

Genes, environments, and sex: factors of importance in atopic diseases in 7–9-year-old Swedish twins

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Various atopic manifestations among adults have been shown to be influenced mainly by genetic factors. With the increase in prevalence of atopic diseases in recent years, especially among children, a great deal of attention has been given to environmental causes. In a study of 1480 Swedish twin pairs, 7–9 years old, we examined the importance of genetic and environmental factors in asthma, hay fever, eczema, and urticaria. Structural equation model fitting showed 33–76% of the variation in liability to the diseases to be due to genetic effects. Shared environmental effects were also important for hay fever and urticaria in both sexes and for eczema among girls. The clustering of atopic disease in families was almost entirely due to a common set of genes, but each disease manifestation also seemed to have specific genes of importance. Investigation of unlike-sex twins showed that boys had a higher cumulative incidence of asthma and hay fever than girls, whereas girls had a higher incidence of eczema. Thus, it may be concluded that although genetic factors are of major importance in atopic manifestation in children, both environmental and sex-related factors play a role.

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The term “atopy” has been used to denote reagenic allergies, to denote an IgE-mediated process in various conditions, and, in a broader sense, to describe symptoms of asthma, allergic rhinitis, conjunctivitis, eczema, and food sensitivity (1). Studies of twins have consistently shown heritabilities over 50% for these diseases as well as for total IgE levels (2–8), suggesting a major genetic contribution to the pathogenesis of atopic diseases. These studies have also consistently shown little or no effect of the family environment; that is, the aggregation of a specific disease in families is primarily due to genetic similarity among family members, and *not* to environmental similarity. However, in principle, all studies are performed on adults, but much of the concern with the increasing prevalence of asthma and other allergic diseases throughout the West is with children (9). This increase in prevalence has primarily been attributed to environmental causes, especially the indoor environment, because the gene pool in a population cannot change between two generations. Therefore, it could be expected that the relative importance of the family environ-

ment in atopic diseases would be higher among children than what is described in the earlier studies among adults.

Currently, there are major efforts to identify genes of importance for asthma and allergies. Several reports indicate susceptibility genes on 5q (10, 11) and 11q (12, 13), and there are recent reports of even more loci on other chromosomes (14). As in most complex diseases, several genes are related to disease occurrence, and the genes of importance might change according to the sample and phenotype (asthma, atopy, IgE levels, bronchial hyperresponsiveness, etc.) under investigation. Thus, it is not surprising that segregation analyses have shown a mixed pattern of inheritance, ranging from recessive, dominance, and codominance to polygenic inheritance (15–19). On the other hand, one would also expect to find a common genetic effect, because epidemiologic studies have indicated that different atopic diseases are related. For example, the offspring of parents with asthma are at an increased risk of allergic rhinitis or atopic dermatitis (20).

Another problem in the literature concerns sex differences in the expression of atopic diseases. Asthma has been reported to be about 150% more prevalent among Swedish boys than girls (21–23). On the other hand, a study of 14-year-olds showed a higher prevalence of both asthma and allergic asthma among girls than boys (24). There are also contradictory results in the international literature on sex differences in atopic manifestations, even though most studies seem to show an excess of asthma and rhinitis in boys and of eczema and urticaria in girls (25–33).

To examine the relative importance of genetic and shared environmental influences in atopic diseases, as well as the degree of a common genetic origin of diseases, we investigated different disease manifestations of twins 7–9 years old. The data were also used to investigate sex differences in disease occurrence.

Material and methods

Subjects

In autumn 1994, all parents of twins born in Sweden between April 1985 and December 1986 were mailed a detailed questionnaire on asthma and allergies as well as other diseases and traits. The twins were identified through the population-based Swedish Twin Registry of virtually all twins born in Sweden since 1886. The base sample comprised 1480 pairs of twins still living in Sweden. Nonresponders were sent up to three reminders, and 1106 (75%) parents responded to the questionnaire. Of the remaining nonresponders, telephone numbers were obtained for an additional 253 twin pairs. These parents were contacted, and the parts of the questionnaire concerning zygosity, demographic information, and asthma and allergic manifestations were completed by an interviewer. Some 233 interviews were completed, resulting in a final response rate of 90% (1339 twin pairs).

Zygosity (for the like-sex twins) was determined by the question, "Are your twins as similar as peas in a pod, or are they no more alike than siblings in general?" If the parent responded, "Similar as peas in a pod", the twins were assumed to be monozygotic (MZ), but if the response was, "No more alike than siblings in general", the twins were assumed to be dizygotic (DZ). This zygosity determination technique has shown a 95% level of validity in Sweden (34) and other countries (35). For the quantitative genetic analyses, the twin pairs were divided into the following five groups: MZ girls ($n=210$), DZ girls ($n=246$), MZ boys ($n=211$), DZ boys ($n=223$), and DZ unlike-sex ($n=387$). The parents of the remaining 62 pairs responded "don't

know" to the zygosity question and could not be assigned a zygosity.

Measures

The questionnaire included both diagnostic items and questions about diagnoses by a physician in order to evaluate different disease classifications. Each disease was classified by a broad criterion and a strict criterion.

Asthma. A subject was classified as asthmatic according to the strict criterion if the parent responded that the child was diagnosed with asthma by a physician, or if the child had parental reported asthma and at least four episodes of asthma symptoms during the last 12 months. A broad diagnosis was given if the child had ever had wheezing with shortness of breath, wheezing without a cold, or parental reported asthma.

Hay fever. A strict diagnosis of hay fever was indicated if the child was diagnosed with hay fever by a physician or if the parent reported more than four illness episodes during the child's lifetime. A broad diagnosis was given if the child had ever had red, itchy eyes or hay fever.

Eczema. A strict diagnosis was assigned if the child had a physician diagnosis of eczema (excluding psoriasis and contact eczema), whereas a broad diagnosis was assigned if the parent responded that the child had had itching, erythema, papules, and dry, scaling skin that improved and worsened over time on areas such as arms, legs, face, or trunk.

Urticaria. The strict diagnosis was assigned if the parent reported that the child had received a physician diagnosis of urticaria, and the broad diagnosis was assumed if the parent responded "yes" to the item, "Has this child had disseminated eruption of migrating, itching wheals?"

Food allergies. One question also asked for food allergies. The responses were then categorized into the following groups: gluten (celiac disease), milk, egg, fish, nuts, and peanuts. This item was not included in the telephone interview of the nonresponders; thus, it had a lower response rate.

Analyses

Twin similarity is normally evaluated by concordance rates, and the most appropriate is the probandwise concordance (36). Probandwise concordance rates, calculated as the probability that a twin will be affected if the other twin is affected,

will be presented. However, the magnitude of the probandwise concordance depends on the prevalence of the disease and therefore does not reflect the magnitude of genetic and environmental effects. Thus, tetrachoric correlations, which are a measure of correlation in disease liability, will also be presented.

In quantitative genetic analyses, the relative importance of genetic and environmental factors in liability to disease is estimated. With binary outcomes (disease/not disease), the assumption of an underlying normal distribution of liability (or susceptibility) to the disease is used. This liability is the sum of effects due to many genetic and environmental factors, and the liability distribution has one threshold value that discriminates between the categories (37, 38). Thus, a subject affected by the disease would exceed the (unmeasured) threshold value of the liability distribution. The importance of genetic effects is indicated by a higher tetrachoric correlation among MZ than DZ pairs. Shared environmental effects reflect a twin similarity that is not explained by genetic effects, whereas nonshared environmental effects are evidenced by within-pair differences. Two-by-two contingency tables of disease status in twin pairs (twin 1 vs twin 2) for the five groups of twins were entered simultaneously into a structural model fitting program (39) to provide estimates of the relative importance of genetic (G), shared environmental (C), and nonshared environmental effects (E). Sex-specific threshold values from the complete sample were used in the models. The path diagram depicted in Fig. 1 was used to obtain estimates of G, C, and E (38), with asthma as an example.

The phenotypic correlations between the two diseases were evaluated in bivariate analyses. Fig. 2 depicts the model used with asthma and hay fever as an example, but, for purposes of clarity, it includes only one of the twins in a pair. The genetic (r_g) and environmental (r_c , r_e) correlations between the diseases indicate the extent to which the same set of genes (or environments) are important for the disease expressions. The portion of phenotypic correlation that may be attributed to genetic or environmental "chains" can be calculated as the product of the relevant paths. For example, the genetic chain in Fig. 2 is equal to $g_a * r_g * g_r$, and represents the component of the phenotypic association that is due to genetic effects. It should be noted that because genetic (or environmental) effects may be of minor importance for a disease, the importance of genetic effects for a phenotypic association may be low, even if there is a high r_g .

In the quantitative genetic analyses, there were no substantial differences in the magnitude of

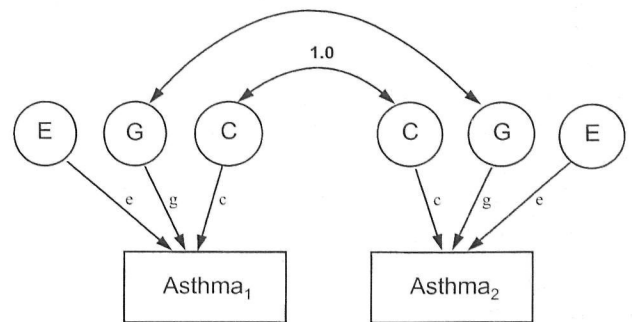


Fig. 1. Path diagram depicting how twin similarity is modeled for genetic and environmental effects. Asthma₁, Asthma₂: asthma in first and second twin in twin pair; G: genetic factor; g: genetic loading; E: nonshared environmental factor; e: nonshared environmental loading; C: shared environmental factor; c: shared environmental loading; MZ: monozygotic twins; DZ: dizygotic twins.

the importance of genetic and environmental influences for the diseases by either the broad or strict criteria. Therefore, only results from the analyses with the broad diagnoses will be presented.

Results

The cumulative incidence rates of the different diseases in the children diagnosed from the questionnaire are shown in Table 1. The table also shows the significance of the sex differences ascertained by performing matched-pair analyses of boys and girls in the unlike-sex twin pairs. Unlike-sex twins provide the best possible comparison group because the two children in an unlike-sex twin pair not only have exactly the same age, but also share (as ordinary siblings) 50% of their segregating genes and probably a significant part of their environments, especially their family environment. The analyses show that boys had more than a double risk of being diagnosed with asthma and hay fever compared to girls. On the other hand, boys had a lower risk of being diagnosed with eczema than girls, a risk that was significant with the broad diagnosis. For urticaria, there also seemed to be a tendency for boys to have a lower risk of being diagnosed, even though the data here were not conclusive.

Twin similarity

Table 2 displays the number of discordant and concordant affected pairs, probandwise concordances, and tetrachoric correlations for the different twin groups. For all disease categories, the concordances and the correlations were consistently higher among monozygotic than among dizygotic twins.

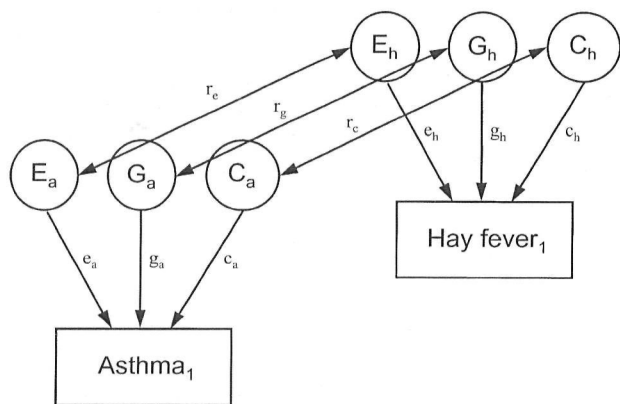


Fig. 2. Path model depicting degree of genetic and environmental correlations between two diseases. Diagram is simplified, and contains only one of twins in pair. 1: disease status for twin one; a: genetic/environmental factor/loading for asthma; h: genetic/environmental factor/loading for hay fever; G: genetic factor; g: genetic loading; E: nonshared environmental factor; e: nonshared environmental loading; C: shared environmental factor; c: shared environmental loading.

This indicates that genetic effects were important in the pathogenesis of asthma, hay fever, eczema, and urticaria.

Model fitting: univariate results

The univariate analyses are presented in Table 3. As indicated by the tetrachoric correlations, there were moderate to substantial genetic effects of importance for all the atopic diseases. Heritabilities ranged from 0.33 (hay fever for boys) to 0.76 (asthma for boys). Genetic effects thus accounted for 33–76% of the variation in liability to atopic diseases. There was no evidence of shared environmental effects for asthma or for eczema in boys. However, shared environmental effects were indicated for hay fever and urticaria for both sexes and for eczema in girls. Finally, nonshared environmental effects were significant for all the diseases, but it should be noted that these effects accounted for only 13–38% of the variation in liability.

Model fitting: bivariate results

The next step in the analyses is to investigate whether and how the different atopic expressions are associated. Table 4 shows the results from bivariate analyses of two diseases at a time. The table presents tetrachoric correlations, which measure the association between two diseases, and also the results from model fitting where the genetic and environmental correlations are estimated. The relative importance of the genetic and environmental

Table 1. Cumulative incidence of 7–9-year-old twins with questionnaire diagnosis of atopic diseases and odds ratio for boys in unlike-sex twin pairs to have questionnaire diagnosis of atopic diseases compared to their twin sisters

Disease	Cumulative incidence		Comparison of boys to their twin sisters	
	Boys	Girls	Odds ratio	95% Confidence interval
Asthma				
Strict diagnosis	0.08	0.04	2.56	1.22–5.37
Broad diagnosis	0.18	0.10	2.19	1.40–3.45
Hay fever				
Strict diagnosis	0.08	0.05	2.25	1.16–4.36
Broad diagnosis	0.12	0.08	2.10	1.24–3.59
Eczema				
Strict diagnosis	0.07	0.09	0.62	0.33–1.18
Broad diagnosis	0.16	0.22	0.64	0.42–0.96
Urticaria				
Strict diagnosis	0.06	0.07	0.71	0.34–1.47
Broad diagnosis	0.12	0.16	0.62	0.38–1.02
Food allergies	0.09	0.10	0.97	0.60–1.57
Gluten	0.0037	0.0101		
Milk	0.0082	0.0155		
Egg	0.0101	0.0046		
Fish/shellfish	0.0101	0.0101		
Nuts	0.0155	0.0137		
Peanuts	0.0027	0.0046		

Numbers of subjects were 1280–1306 for boys and 1323–1359 for girls for asthma, hay fever, eczema, and urticaria diagnoses, and 1094 for both boys and girls for food allergy diagnoses.

chains for the phenotypic correlations is also included in the table.

For the association between asthma and hay fever, the genetic correlation is 0.90, and the association is entirely due to genetic effects. This means that most of the genes that are important for the development of asthma are also important for hay fever. Furthermore, familial clustering of asthma and hay fever seems to be due completely to genetic effects in common with the diseases. The genetic correlations in the other analyses range from 0.35 to 0.73, indicating that there are common sets of genes for all the diseases. The fact that the genetic correlation is not unity indicates that there are also genetic effects unique to each of the atopic diseases. On the other hand, the association between any two diseases is almost entirely explained by the genetic pathway (chain). The high shared environmental correlation indicates that when shared environmental effects are important for two diseases, the same effects seem to operate in both diseases. However, the confidence intervals are broad, and caution is warranted in drawing conclusions. Nonshared environmental effects seem to be of little importance in the association between these diseases.

Table 2. No. of concordant and discordant affected twin pairs, probandwise concordance, and tetrachoric correlations for broad diagnoses of atopic diseases for different twin groups

	Boys		Girls		Unlike-sex DZ
	MZ	DZ	MZ	DZ	
Asthma					
No. of concordant affected pairs	25	9	8	4	14
No. of discordant affected pairs	30	52	23	36	83
Probandwise concordance	0.62	0.26	0.41	0.18	0.25
Tetrachoric correlation	0.79	0.25	0.64	0.27	0.26
Hay fever					
No. of concordant affected pairs	15	11	11	6	13
No. of discordant affected pairs	20	20	15	23	59
Probandwise concordance	0.60	0.43	0.59	0.34	0.31
Tetrachoric correlation	0.81	0.63	0.85	0.60	0.44
Eczema					
No. of concordant affected pairs	16	14	36	17	23
No. of discordant affected pairs	27	52	26	51	95
Probandwise concordance	0.54	0.35	0.73	0.40	0.33
Tetrachoric correlation	0.73	0.38	0.88	0.48	0.32
Urticaria					
No. of concordant affected pairs	12	8	25	12	19
No. of discordant affected pairs	22	33	23	39	65
Probandwise concordance	0.52	0.33	0.68	0.38	0.37
Tetrachoric correlation	0.74	0.48	0.87	0.54	0.50

MZ: monozygotic twins; DZ: dizygotic twins.

Discussion

The prevalence of IgE-mediated diseases is increasing in the industrialized world, and a major concern is the increase in atopic manifestations in children. To our knowledge, this study showing major

genetic effects of atopic manifestations in children is the first to evaluate allergy in a population-based sample of young twins. The cumulative incidences of asthma, hay fever, eczema, and urticaria agree with results from the general Swedish population (40). Therefore, the twin sample may be assumed to be representative of the general population.

Univariate results

Major influences of genetic effects were found for all atopic manifestations studied. Heritabilities ranged from 0.33 for hay fever for boys to 0.76 for asthma for boys. These results are compatible with earlier studies on adults (2, 3, 8), and indicate that genetic effects are of significant importance for asthma and allergies during the entire life span. Even though this result is not surprising, it should be viewed in the light of the current discussion of environmental effects of importance in the increase in atopic manifestations during the last decade (9). Because the primary reason for the increase must be environmental (there cannot be a change in the gene pool between two generations), it has been assumed that the relative importance of genetic effects would diminish. However, the results presented here indicate that even though the changing environment increases the cumulative incidence of diseases, a genetic predisposition is still necessary to develop atopic manifestations. The difference is that patients with less genetic susceptibility now get the disease. This indicates that younger children may not be well suited for use in linkage studies because there is a greater chance that they have a lower genetic predisposition to disease.

An interesting result of this study was the indication of shared environmental effects for hay fever and urticaria in both sexes and for eczema in girls. Most earlier twin studies have failed to show any effect of the shared environment on atopic

Table 3. Parameter estimates and 95% confidence intervals from quantitative genetic analyses of genetic and environmental effects for broad diagnoses of atopic diseases

	Parameter estimate 95% confidence interval						Fit of model		
	Boys			Girls					
	G	C	E	G	C	E	χ^2	df	P
Asthma	0.76 0.37–0.87	0 0.00–0.33	0.24 0.13–0.41	0.62 0.01–0.81	0 0.00–0.52	0.38 0.19–0.64	10.84	11	0.46
Hay fever	0.33 0.00–0.89	0.48 0.00–0.82	0.19 0.08–0.39	0.70 0.00–0.92	0.14 0.00–0.82	0.16 0.06–0.38	6.58	11	0.83
Eczema	0.74 0.15–0.87	0 0.00–0.47	0.26 0.13–0.45	0.71 0.31–0.93	0.16 0.00–0.51	0.13 0.07–0.25	10.35	11	0.49
Urticaria	0.54 0.00–0.86	0.21 0.00–0.70	0.25 0.12–0.47	0.60 0.13–0.91	0.25 0.00–0.65	0.15 0.07–0.29	10.68	11	0.47

G: genetic effects; C: shared environmental effects; E: nonshared environmental effects.

Table 4. Phenotypic correlations, correlations between genetic and environmental factors, and proportion of correlation due to genetic and environmental chains for two atopic diseases

Diseases	Phenotypic correlation ^a	Genetic/environmental correlation between diseases			Proportion of correlation due to chain		
		r_g	r_c	r_e	Genetic	Shared environmental	Nonshared environmental
Asthma and hay fever	0.54	0.90 (0.67–1.00)	*	0.00 (0.00–0.42)	100%	*	0%
Asthma and eczema	0.30	0.35 (0.23–0.48)	*	0.25 (0.00–0.68)	85%	*	15%
Asthma and urticaria	0.29	0.48 (0.30–0.69)	*	0.05 (0.00–0.64)	98%	*	2%
Hay fever and eczema	0.49	0.73 (0.46–1.00)	1.00 (0.00–1.00)	0.00 (0.00–0.35)	96%	4%	0%
Hay fever and urticaria	0.39	0.45 (0.05–0.90)	0.39 (0.00–1.00)	0.30 (0.00–0.82)	69%	19%	12%
Eczema and urticaria	0.47	0.48 (0.25–0.73)	1.00 (0.00–1.00)	0.20 (0.00–0.66)	76%	17%	7%

^a Tetrachoric correlation.

* Parameter not estimated because there was no evidence of shared environmental effects for asthma in univariate analyses.

 r_g : correlation between latent genetic factors for two diseases; r_c : correlation between latent shared environmental factors for two diseases. r_e : correlation between latent nonshared environmental factors for two diseases.

manifestation (2, 3, 8); all twin similarity has been attributed to genetic effects. A Finnish study reported shared environmental effects for men with a very strict diagnosis of asthma (hospital admission or enrollment with the social insurance institution requiring chronic antiasthma medication) (6). However, that study had very few concordant pairs; accordingly, confidence intervals around parameter estimates became wide. The shared rearing environmental parameters in the present study also had relatively broad confidence intervals and all included zero. However, the consistency of results indicates that shared environmental effects were important in at least some of the diseases. In the light of the discussion about the importance of indoor environments for atopic diseases, it is easy to suggest what these effects could have been. For example, pets, passive smoking, and house-dust mites all involve allergens that are shared by members in a twin pair in the ages studied here and therefore could have contributed to the shared environmental parameter.

Bivariate results

The genetic correlations between any two disease manifestations ranged from 0.35 to 0.90, indicating that there are sets of genes in common for all these diseases. The associations among any two of the diseases are almost entirely explained by the genetic pathway. On the other hand, none of the genetic correlations reached unity, and with the possible exception of the association between

asthma and hay fever, the results suggest that there were substantial genetic effects independent of each disease manifestation. A similar finding was indicated in a family study of adults with atopic dermatitis, showing a specific inheritance of the skin disease independent of the inheritance of respiratory atopy (41). These results have implications for a study designed to locate genes of importance in atopy. If the goal is to find a gene for general susceptibility to atopic diseases, subjects should probably be identified through families with an aggregation of any type of atopic manifestation. However, this study design would also include subjects in whom different susceptibility genes are important for different disease manifestations. Thus, there may be a lack of power to detect true linkage. One way to improve power would be to include only heavily loaded families, that is, families in which several members have several atopic diseases. A different approach might be to include only families in which the affected members have the same manifestation. However, the gene of interest in this case is probably not a susceptibility gene for atopy but rather one more specific to the organ system under study.

Sex differences

There were sex differences in the disease manifestation. Boys had more than a double risk of being diagnosed with asthma and hay fever compared with girls, while girls had a higher risk of being diagnosed with eczema. Earlier studies have been inconsistent

with regard to sex differences in atopic diseases (21, 23-33). As shown by the present study, these diseases are strongly influenced by genetic influences, and some manifestations also seem to be influenced by shared environmental effects. A good estimate of the magnitude of the sex differences would ideally be obtained after control for genetic and shared environmental effects. Because these effects are controlled for as far as possible in the matched-pair analysis in this study, it seems clear that there are sex differences in the cumulative incidence of different atopic manifestations among 7-9-year-old children. Boys more often have airway disease while girls more often have eczema. The basis of these sex differences is still unclear. One obvious reason may be that boys and girls are exposed to different environmental risk factors (e.g., pets, sports). One might speculate that physiologic differences in development result in relatively more limited airways for boys during childhood and thus an increase in airway symptoms. Another interpretation is that physicians are sex-biased in diagnosis of asthma and allergic rhinitis, or that symptoms of the same underlying disease are perceived differently for boys and girls. In a Swiss study, 31% of all boys reporting asthma symptoms received bronchodilator treatment, compared to 15% of the girls reporting symptoms. For nearly all asthma-related symptoms, significantly more boys than girls received treatment (42). Thus, it is possible that physicians use diagnostic tools that work better for boys than for girls.

Conclusions

This study shows that genetic effects are of major importance in atopic diseases in 7-9-year-old children, even though an increase in these diseases has been seen in the last decades. Of the variation in liability to asthma, hay fever, eczema, and urticaria, 33-76% was due to genetic effects. There were also moderate shared environmental effects, at least for some of the manifestations. The clustering of atopic disease in families was almost entirely due to common sets of genes for the diseases, but the disease manifestations also seem to have had disease-specific genes of importance. Furthermore, intrapair differences within unlike-sex twins, whereby boys had a higher cumulative incidence of asthma and hay fever and girls had a higher incidence of eczema, indicate that sex-related factors were important in the diseases.

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