

Cross-sectional study of allergic disorders in relation to familial factors in Japanese adolescents

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Aim: The roles of heredity and the household environment in the development of allergic disorders are not clearly established. This study examined the relationship between selected familial factors and the prevalence of symptoms of wheeze, atopic eczema and rhinoconjunctivitis in Japanese adolescents. **Methods:** Study subjects were 5539 students aged 12–15 y in Suita City. A questionnaire ascertained gender, grade, number of older siblings, maternal age at childbirth, smoking in the household, domestic pets and parental history of allergy, as well as signs and symptoms of allergy in the previous 12 mo. The latter were based on diagnostic criteria from the International Study of Asthma and Allergies in Childhood. **Results:** Male gender was independently associated with an increased prevalence of wheeze and a decreased prevalence of atopic eczema. The prevalence of rhinoconjunctivitis, but not wheeze or atopic dermatitis, significantly increased with advancing grade. A significant inverse dose–response relationship between the number of older siblings and the prevalence of rhinoconjunctivitis, but not wheeze or atopic dermatitis, was observed. Maternal age at childbirth, smoking in the household and domestic pets were not apparently related to any of the allergic disorders. A positive maternal allergic history was more evidently associated with an increased prevalence of wheeze and rhinoconjunctivitis, but not atopic eczema, than a positive paternal allergic history.

Conclusion: The findings suggest that the factors associated with allergic disorders in Japan are largely the same as those already identified in Western populations.

Key words: Allergic rhinitis, atopic dermatitis, environment, heredity, wheeze

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The International Study of Asthma and Allergies in Childhood (ISAAC) has shown that the prevalence values of childhood allergic disorders are very high in Japan, similar to those in Western countries (1–3), but the reasons are unknown. A twin-family study in Finland indicated that genetic factors are of great importance in the development of asthma (4). Maternal atopy is generally acknowledged as a stronger predictor of allergic disorders in offspring than is paternal atopy (5–7); however, reports have shown that a paternal history of allergy had a more prominent association (8, 9). A cohort study of 4-y-old children in the UK showed that a family history of atopy was significantly related to an increased risk of asthma and rhinitis, but not eczema (10). Thus, the magnitude of the contribution of heredity is inconclusive.

The worldwide variations in prevalence of allergic disorders suggest that environmental factors are important determinants of disease expression (1–3, 11). However, the role of environmental factors is still not clearly established. Among environmental factors that have been examined are passive smoking (5, 7, 8, 10,

12–14), exposure to domestic pets (5, 8, 10) and maternal age at childbirth (9, 15, 16), but the results are inconsistent. A review of the sibling effect demonstrated that an inverse association with the number of siblings is more evident for hayfever and sensitization than for asthma and eczema, showing a stronger effect for older than for younger siblings (17).

To assess the impact of heredity and environment on the manifestation of allergic disorders, the present study examined the association between selected familial factors and the prevalence of symptoms of wheeze, atopic eczema and rhinoconjunctivitis in Japanese adolescents over a 12 mo period using the diagnostic criteria of the ISAAC.

Materials and Methods

Study population

Suita City, with a total population of almost 350 000, is a suburban residential city in western Japan. All 18 public junior high schools in Suita City took part in

surveys from 22 to 26 October 2001, of general medical history and subjective symptoms, conducted by the Suita City Municipal Board of Education. Details of the health survey have been described elsewhere (18, 19). In brief, a questionnaire was distributed through all public junior high schools to the parents of the entire school population of 9008 schoolchildren aged 12–15 y. In total, 6845 questionnaires (76%), which were answered by the parents, were returned. A total of 1306 children was excluded because of missing or illogical data on the factors under study. The final analysis comprised 5539 subjects (61%).

Measurement

The questionnaire included the ISAAC core questions on symptoms in the past 12 mo of wheeze, atopic eczema and rhinoconjunctivitis. The questionnaire also inquired about gender, grade, number of older siblings, maternal age at childbirth, smoking in the household, indoor domestic pets (cats, dogs or birds), and maternal and paternal history of asthma, atopic dermatitis and allergic rhinitis. Smoking in the household was defined as positive if 10 or more cigarettes a day were smoked inside the house.

Statistical analysis

The number of older siblings was classified into three categories (0, 1 and ≥ 2), and maternal age at childbirth was also classified into three categories (<25, 25–29 and ≥ 30 y). Logistic regression analysis was used to estimate crude odds ratios (ORs) and 95% confidence intervals (95% CIs). Multiple logistic regression analysis was used to control for the potential confounding effects of selected factors. Trend of association was assessed by a logistic regression model assigning scores to the levels of the independent variable. *p*-Values (two-sided) less than 0.05 were regarded as statistically significant. All computations were performed using PC-SAS version 6.12 (SAS Institute, Cary, NC, USA).

Results

There was no clear difference between the 6845 participants and 2163 non-participants in terms of gender and grade. Study subjects were less likely to have two or more older siblings, fathers with a history of asthma and mothers with a history of each of the allergic disorders, and were more likely to have mothers aged 25–29 y at childbirth than participants who were excluded because of incomplete data but who did answer questions on these issues. There was no statistically significant difference between the excluded participants and study subjects regarding gender, grade, smoking in the household, indoor domestic pets, a paternal history of atopic eczema and allergic rhinitis, and the prevalence of any of the outcomes.

The overall prevalence values for symptoms of

Table 1. Distribution of selected familial factors in 5539 children in Suita, Japan, 2001.

Factor	n (%)
Male gender	2698 (48.7)
Grade	
1	1896 (34.2)
2	1869 (33.7)
3	1774 (32.0)
Older siblings	
0	2614 (47.2)
1	2120 (38.3)
≥ 2	805 (14.5)
Maternal age at childbirth (y)	
<25	812 (14.7)
25–29	2733 (49.3)
≥ 30	1994 (36.0)
Smoking in household	2647 (47.8)
Indoor domestic pets (cats, dogs and birds)	1045 (18.9)
Paternal history of asthma	348 (6.3)
Paternal history of atopic dermatitis	239 (4.3)
Paternal history of allergic rhinitis	1716 (31.0)
Maternal history of asthma	338 (6.1)
Maternal history of atopic dermatitis	292 (5.3)
Maternal history of allergic rhinitis	2328 (42.0)

wheeze, atopic eczema and rhinoconjunctivitis in the previous 12 mo were 6.7%, 14.5% and 23.9%, respectively.

Table 1 shows the distribution of selected familial factors under study in 5539 children. About half of the children had no older siblings and had at least one smoker in the household. Only 15% of children were born to mothers under the age of 25 y. Many more children had parents with a history of allergic rhinitis than parents with a history of asthma or atopic eczema.

Table 2 presents adjusted ORs and 95% CIs of allergic disorders in relation to selected familial factors. Little difference was found between crude and adjusted ORs for each factor. After adjustment for selected familial factors under study, male gender was independently associated with an increased prevalence of wheeze (adjusted OR 1.37, 95% CI 1.11–1.70). There was no statistically significant association between grade, older siblings, maternal age at childbirth, smoking in the household or indoor domestic pets and the prevalence of wheeze. Both paternal and maternal histories of asthma and maternal atopic dermatitis were independently associated with an increased prevalence of wheeze. Paternal atopic dermatitis and both maternal and paternal allergic rhinitis did not influence the prevalence of wheeze.

There was an independent inverse relationship between male gender and atopic eczema (adjusted OR 0.81, 95% CI 0.69–0.94). Grade, older siblings, maternal age, smoking in the household and indoor domestic pets were not materially associated with the prevalence of atopic dermatitis. With the exception of paternal asthma and maternal rhinitis, parental allergic

Table 2. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of allergic disorders in relation to selected familial factors in 5539 children in Suita, Japan, 2001.

Factors	Wheeze		Atopic dermatitis		Allergic rhinoconjunctivitis	
	Prevalence	OR (95% CI) ^a	Prevalence	OR (95% CI) ^a	Prevalence	OR (95% CI) ^a
Gender						
Female	163/2841 (5.7%)	1.00	450/2841 (15.8%)	1.00	681/2841 (24.0%)	1.00
Male	206/2698 (7.6%)	1.37 (1.11–1.70)	352/2698 (13.1%)	0.81 (0.69–0.94)	644/2698 (23.9%)	0.99 (0.87–1.13)
Grade						
1	142/1896 (7.5%)	1.00	264/1896 (13.9%)	1.00	415/1896 (21.9%)	1.00
2	122/1869 (6.5%)	0.89 (0.69–1.15)	279/869 (14.9%)	1.10 (0.92–1.32)	453/1869 (24.2%)	1.17 (1.00–1.37)
3	105/1774 (5.9%)	0.80 (0.61–1.04)	259/1774 (14.6%)	1.06 (0.88–1.28)	457/1774 (25.8%)	1.27 (1.09–1.49)
Older siblings						
0	158/2614 (6.0%)	1.00	356/2614 (13.6%)	1.00	686/2614 (26.2%)	1.00
1	152/2120 (7.2%)	1.21 (0.95–1.55)	327/2120 (15.4%)	1.16 (0.98–1.38)	490/2120 (23.1%)	0.88 (0.76–1.02)
≥2	59/805 (7.3%)	1.27 (0.89–1.79)	119/805 (14.8%)	1.08 (0.84–1.38)	151/805 (18.8%)	0.70 (0.56–0.87)
Maternal age at childbirth (y)						
<25	49/812 (6.0%)	1.00	120/812 (14.8%)	1.00	219/812 (27.0%)	1.00
25–29	184/2733 (6.7%)	1.08 (0.77–1.53)	373/2733 (13.7%)	0.91 (0.72–1.15)	672/2733 (24.6%)	0.88 (0.73–1.06)
≥30	136/1994 (6.8%)	1.12 (0.77–1.64)	309/1994 (15.5%)	1.10 (0.85–1.42)	434/1994 (21.8%)	0.88 (0.71–1.08)
Smoking in household ^b						
No	193/2892 (6.7%)	1.00	417/2892 (14.4%)	1.00	687/2892 (23.8%)	1.00
Yes	176/2647 (6.7%)	0.97 (0.78–1.21)	385/2647 (14.5%)	1.04 (0.89–1.22)	638/2647 (24.1%)	1.11 (0.98–1.27)
Indoor domestic pets ^c						
No	285/4494 (6.3%)	1.00	646/4494 (14.4%)	1.00	1087/4494 (24.2%)	1.00
Yes	84/1045 (8.0%)	1.28 (0.98–1.65)	156/1045 (14.9%)	1.03 (0.85–1.25)	238/1045 (22.8%)	0.95 (0.80–1.12)
Paternal history of asthma						
No	314/5191 (6.1%)	1.00	739/5191 (14.2%)	1.00	1230/5191 (23.7%)	1.00
Yes	55/348 (15.8%)	3.07 (2.21–4.19)	63/348 (18.1%)	1.24 (0.92–1.65)	95/348 (27.3%)	1.17 (0.90–1.50)
Paternal history of atopic dermatitis						
No	347/5300 (6.6%)	1.00	737/5300 (13.9%)	1.00	1256/5300 (23.7%)	1.00
Yes	22/239 (9.2%)	1.11 (0.68–1.74)	65/239 (27.2%)	2.11 (1.55–2.85)	69/239 (28.9%)	1.11 (0.82–1.50)
Paternal history of allergic rhinitis						
No	254/3823 (6.6%)	1.00	503/3823 (13.2%)	1.00	792/3823 (20.7%)	1.00
Yes	115/1716 (6.7%)	0.93 (0.73–1.18)	299/1716 (17.4%)	1.34 (1.14–1.57)	533/1716 (31.1%)	1.57 (1.37–1.80)
Maternal history of asthma						
No	316/5201 (6.1%)	1.00	734/5201 (14.1%)	1.00	1211/5201 (23.3%)	1.00
Yes	53/338 (15.7%)	2.58 (1.85–3.56)	68/338 (20.1%)	1.36 (1.01–1.79)	114/338 (33.7%)	1.41 (1.10–1.79)
Maternal history of atopic dermatitis						
No	330/5247 (6.3%)	1.00	714/5247 (13.6%)	1.00	1227/5247 (23.4%)	1.00
Yes	39/292 (13.4%)	2.11 (1.44–3.02)	88/292 (30.1%)	2.51 (1.91–3.27)	98/292 (33.6%)	1.35 (1.04–1.75)
Maternal history of allergic rhinitis						
No	190/3211 (5.9%)	1.00	430/3211 (13.4%)	1.00	519/3211 (16.2%)	1.00
Yes	179/2328 (7.7%)	1.23 (0.99–1.53)	372/2328 (16.0%)	1.15 (0.98–1.34)	806/2328 (34.6%)	2.62 (2.31–2.99)

^a Based on multiple logistic regression controlling for gender, grade, older siblings, maternal age at childbirth, smoking in household, indoor domestic pets, paternal history of asthma, atopic dermatitis and allergic rhinitis, and maternal history of asthma, atopic dermatitis and allergic rhinitis.

^b At least 10 cigarettes a day smoked inside the house.

^c Cats, dogs and birds.

history was independently associated with an increased prevalence of atopic dermatitis.

The prevalence of rhinoconjunctivitis was not markedly different between genders. Higher grade was independently related to an increased prevalence of rhinoconjunctivitis, showing a positive dose–response relationship (p for linear trend = 0.003). In contrast, there was a significant inverse association between two or more older siblings and rhinoconjunctivitis (p for linear trend = 0.002). No apparent relationship was found between maternal age, smoking in the household or indoor domestic pets and rhinoconjunctivitis. Maternal but not paternal histories of asthma and eczema and both paternal and maternal rhinitis were

independently associated with an increased prevalence of rhinoconjunctivitis.

When subjects were divided according to parents with at least one allergic disorder, a positive allergic history in both parents doubled the prevalence of wheeze and atopic dermatitis and quadrupled the prevalence of rhinoconjunctivitis (Table 3). A positive maternal allergic history was more evidently associated with an increased prevalence of wheeze and rhinoconjunctivitis, but not atopic eczema, than a positive paternal allergic history. However, a clear positive dose–response association was observed for all of the allergic disorders in the offspring (p for linear trend <0.0001 for each allergic disorder). No marked

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of allergic disorders according to parents with at least one allergic disorder in 5539 children in Suita, Japan, 2001.

Parental history	Adjusted OR (95% CI) ^a		
	Wheeze	Atopic dermatitis	Rhinoconjunctivitis
Neither parent	1.00	1.00	1.00
Father only	1.19 (0.84–1.68)	1.61 (1.28–2.02)	1.64 (1.33–2.02)
Mother only	1.49 (1.13–1.98)	1.42 (1.16–1.73)	2.82 (2.38–3.35)
Both parents	2.08 (1.56–2.76)	1.98 (1.61–2.43)	4.10 (3.44–4.91)
<i>p</i> for linear trend	<0.0001	<0.0001	<0.0001

^a Based on multiple logistic regression controlling for gender, grade, older siblings, maternal age at childbirth, smoking in household and indoor domestic pets.

differences between genders were found ($p = 0.84$, 0.32 and 0.88 for homogeneity of OR for wheeze, atopic eczema and rhinoconjunctivitis, respectively).

Discussion

In the present study, male gender was independently associated with an increased prevalence of wheeze and a decreased prevalence of atopic eczema. There was no relation between gender and rhinoconjunctivitis. Previous findings on gender and allergic disorders were not necessarily consistent. Phase I of the ISAAC study reported that, on average, prevalence values of symptoms of asthma and atopic dermatitis in the 13–14-y age group were higher for females than for males, although the proportion of females and males studied varied among the centers in 56 countries (1, 2). A longitudinal study of children aged 5–9 y showed that male gender was independently associated with a 2.4-fold increased risk of asthma (13), whereas gender was unrelated to asthma in a case–control study of children aged 3–4 y in Canada (8). More information is needed regarding the question of whether the association between gender and allergic disorders is age related in Japan.

The prevalence of rhinoconjunctivitis, but not wheeze or atopic dermatitis, significantly increased with advancing grade in the present study. The ISAAC showed prevalence values for symptoms of wheeze, atopic eczema and rhinoconjunctivitis in the previous 12 mo of 17.3%, 16.9% and 7.8%, respectively, in Japanese children aged 6–7 y, and 13.4%, 10.5% and 14.8%, respectively, in those aged 13–14 y (1–3). The present results partially agree with these observations. The older children may have had more time to be sensitized to cedar pollen with increasing grade.

A significant inverse dose–response relationship between the number of older siblings and the prevalence of rhinoconjunctivitis, but not wheeze or atopic dermatitis, was observed in this survey. Karmaus and Botezan reviewed 53 different studies, mainly in

Europe, on the sibling effect in allergic disorders (17). For hayfever, all 17 reviewed studies found a significant inverse relation with sibling size; for eczema, 9 of 11 studies reported an inverse association; and for asthma or wheeze, 21 of 31 studies showed such an effect. Six of seven analyses revealed a stronger protective effect by having older siblings than by having younger siblings. The present findings are in partial agreement with these observations. Karmaus and Botezan suggested that it is time to consider alternative explanations such as *in utero* programming or endocrine effects rather than the prevailing “hygiene hypothesis” (17). The *in utero* environment is likely to change with parity and the organochlorine burden seems to decrease with an increasing number of children (17, 20). The interpretation that the sibling effect was a causal factor related to the clinical manifestation of rhinoconjunctivitis, but not wheeze or atopic dermatitis, is problematic since in the present study only 15% of children had two or more older siblings. It may be difficult to detect a clear inverse relationship of sibling size with wheeze or atopic eczema in a population with fewer children.

The current research showed that maternal age at childbirth, smoking in the household and indoor domestic pets were not apparently related to any of the allergic disorders. A retrospective cohort study of Swedish conscripts showed that young maternal age was independently associated with an increased risk of asthma, but a decreased risk of allergic rhinitis (15). A historical cohort study of UK adolescents also found a significant inverse association between young maternal age and hayfever (16). In a prospective study of British children, maternal age did not affect the risk of atopic eczema (9). The current results may reflect similar patterns of childcare irrespective of maternal age among the mothers of the study subjects. With regard to smoking, a significant positive association between parental smoking at home and wheeze was observed in a cross-sectional study of UK primary schoolchildren (12). A case–control study in Canada showed a significant positive relationship between heavy maternal smoking and persistent asthma among children (14). A cohort study in the UK found that the effect of maternal smoking on wheeze seen at 1 and 2 y was lost by the age of 4 y (10). There was no material association between parental smoking and asthma in a longitudinal study of USA children aged 5–9 y (13). Two reviews have suggested that parental smoking is unlikely to increase the risk of allergic sensitization in children (21, 22). Passive smoking may not be causal in adolescents, although parental smoking could account for infantile allergic sufferers. In addition, people in the household with allergic children may have altered their smoking habits. Alternatively, the dichotomization of smoking in the household at 10 or more cigarettes a day versus 0–9 cigarettes a day could have masked a true positive association in this investigation. These findings corroborate the few previous observations showing no

relation between exposure to pets and allergic disorders (5, 10, 23).

In a cross-sectional study of German children aged 9–11 y, only paternal asthma had a strong influence on asthma in a child, while the influence of the mother was more decisive for allergic rhinitis and atopic eczema (24). A cohort study on the Isle of Wight demonstrated that maternal atopy had a marked influence on the development of atopic disease (10). The present results are generally in agreement with these previous observations. With regard to background other than heredity, mothers in Japan are more likely to be at home than fathers. Therefore, the sharing of the home environment is stronger between mothers and their offspring than between fathers and their offspring. However, caution should be exercised when interpreting the present findings. It is probable that most mothers filled out the questionnaire alone. Thus, the maternal effect may have been overestimated while the paternal effect may have been underestimated.

The current investigation had methodological advantages in that the prevalence of allergic disorders was assessed by validated core questions in the ISAAC Phase I study and that study subjects were homogeneous in terms of age and residential background. There are several weaknesses that should be considered. Of 9008 public junior high school students in Suita City, only 5539 (61%) were included in the study. It is difficult to know whether that loss is selective concerning exposure, outcome or both. The parents did not necessarily have to answer questions that could be considered an invasion of privacy. In particular, 830 participants and 547 participants were excluded because they did not reply to the question regarding a paternal and maternal history of allergy, respectively. Therefore, the study subjects were less likely to have parents with a history of any of the allergic disorders than the excluded participants. However, there was no substantial difference between the excluded participants and study subjects with respect to basic characteristics such as gender, grade and the prevalence of each of the allergic disorders. Study subjects were adolescent children who lived an urban lifestyle. Moreover, the prevalence values of allergic disorders observed in the present population were not equal to those reported for Japanese children in the ISAAC (1–3). Thus, it may be difficult to generalize the present findings. Within multifactorial pathogenesis, several contributing environmental factors have been linked to allergic disorders. However, no allowance was made for external factors such as aeroallergens, food allergens and air pollution.

In conclusion, the present findings suggest that the factors associated with allergic disorders in Japan are largely the same as those already identified in Western populations. Prospective epidemiological studies are required to obtain clearer insights into the underlying mechanisms for exposure–response relationships in Japan.

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References

1. 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: 315–35
2. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood. *J Allergy Clin Immunol* 1999; 103: 125–38
3. Strachan DP, Sibbald B, Weiland SK, Ait-Khaled N, Anabwani G, Anderson HR, et al. Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997; 8: 161–76
4. Laitinen T, Räsänen M, Kaprio J, Koskenvuo M, Laitinen LA. Importance of genetic factors in adolescent asthma. A population-based twin-family study. *Am J Respir Crit Care Med* 1998; 157: 1073–8
5. Arshad SH, Stevens M, Hide W. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993; 23: 504–11
6. Kuehr J, Karmaus W, Forster J, Frischer T, Hendel-Kramer A, Moseler M, et al. Sensitization to four common inhalant allergens within 302 nuclear families. *Clin Exp Allergy* 1993; 23: 600–5
7. Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax* 1998; 53: 927–32
8. Infante-Rivard C. Childhood asthma and indoor environmental risk factors. *Am J Epidemiol* 1993; 137: 834–44
9. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. *Br Med J* 1997; 314: 1003–8
10. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. *J Allergy Clin Immunol* 1998; 101: 587–93
11. 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
12. Somerville SM, Rona RJ, Chinn S. Passive smoking and respiratory conditions in primary school children. *J Epidemiol Community Health* 1988; 42: 105–10
13. Sherman CB, Tosteson TD, Tager IB, Speizer FE, Weiss ST. Early childhood predictors of asthma. *Am J Epidemiol* 1990; 132: 83–95
14. Infante-Rivard C, Gautrin D, Malo JL, Suissa S. Maternal smoking and childhood asthma. *Am J Epidemiol* 1999; 150: 528–31
15. Bråbäck L, Hedberg A. Perinatal risk factors for atopic disease in conscripts. *Clin Exp Allergy* 1998; 28: 936–42
16. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. *Arch Dis Child* 1996; 74: 422–6
17. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. *J Epidemiol Community Health* 2002; 56: 209–17
18. Miyake Y, Yura A, Iki M. Relationship between distance from major roads and adolescent health in Japan. *J Epidemiol* 2002; 12: 418–23
19. Miyake Y, Yura A, Iki M. Breastfeeding and the prevalence of symptoms of allergic disorders in Japanese adolescents. *Clin Exp Allergy* 2003; 33: 312–16

20. Vartiainen T, Saarikoski S, Jaakkola JJ, Tuomisto J. PCDD, PCDF, and PCB concentrations in human milk from two areas in Finland. *Chemosphere* 1997; 34: 2571–83
21. Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitization in children. *Thorax* 1998; 53: 117–23
22. Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. *Thorax* 1998; 53: 204–12
23. Henriksen AH, Holmen TL, Bjerner L. Sensitization and exposure to pet allergens in asthmatics versus non-asthmatics with allergic rhinitis. *Respir Med* 2001; 95: 122–9
24. Dold S, Wjst M, von Mutius E, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child* 1992; 67: 1018–22

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