

Clinical aspects of allergic disease

Childhood antecedents of allergic sensitization in young British adults

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Objective: This study was designed to investigate whether associations of self-reported hay fever with sibship size, birth order, infant feeding, and childhood socioeconomic status reflect variations in sensitization to common aeroallergens.

Methods: One thousand three hundred sixty-nine persons born throughout Britain in 1958 were followed up to age 34 to 35 years. The cohort included 1050 subjects with a history of asthma, wheezy bronchitis, wheezing, or pneumonia and 319 with no history of wheezing illness at ages 7, 11, 16, 23, or 33 years. Skin prick tests with extracts of mixed grass pollen, house dust mite (Der p 1), and cat fur were performed; and wheal diameters were measured.

Results: The prevalence of positive skin test results (≥ 3 mm wheal) was independently related ($p < 0.01$) to male sex, reduced numbers of older siblings (but not younger siblings), and higher socioeconomic status in childhood. Current cigarette smoking and maternal smoking during pregnancy were independently associated ($p < 0.01$) with a reduced prevalence of skin prick test positivity. No significant independent effects ($p > 0.10$) were found for adult social class, maternal age, birth weight, gestation, breast feeding, preschool nursery attendance, urban birthplace, or gas stove exposure.

Conclusion: Factors related to small families and relative affluence in childhood promote atopic sensitization to a variety of aeroallergens in later life. These observations are consistent with the suggestion that early infection may protect against subsequent allergic disease. (*J Allergy Clin Immunol* 1997;99:6-12.)

Key words: Atopy, skin prick tests, socioeconomic variations, siblings

The prevalence of hay fever, as reported at age 23 years by a national sample of British adults, was related to smaller numbers of older and younger siblings (the former having the stronger effect), increasing maternal age, breast feeding, and relative affluence in childhood (as indicated by father's occupation, owner-occupied housing, and exclusive use of all household amenities). Hay fever was

less common among cigarette smokers and persons born in the north of England and Scotland.¹

One unifying explanation for the associations with family circumstances in childhood is that they reflect a reduced risk of infectious illness in early life.¹⁻³ The hypothesis that early infection may protect against allergic sensitisation^{2,3} is attractive in that it may explain some international variations and time trends in allergic diseases.¹ There is experimental support for "programming" of the allergic response by cytokines at critical stages of differentiation of helper T lymphocytes,⁴ and bacterial and viral infections are known to influence cytokine levels in the direction that would inhibit the development of T_{H2} cells, which are implicated in IgE-mediated allergy.⁵

Among German children, the prevalence of skin prick test reactions to common aeroallergens was inversely related to sibship size,⁶ but no information was available to evaluate the relative importance of older and younger siblings. Among teenage children in Sheffield, England, doctor-

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TABLE I. Prevalence (%) of atopy, specific aeroallergen sensitization, and mean wheal diameter by father's social class and sibship size in childhood

	No. tested	Percent with ≥ 3 mm wheal to				Percent with any wheal ≥ 1 mm	Geometric mean wheal diameter*
		Der p 1	Grass	Cat	Any		
Father's social class† at birth of child							
I	68	25.0	36.8	13.2	47.1	51.5	2.18
II	202	22.8	29.7	12.9	41.6	59.4	1.65
IIIN	141	20.6	28.4	12.8	38.3	60.3	1.67
IIIM	671	18.5	21.5	9.8	31.9	51.6	1.44
IV	147	13.6	18.4	4.1	24.5	42.9	1.35
V	97	16.5	15.5	5.2	24.7	40.2	1.44
Other	43	16.3	16.3	4.7	30.2	55.8	1.21
No. of older siblings at age 11							
0	588	21.6	29.1	11.7	38.3	57.0	1.65
1	486	18.1	21.6	8.6	32.7	51.9	1.42
2	204	15.2	14.7	9.8	25.5	43.1	1.38
3+	91	14.3	13.2	1.1	23.1	40.7	1.34
No. of younger siblings at age 11							
0	488	17.0	24.4	9.2	33.4	51.0	1.51
1	471	20.4	24.0	11.7	35.5	55.2	1.54
2	256	21.5	23.4	9.8	34.4	54.3	1.51
3+	154	16.2	16.9	4.6	25.3	41.6	1.45

*Geometric mean of the three allergen wheal diameters (in millimeters) among those with at least one wheal ≥ 1 mm.

†I = professional and executive, II = managerial, IIIN = skilled nonmanual, IIIM = skilled manual, IV = semiskilled, V = unskilled, other = armed forces, unemployed, or no male head of household.

diagnosed hay fever and skin prick test reactions to grass pollen were more strongly related to the number of older siblings than to the number of younger siblings.⁷

There are no published data relating measures of allergic sensitization in adults to family circumstances in childhood. We took the opportunity to examine these associations among members of the British 1958 birth cohort previously studied at age 23 years,¹ using the results of skin prick tests performed on a sample of the cohort at age 34 to 35 years.

METHODS

Subjects

The origins and nature of the National Child Development Study (British 1958 cohort) are described elsewhere.^{1,8} Briefly, all births in Britain during 1 week (March 3 to 9, 1958) were included in a perinatal morbidity survey, and members of the cohort (or their parents) were interviewed in 1965, 1969, 1974, 1981, and 1991. There were 17,414 births included in the perinatal morbidity survey, and 1145 immigrants with the same birth dates were included subsequently. Among 18,559 subjects who had participated in one or more follow-ups, there were 5470 who had contributed data at birth and ages 7, 11, 16, 23, and 33 years. We selected all subjects

with a history of asthma, wheezy bronchitis, or pneumonia at any of the postnatal follow-ups (2174 patients) and a random 20% sample of the remainder (706 control subjects). Among the 2880 eligible subjects, 265 cohort members who currently lived in the more remote areas were excluded, and the remaining 2615 (1989 patients, 626 control subjects) were invited to participate in a further study involving measurements of ventilatory function and allergic sensitization during August 1992 to July 1993. This supplementary study was approved by the local research ethics committees of 215 health districts in England, Scotland, and Wales.

After a single reminder, 1875 (72%) subjects responded; 1594 (61%) agreed to take part, and 1449 (55%) were examined in their homes by one of 20 research nurses who were trained together before the study. Thirty-five subjects refused skin prick tests. Certain others lacked information on one or more variables included in the logistic regression models. The analyses presented here are therefore restricted to 1369 subjects with complete data for all relevant variables.

Skin prick tests

Skin prick tests were performed on the volar aspect of the forearm by using 1 mm flanged lancets and extracts of mixed grass pollen, house dust mite (*Dermatophagoides pteronyssinus*), cat fur, histamine (1:999, positive

TABLE II. Prevalence (%) of atopy by number of older and younger siblings at age 11

	No. of younger siblings at age 11			Total
	0	1	2+	
No. of older siblings				
0	40.2 (49/122)	42.0 (99/236)	33.4 (77/230)	38.3 (225/588)
1	32.1 (76/237)	35.5 (50/141)	30.5 (33/108)	32.7 (159/486)
2+	29.4 (38/129)	19.1 (18/94)	23.6 (17/72)	24.7 (73/295)
Total	33.4 (163/488)	35.4 (167/471)	31.0 (127/410)	33.4 (457/1369)

control), and diluent (negative control). The test solutions used by each nurse were prepared from single batches by Allergopharma, Germany. Skin prick test reactions to each extract were recorded after 10 minutes as the maximum wheal diameter and the diameter perpendicular to the maximum. The average of these two diameters was calculated.

Statistical analysis

The analyses presented here follow the current convention⁹ of defining a positive reaction as an allergen wheal with average diameter 3 mm or more greater than the average diameter of the wheal produced by the negative control. Very similar results were obtained by classifying as positive those reactions greater than or equal to the histamine wheal. For certain descriptive purposes (Table I), data are also presented as the geometric mean of the three allergen wheal diameters, among subjects with one or more detectable wheals. The geometric mean is used because the distribution of mean wheal sizes is positively skewed.

Social class in childhood was derived from the father's occupation recorded at the time the subject was born, by using the Registrar-General for England and Wales 1951 classification. Social class in adulthood was derived from the subject's current or last occupation as reported at age 33 years and coded to the Registrar-General's 1990 classification. Place of birth was classified by 1951 standard region and degree of urbanization. The regions were aggregated into three groups, as in the earlier analysis of hay fever at age 23 years (Southeast: East Midlands, East Anglia, Greater London, Southeastern, Southern; Southwest: Southwestern, Wales, West Midlands; North: Scotland, Northern, East and West Ridings, Northwestern). The more heavily urbanized areas were identified as the pre-1974 county boroughs and London boroughs, which included major cities and most larger towns in 1958.

Information on maternal age, gestational age, birth weight, and maternal smoking during pregnancy was obtained from perinatal records. Mode of infant feeding and preschool educational experience were ascertained from parents at the 7-year follow-up, and family composition (including older siblings who had moved away from home) was recorded at the 11-year follow-up. Information about the subjects' own smoking habits and cooking fuels used in the household at age 11 years was obtained by interview at age 34 to 35 years.

Tabulations were derived by the FREQ procedure in Statistical Analysis System (SAS Institute).¹⁰ Multiple logistic regression models were fitted by using the Generalised Interactive Modelling System (GLIM).¹¹ The outcome variable in these models was, in turn, the prevalence of a positive (i.e., ≥ 3 mm) skin prick test reaction to any of the three allergens ("atopy") and to each of the three allergens separately. All models included dummy variables representing each of the 20 field workers and indicating whether the individual had been selected as a patient or control subject, in addition to the explanatory variables of interest.

RESULTS

The 1369 subjects included in this analysis represent 52% of the target sample of 2615. Compared with these 1369 subjects, the 1246 cohort members who did not respond or who were excluded from the analysis were somewhat less likely to be female (48% vs 51%), to have a nonmanual occupation (59% vs 65%), to have been affected by eczema before the age of 7 years (8% vs 11%), or to have reported hay fever in the past year at age 23 (16% vs 22%).

Among the 1369 subjects, 730 (53%) had a detectable skin prick test reaction to one or more of the three aeroallergens tested, and 457 (33%) had one or more reactions of wheal diameter 3 mm or greater. With the 3 mm cutoff, 259 (19%) had a positive reaction to dust mite, 318 (23%) to grass pollen, and 132 (10%) to cat fur. The proportion of patients with one or more positive reactions was 38% (395 of 1050), and the corresponding proportion of control subjects was 19% (62 of 319). Allowing for the 1 in 5 sampling strategy for control subjects, the estimated prevalence of skin prick test reactions of 3 mm or greater in the entire cohort is 27%. This may be an overestimate because the response rate was somewhat higher among subjects with a history of hay fever or eczema.

The prevalence of skin prick test positivity was strongly related to father's social class, sibship size, and birth order, as shown in Table I. The groups

with a higher prevalence of atopy, defined as one or more wheals of 3 mm or greater in diameter, were also the groups with a higher prevalence of any detectable aeroallergen wheal and with a greater mean wheal diameter among those with positive skin prick test reactions.

Although social class in childhood was influential, there was little variation in the prevalence of atopy with social class in adulthood (on the basis of the subject's own occupation). The proportions with one or more wheals of 3 mm or greater in diameter were 36% (182 of 511) among professional workers, 33% (177 of 543) among skilled workers, 30% (73 of 245) among semiskilled or unskilled workers, and 36% (25 of 70) among those in the armed forces or with no current or previous occupation. The number of older siblings had a more powerful independent effect on the prevalence of atopy than did the number of younger siblings, when both were considered together (Table II).

Table III shows the relationship of atopy to a range of other dichotomous variables. Male subjects were more likely than female subjects to have skin prick test reactions of 3 mm or greater, whereas atopy was significantly less common among current smokers and among the offspring of mothers who smoked. The maternal smoking effect was evident mainly among subjects selected as patients (28% vs 42%), whereas among control subjects without a history of chest illness, there was little association of atopy with maternal smoking (18% vs 20%). In contrast, the apparent protective effect of current smoking was consistent in both the patient group (29% vs 41%) and among control subjects (15% vs 21%).

Weak and nonsignificant bivariate associations were found between skin prick test positivity and other indicators of early air pollution exposure: birth in an urban area and use of gas for cooking (Table III). Attendance at a preschool playgroup or nursery did not influence the prevalence of sensitization in adulthood. A significantly higher prevalence of atopy was found among subjects born in the Southeast and those who were breast-fed as infants (Table III).

After adjustment for birth order and father's social class, there were only weak associations between atopy and maternal age, gestational age, birth weight, or height at age 7 years. None of these associations were statistically significant at the 5% level. When the 457 atopic subjects were compared with 912 nonatopic subjects, the differences in means $\pm$ SD were as follows: maternal

TABLE III. Prevalence (%) of atopy by selected dichotomous risk factors

Risk factor	Prevalence of atopy if	
	Factor present	Factor absent
Male sex	38.1 (258/678)	28.8 (199/691)
Born in Southeast region*	37.7 (225/597)	30.1 (232/722)
Born in major town or city*	33.1 (191/577)	33.6 (266/792)
Mother smoked during pregnancy	25.5 (106/416)	36.9 (348/943)
Breast-fed (any duration)	34.8 (339/974)	29.9 (118/395)
Attended preschool nursery	35.5 (102/287)	32.3 (320/990)
Gas cooking used at age 11	31.5 (254/806)	36.1 (197/546)
Gas cooking used currently	33.6 (293/873)	32.9 (164/495)
Current active smoker	26.5 (110/415)	36.4 (347/954)

*See Methods section for definitions.

age, 27.48 ± 0.25 years versus 27.22 ± 0.18 years; gestational age, 282.74 ± 0.57 days versus 281.32 ± 0.53 days; birth weight 3377.2 ± 20.9 gm versus 3338.0 ± 17.0 gm; height at age 7, 48.19 ± 0.11 inches versus 48.25 ± 0.08 inches.

Table IV shows the independent effects of sex, sibship size, father's social class, breast feeding, region of birth, maternal smoking during pregnancy, and current smoking on the prevalence of positive skin prick test reactions (≥ 3 mm) to each of the three allergens and to one or more allergens. After adjustment for other factors, breast feeding, region of birth, and adult social class were no longer significant predictors of atopy; and the number of younger siblings was significantly related only to grass pollen sensitization. In contrast, the independent effects of sex, birth order, maternal smoking, and current smoking were strong and consistent across the three allergens tested. Father's social class was strongly and independently related to atopy, mainly because of its significant association with grass pollen sensitization. Skin prick test positivity to mites and cat fur did not vary significantly ($p > 0.05$) with father's social class, after adjustment for other factors.

DISCUSSION

This study is the first to relate prospectively recorded information on perinatal and childhood

TABLE IV. Mutually adjusted odds ratios (and 95% confidence intervals) for atopy and sensitization to each allergen

	Any allergen wheal ≥ 3 mm			Der P 1 ≥ 3 mm		Grass ≥ 3 mm		Cat ≥ 3 mm	
	OR	95% CI	χ^2	OR	χ^2	OR	χ^2	OR	χ^2
Sex									
Male	1.00	Reference		1.00		1.00		1.00	
Female	0.57	0.44-0.74	17.9*	0.45	25.2*	0.65	8.9†	0.79	1.2 NS
Father's social class at birth of child									
I	1.00	Reference		1.00		1.00		1.00	
II	1.00	0.55-1.81		1.15		0.86		1.32	
IIIN	0.87	0.46-1.64		1.01		0.83		1.21	
IIIM	0.74	0.43-1.27	6.5‡	1.01	1.0 NS	0.62	5.4‡	1.18	1.9 NS
IV	0.52	0.27-1.01		0.62		0.57		0.45	
V	0.64	0.31-1.33		0.96		0.57		0.64	
Other†§	0.60	0.25-1.44		0.71		0.37		0.40	
Older siblings at age 11									
0	1.00	Reference		1.00		1.00		1.00	
1	0.71	0.54-0.95		0.75		0.60		0.62	
2	0.53	0.36-0.79	14.2*	0.63	5.9‡	0.38	24.2*	0.87	7.0‡
3+	0.49	0.28-0.86		0.56		0.37		0.08	
Younger siblings at age 11									
0	1.00	Reference		1.00		1.00		1.00	
1	0.94	0.70-1.26		1.09		0.80		1.13	
2	0.92	0.64-1.31	2.7 NS	1.22	1.0 NS	0.79	4.7‡	0.83	2.9 NS
3+	0.64	0.41-1.02		0.92		0.56		0.44	
Region of birth									
SE	1.00	Reference		1.00		1.00		1.00	
SW	1.22	0.77-1.93	2.3 NS	1.34	2.0 NS	1.10	0.6 NS	0.50	3.4 NS
N	0.82	0.56-1.22		0.87		0.88		0.95	
Breast-fed									
No	1.00	Reference		1.00		1.00		1.00	
Yes	1.09	0.82-1.45	0.4 NS	0.93	0.2 NS	0.93	0.2 NS	1.21	0.6 NS
Mother smoked									
No	1.00	Reference		1.00		1.00		1.00	
Yes	0.64	0.48-0.85	9.5†	0.66	5.6‡	0.67	6.1†	0.53	6.3‡
Current smoker									
No	1.00	Reference		1.00		1.00		1.00	
Yes	0.56	0.42-0.74	17.0*	0.54	12.4*	0.59	10.8*	0.68	2.8 NS

Odds ratios are adjusted by multiple logistic regression for observer, patient/control subject status, and adult social class (seven categories) in addition to all other factors shown in the table. For definition of father's social class, see footnote to Table I.

OR, Odds ratio; CI, confidence interval; NS, not significant; SE, Southeast; SW, Southwest; N, North.

* $p < 0.001$.

† $p < 0.01$.

‡ $p < 0.05$.

§Excluded from the test for trend for father's social class. Chi square values are 1 df for trend except for region of birth (2 df heterogeneity test).

factors to measures of aeroallergen sensitization in adult life. It broadly confirms earlier observations of the epidemiology of hay fever¹ and infant eczema² in the same cohort, suggesting that the higher prevalence of these allergic diseases among smaller, more affluent families and among first-born children is not an artefact of symptom recog-

nition, parental recall, or diagnostic labeling but indicates the underlying epidemiology of atopy. These associations reflect the influence of factors operating in Britain during the late 1950s and 1960s and are not necessarily relevant to more recent cohorts born in Britain or elsewhere. However, the inverse association of atopy with sibship

size is consistent with findings from British children born in the late 1970s⁷ and German children born in the early 1980s.⁶

Our stratified sample contained proportionately more patients (subjects with a history of asthma, wheezing, or pneumonia) than would have been obtained by random sampling of the cohort. The effects that we demonstrate therefore reflect to a greater extent associations present within the patient group than those within the control subjects. However, in the final logistic regression model we not only adjusted for patient/control subject status but also explored possible statistical interactions between each explanatory variable and patient/control subject status: none were significant ($p > 0.15$ in each case). For these variables, the results based on our stratified sample can be extrapolated with reasonable confidence to the general population.

Our results are consistent with those of many other studies in demonstrating a higher prevalence of atopy among male subjects than female subjects. This contrasts with the equal prevalence of self-reported hay fever among men and women of this cohort at age 23 years,¹ suggesting differential symptom recognition by the two sexes. Variations in hay fever prevalence by region of birth¹ were not confirmed in this study, but this may be due to the loss of statistical power involved in the adjustment for operator effects, which effectively means stratifying by current region of residence (the nurses being assigned to fieldwork on a geographic basis).

Maternal smoking during pregnancy was associated with a reduced prevalence of atopy in our sample. Maternal smoking is more strongly related to the incidence of wheezing among nonatopic subjects than among atopic cohort members,¹² so our stratified sampling design may have led to a higher proportion of nonatopic offspring of smoking mothers among our patients than would have arisen in a random sample of the cohort. However, this can only be a partial explanation because there was also an inverse relationship between maternal smoking and atopy among the randomly selected control subjects. Some studies have demonstrated an increased prevalence of skin prick test positivity among children whose parents smoke,^{13, 14} although the excess is not consistently found in all countries or for all allergen sensitivities.¹⁴ No association¹⁵ or a reduced prevalence⁶ of skin prick test positivity was observed among German children whose mothers smoked. The reduced prevalence of atopy among current smokers runs counter to the observation that smokers are at increased risk of sensitization to some, but not all,

occupational allergens.¹⁶ It may reflect selective avoidance of cigarettes by atopic teenagers, because the presence of hay fever at age 11 years predicted a lower prevalence of smoking at age 23 years in this cohort.¹

There is currently much interest in the possibility that outdoor or indoor air pollution may play a role in promoting allergic sensitization.¹⁷ In the late 1950s and early 1960s, most major towns and cities of Britain experienced levels of ambient smoke and sulfur dioxide pollution comparable to those in the more polluted parts of Eastern Europe in recent years,¹⁷ yet no marked effect of birthplace on the prevalence of allergic sensitization is evident. Gas cooking, a major source of indoor nitrogen dioxide exposure, was associated with a slightly lower prevalence of atopy. These observations, although based on relatively crude indicators, lend no support to the air pollution hypothesis.

Perinatal factors, especially intrauterine growth¹⁸ and infant feeding,¹⁹ have been proposed as "programming" influences on the developing immune system. Our findings do not suggest an important influence of either, although we lack the specific information required to evaluate the effect of neonatal head circumference¹⁸ or prolonged, exclusive breastfeeding¹⁹ in this cohort. Nevertheless, our findings would be more consistent with those for self-reported hay fever in the whole cohort,¹ suggesting a modest increase in risk of atopy and allergic disease among breast-fed infants.

The dominant influences on aeroallergen sensitization in this national birth cohort were those related to social class and family size in early childhood. As previously postulated,² these patterns may reflect the reduced likelihood of cross-infection within smaller, more affluent families. We therefore expected that early exposure to organized child care outside the home would protect against subsequent atopy, but this was not the case. Because the first postnatal follow-up of this cohort occurred at age 7 years, there is inadequate information to assess the incidence of infectious illnesses among cohort members in early childhood. Detailed studies of the patterns of social interaction and infectious illness in relation to socioeconomic status, sibship size, birth order, and preschool child care in more recent cohorts are required to elucidate the biologic mechanisms underlying these intriguing epidemiologic observations.

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REFERENCES

1. Strachan DP. Epidemiology of hay fever: towards a community diagnosis. *Clin Exp Allergy* 1995;25:296-303.
2. Strachan DP. Hay fever, hygiene and household size. *Br Med J* 1989;299:1259-60.
3. Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: Could they be protective? *Thorax* 1994;49:1189-91.
4. Holt PG. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. *Lancet* 1994;344:456-8.
5. Romagnani S. Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. *Int Arch Allergy Immunol* 1992;98:279-85.
6. von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Reitmar P, Thiemann HH. Skin test reactivity and number of siblings. *Br Med J* 1994;308:692-5.
7. Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection and hay fever in adolescence. *Arch Dis Child* 1996;74:422-6.
8. Ferri E, editor. Life at 33. The fifth follow-up of the National Child Development Study. London: National Children's Bureau and City University, 1993.
9. Dreborg S, editor. Skin tests used in type I allergy testing. Position paper prepared by the sub-committee on skin tests of the European Academy of Allergology and Clinical Immunology. *Allergy* 1989;44(suppl):22-30,52-9.
10. SAS System Inc. SAS/STAT user's guide, version 6, 4th ed. Cary(NC): SAS System Inc., 1990.
11. Francis B, Green M, Payne C, editors. The GLIM system release 4 manual. Oxford: Clarendon Press, 1993.
12. Strachan DP, Butland BK, Anderson HR. The incidence and prognosis of asthma and wheezing illness among British children and young adults born in 1958. *Br Med J* 1996;312:1195-9.
13. Ronchetti R, Bonci E, Cutrera R, de Castro G, Indinnimeo L, Midulla F, et al. Enhanced allergic sensitisation related to parental smoking. *Arch Dis Child* 1992;67:496-500.
14. Bråbäck L, Breborowicz A, Julge K, Knutsson A, Riikjäär MA, Vasar M, et al. Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Arch Dis Child* 1995;72:487-93.
15. Kuehr J, Frischer T, Karmaus W, Meinert R, Barth R, Hermann-Kunz E, et al. Early childhood risk factors for sensitization at school age. *J Allergy Clin Immunol* 1992;90:358-63.
16. Chang-Yeung M. Occupational asthma. *Chest* 1990;98(suppl 5):148-61.
17. Department of Health Committee on the Medical Effects of Air Pollutants. Asthma and outdoor air pollution. London: HMSO, 1995:85-176.
18. Godfrey KM, Barker DJP, Osmond C. Disproportionate fetal growth and raised IgE concentration in adult life. *Clin Exp Allergy* 1994;24:641-8.
19. Saarinen UM, Kajosaari M. Breastfeeding as prophylaxis against atopic disease: prospective follow-up study until 17 years old. *Lancet* 1995;346:1065-9.

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