.07	1	<0.001
E	—	—	1.00	186.76	2	<0.001
2003						
ADE	0.85 (0.46–0.95)	0.06 (0.00–0.45)	0.09 (0.05–0.15)			
AE	0.91 (0.85–0.95)	—	0.09 (0.05–0.15)	0.09	1	0.759
DE	—	0.92 (0.87–0.95)	0.08 (0.05–0.13)	17.72	1	<0.001
E	—	—	1.00	271.28	2	<0.001

For each model (ACE, AE, CE and E for 1994 & ADE, AE, DE and E for 2003) variance components sum to 1.00 (100%); the preferred model based on parsimony and goodness of fit is highlighted in bold print. The estimate of each component (A, C/D and E) is the proportion of the total phenotypic variance (susceptibility to asthma) that is accounted for by the specific components. $\Delta-2 \log Q$, difference in model fit (log-likelihood) between saturated model and nested model. Δdf , difference in degrees of freedom between saturated model and nested model.

^a Variance components (95% confidence intervals) of asthma susceptibility due to additive genetic factors (A), shared environmental factors (C), non-shared genetic factors (D), and non-shared environmental factors (E) adjusted for age and sex.

took place.¹⁶ We found about a 4% increase in the prevalence of asthma, mostly among adolescent boys, which is somewhat contradictory to other findings from Scandinavia, where girls apparently experienced the highest increase in prevalence.^{17,18} Many previous studies speculate on the role of environmental changes as the primary cause for the increased prevalence in asthma, mainly due to the assumption that changes in our genetic make-up could not have occurred over just a few generations within one country.¹⁹ The observed increase in the heritability of asthma over a nine year period in the present study of Danish adolescent twins could therefore suggest, but is not proof of, that individual differences in genetic liability for asthma are expressed more due to environmental changes.

The strength of this study is the almost complete ascertainment of two large comparable nationwide samples of twins. The twins for the study were systematically included through the national civil registration list, which is the least biased way to include twins for this type of survey.²⁰ Furthermore, the purpose of the study was multidisciplinary and not specifically to report on asthma. We observed a lower response rate in the 2003-survey (68%) compared with the 1994-survey (86%), which could have induced selective missingness of subjects in 2003. Information on reasons for non-participation was not available. At present, there is little reason to assume that the missingness was non-random with respect to asthma susceptibility per se. Non-randomness with respect to environmental factors influencing asthma susceptibility and maybe even asthma heritability (e.g., socioeconomic status, polluted living environment, diet), however, can at the moment not be excluded.

In the 2003-cohort, the questionnaires were addressed to and answered by the parents of the twins aged 12–15 years, whereas this was not the case in 1994. To explore the possible bias resulting from this difference in study design, we performed sensitivity analysis restricted to twins aged 16–20 years, who themselves responded to the questionnaire, and found a 17% increase in the heritability between 1994 and 2003. This suggests an even more pronounced change in the genetic liability to asthma in this age group, where the response type was uniform across the two examinations.

In 2003, the asthma question in the survey consisted only of a 'yes' check box, such that leaving the check box blank indicated a negative response by the respondent. In contrast, the asthma question in 1994 consisted of both 'yes' and 'no' check boxes. We cannot rule out that this difference in design of the asthma question may have influenced the results. Particularly, one could argue that having provided only one check box in the 2003-survey could have contributed both to a higher prevalence and similarity between twins for asthma, and reduced the overall variance in the dataset.

We have previously performed a clinical examination of the population studied in 2003 and have shown that the question on asthma used herein is a reasonably good indicator of asthma with a misclassification rate of less than 12%.²¹

As it is unlikely that a genetic change has occurred over a time-span as short as nine years, we infer from this study that the most likely explanation for the increase in the prevalence of asthma seen during the past decades is a change in the environmental circumstances of the population. Such

a change, which is probably widespread and includes multiple alterations in lifestyle associated with westernisation, has induced an increase in the genetic liability to asthma due to an increased expression of susceptibility genes for the disease. This inference pertains to recent years' findings from genetic and epidemiological studies of asthma, which have consistently found an increase in prevalence of the disease. However, even though our findings support an increase in heritability over time we still have to admit to the large gaps in knowledge about what really causes asthma. More than a hundred genes have been related to asthma, but only a subset of these has been replicated consistently in subsequent studies.²² Moreover, most of the identified susceptibility genes only show weak associations with asthma and the genotype by environment interactions that seemingly account for this vast variation between findings have not yet been discovered.²³ Processing this complex information is a major challenge for future research, and as molecular genetics advances the specific pathways by which environmental exposures interact with genetics in the expression of asthma will possibly be elucidated.

Conflicts of interest statement

None.

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