Childhood exposure to infection and risk of adult onset wheeze and atopy

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Abstract

***Background*—The prevalence of asthma and allergic diseases in children and young adults is inversely associated with family size. It has been suggested that more frequent exposure to infections in a large family group, particularly those spread by the faecal-oral route, may protect against atopic diseases, although not all published data support this hypothesis. Whether similar considerations apply to adult onset wheeze is unknown. The relationship between adult onset wheezing and atopy measured in adulthood and childhood exposure to a range of infections was investigated.**

***Methods*—A nested case control study of participants in a 30 year follow up survey was conducted. Questionnaire data on childhood infections had been obtained in a 1964 survey. In 1995 a further questionnaire on respiratory symptoms and other risk factors for wheezing illness was administered, total IgE, skin and RAST tests were performed, and serum was stored. In 1999 serological tests for hepatitis A, *Helicobacter pylori*, and *Toxoplasma gondii* were performed on the stored samples. Information from the 1964 questionnaires was available for 97 cases and 208 controls and serological tests were obtained for 85 cases and 190 controls. The potential risk factors were examined for all cases, those who reported doctor diagnosed asthma, those who described persistent cough and phlegm with wheeze, and subjects stratified by atopic status.**

***Results*—The sibship structure was similar in cases and controls. In univariate analysis of all cases, childhood infections reported by parents as acquired either before or after the age of three years did not influence case:control or atopic status. Seropositivity was also similar for all cases and controls, but cases in the subgroup with chronic cough and phlegm were more likely to be seropositive for hepatitis A and *H pylori*. Seropositivity was unrelated to atopic status. In multivariate analyses both the effect of having two or more younger siblings (OR 0.1, 95% CI 0.03 to 0.8) and of acquiring measles up to the age of three (OR 0.2, CI 0.03 to 0.8) were significantly related to a lower risk of doctor diagnosed asthma.**

***Conclusions*—In these well characterised subjects, exposure to infections as measured by parental reports obtained at age 10–14 years and by serological tests obtained in adulthood did not influence the development of wheezing symptoms or atopic status in adulthood. However, early exposure to measles and family size may be associated with a lower risk of adult onset doctor diagnosed asthma.**

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Keywords: childhood infections; family size; adult onset wheeze; asthma; atopy

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The prevalence of asthma and atopic diseases is increasing in developed countries.[1 2] It has been suggested that this is the result of declining exposure to infection as a consequence of smaller family size, improved hygiene, and modern vaccination programmes.[3 4] It is suggested that exposure to bacterial and viral infections, which may occur more frequently in large families, selectively enhances differentiation of T helper cells to the Th1 subtype with resultant suppression of the Th2 subtype which is implicated in IgE mediated allergy.[5] An inverse relationship between family size and manifestations of allergy has been found consistently throughout childhood,[2 6 7] adolescence,[8] and on into early adulthood.[9–11] Three studies have provided more direct evidence that childhood exposure to infections such as measles,[12] tuberculosis,[13] or hepatitis A[4] might prevent atopic disease. In the last study which involved Italian military recruits, an effect of family size remained even after adjusting for hepatitis A positivity. However, not all studies have supported the infection hypothesis. We have previously reported in a 1964 cohort of Aberdeen schoolchildren that, although large sibships conferred some protection against the presence of eczema or hayfever, this finding was not explained by common childhood infections.[14] In our data there were conflicting relationships between exposure to infection and atopic disease; although measles had some protective effect against asthma, it was found that the more infections children had, the more likely they were to have atopic disease. In a cohort of British adolescents Strachan and colleagues found the expected inverse relationship between hayfever and family size, but were unable to demonstrate a relationship between hayfever and infections in the first month of life.[8] One explanation for these conflicting results might be that the nature of the infection is important. In a further report on Italian military recruits Matricardi *et al* have suggested that infections such as hepatitis A and *Toxoplasma gondii* which are spread by the faecal-

oral route modify the risk of allergy, whereas viruses spread by other routes, including airborne droplets, have no effect.[15]

Whether the family size effect and the infection hypothesis are relevant to adult onset asthmatic symptoms or atopic status in middle age is unknown. We have investigated this in a nested case-control study in which we have examined relationships between adult onset wheezing and atopy measured in adulthood and sibship structure, childhood infections, and seropositivity to hepatitis A, *Helicobacter pylori*, and *Toxoplasma gondii* in those individuals in the Aberdeen cohort who had no childhood wheezing symptoms.

Methods

A nested case control study of participants in a 30 year follow up survey was conducted in the Grampian region of Scotland. Subjects had originally been identified in a 1964 random survey of 2511 Aberdeen schoolchildren aged 10–14 years.[16] The outcome at age 34–40 years for the 288 children who were wheezy in childhood, together with 167 children selected from those who were asymptomatic, has been described.[17] In 1995 we attempted to contact the remaining 2056 individuals aged 39–45 years: adult onset wheeze, defined as any occurrence of wheezing or whistling in the chest on or after the age of 15, was reported by 177 of the 1542 (11.5%) subjects who responded to our follow up survey.[18] In this nested case control study all 113 respondents with adult onset wheeze who resided locally and 267 comparison subjects randomly selected from the local respondents who had never wheezed were invited to take part in further investigations.[19] Ethical approval for the study was obtained from the Grampian Health Board and the University of Aberdeen Joint Ethical Committee and all participants gave informed consent.

Subjects were contacted in random order over a seven month period from April to October 1995 and interviewed about respiratory symptoms, socioeconomic status, smoking habit, and family history of atopic disease. Social class, based on the subject's own occupation, was defined as manual or non-manual using the 1991 UK standard occupational classification. Smoking habit was categorised as never, former, and current. For family history of atopic disease, each occurrence of asthma, eczema, or hayfever in parents and siblings was counted and a variable categorised as no affected relatives, one affected relative, and more than one affected relative.

Atopic status was determined by skin reactivity, specific and total IgE. Skin and specific IgE tests were expressed as positive if at least one antigen (house dust mite, cat or mixed grass pollen) showed a weal diameter of 3 mm or more greater than the negative control or a RAST class of one or more (that is, $\geqslant$0.35 IU/ml). Total IgE results greater than 120 IU/ml were considered positive. Overall atopic status was expressed as a cumulative variable summing the positive measures and categorised as no measures positive, any one, any two, or all three measures positive.

Interviews conducted in 1964 with the parents of these subjects contained questions on sibship structure, common childhood infections, and the age at which these infections occurred. The structure of the sibship was considered by number of older, number of younger, and total number of siblings. For each infection, including measles, pertussis, rubella, mumps and varicella, a variable was stratified as: never had infection before 1964 study; infection occurred up to age of three; or infection occurred after the age of three. The three year cut off was chosen as the age by which atopic status will have been established in the majority of subjects. Analyses based on a one or two year cut off yielded similar results to those reported. In order to examine the effect of repeated exposure to infection, several summary measures of infection were examined. The sum of all infections occurring on or before the age of three was stratified as none, any one, two, or three or more infections. Measles and pertussis occurring up to the age of three were combined since they have important respiratory manifestations. The sum of the other three (rubella, mumps, and varicella) was stratified as none, any of the three, and two or more occurring on or before the age of three years.

Serological ELISA tests for total antibody to hepatitis A (Organon Technika), IgG antibodies to *Helicobacter pylori* (Sigma), and IgG antibodies to *Toxoplasma gondii* (Beckmann Access) were performed on serum samples stored since 1995.

The associations of adult onset wheeze with number of siblings, individual childhood infections, the sum of these infections, and serological tests was assessed by χ^2 and Fisher's exact tests where appropriate. In an attempt to address the heterogeneous nature of adult onset wheeze, the potential risk factors were examined in all cases and in two subgroups: those who reported doctor diagnosed asthma and those who described cough and phlegm for as much as three months per year in addition to wheeze. The potential risk factors were also examined among the subjects stratified by atopic status. Logistic regression was used to assess the independent effect of sibship size and infections on atopic disease after adjustment for potential confounding by sex, social class based on subject's own occupation, smoking habit, atopy, and family history of atopic disease. The statistical software program Stata Release 4 (Stata Corporation, Texas, USA) was used for the analyses.

Results

Interview data were obtained from 319 (84%) of the 380 subjects who were invited to participate in the case control study; these included 102 cases and 217 controls. Subjects who participated did not differ from those who declined to participate in terms of age, sex, smoking habit, or social class. Information from the 1964 questionnaires on sibship structure and childhood

infections was available for 97 cases and 208 controls. Serological tests were obtained for 85 cases and 190 controls.

The sibship structure was similar for cases and controls (table 1). While atopic subjects were more likely to have two or more younger siblings, this difference was driven mainly by the category of two younger siblings and no linear trend was evident. There were no significant differences among cases and controls or among atopic and non-atopic subjects with regard to whether childhood infections re-

Table 1 Sibship structure in cases with adult onset wheeze and in subjects regrouped according to atopic status

	Wheeze (n=97)	*Controls (n=208)*	*Wheeze + asthma (n=23)*	*Wheeze + cough/phlegm (n=28)*	*Atopy positive (n=154)*	*Atopy negative (n=129)*
Number of older siblings						
0	34 (35.0%)	71 (34.1%)	7 (30.4%)	10 (35.7%)	59 (38.4%)	41 (31.8%)
1	28 (28.9%)	62 (39.8%)	8 (34.8%)	9 (32.1%)	43 (27.9%)	37 (28.7%)
2	20 (20.6%)	42 (20.2%)	5 (21.7%)	4 (14.3%)	29 (18.8%)	29 (22.5%)
3 or more	15 (15.5%)	33 (15.9%)	3 (13.1%)	5 (17.9%)	23 (14.9%)	22 (17.0%)
Number of younger siblings						
0	36 (37.1%)	83 (40.0%)	12 (52.2%)	8 (28.6%)	57 (37.0%)	54 (41.8%)
1	35 (36.1%)	67 (32.2%)	9 (39.1%)	8 (28.6%)	46 (29.9%)	49 (38.0%)
2	15 (15.5%)	34 (16.3%)	2 (8.7%)	6 (21.4%)	32 (20.8%)	12 (9.3%)
3 or more	11 (11.3%)	24 (11.5%)	0 (0%)	6 (21.4%)	19 (12.3%)	14 (10.9%)*
Total number of siblings						
0	8 (8.3%)	17 (8.2%)	4 (17.4%)	1 (3.6%)	13 (8.4%)	11 (8.5%)
1	28 (28.9%)	52 (25.0%)	7 (30.4%)	6 (21.4%)	38 (24.7%)	34 (26.4%)
2	19 (19.6%)	55 (26.4%)	6 (26.2%)	6 (21.4%)	39 (25.3%)	32 (24.8%)
3	21 (21.6%)	45 (21.6%)	3 (13.0%)	8 (28.6%)	32 (20.8%)	30 (23.2%)
4 or more	21 (21.6%)	39 (18.8%)	3 (13.0%)	7 (25.0%)	32 (20.8%)	22 (17.1%)

*$p \leq 0.05$ (χ^2 tests of independence).

Table 2 Childhood infections in cases with adult onset wheeze and in subjects regrouped according to atopic status

	Wheeze (n=97)	*Controls (n=208)*	*Wheeze + asthma (n=23)*	*Wheeze + cough/phlegm (n=28)*	*Atopy positive (n=154)*	*Atopy negative (n=128)*
Measles						
No	14 (14.7%)	21 (10.3%)	4 (17.4%)	3 (11.1%)	16 (10.7%)	16 (12.6%)
⩽ age 3	30 (31.6%)	74 (36.3%)	4 (17.4%)	8 (29.6%)	50 (33.6%)	44 (34.6%)
> age 3	51 (53.7%)	109 (53.4%)	15 (65.2%)	16 (59.3%)	83 (55.7%)	67 (52.8%)
Rubella						
No	48 (50.5%)	125 (61.3%)	15 (65.2%)	16 (59.3%)	88 (58.3%)	69 (54.8%)
⩽ age 3	6 (6.3%)	12 (5.9%)	0 (0%)	2 (7.4%)	12 (7.9%)	5 (4.0%)
> age 3	41 (43.2%)	67 (32.8%)	8 (34.8%)	9 (33.3%)	51 (33.8%)	52 (41.2%)
Pertussis						
No	81 (83.5%)	163 (78.4%)	17 (73.9%)	25 (86.2%)	130 (84.4%)	98 (76.6%)
⩽ age 3	7 (7.2%)	23 (11.0%)	1 (4.3%)	2 (6.9%)	8 (5.2%)	16 (12.5%)
> age 3	9 (9.3%)	22 (10.6%)	5 (21.7%)	2 (6.9%)	16 (10.4%)	14 (10.9%)
Mumps						
No	61 (63.5%)	130 (63.1%)	15 (65.2%)	17 (60.7%)	96 (62.7%)	81 (64.3%)
⩽ age 3	9 (9.4%)	9 (4.4%)	1 (4.4%)	1 (3.6%)	7 (4.6%)	9 (7.1%)
> age 3	26 (27.1%)	67 (32.5%)	7 (30.4%)	10 (35.7%)	50 (32.7%)	36 (28.6%)
Varicella						
No	38 (40.9%)	76 (37.4%)	3 (14.3%)	13 (48.2%)	57 (38.2%)	50 (40.3%)
⩽ age 3	14 (15.0%)	31 (15.3%)	3 (14.3%)	3 (11.1%)	22 (14.8%)	17 (13.7%)
> age 3	41 (44.1%)	96 (47.3%)	15 (71.4%)	11 (40.7%)	70 (47.0%)	57 (46.0%)
Sum of all infections						
None	46 (51.1%)	96 (49.5%)	15 (71.4%)	13 (54.2%)	74 (51.7%)	62 (52.1%)
Any 1	30 (33.3%)	68 (35.1%)	4 (19.0%)	8 (33.3%)	51 (35.7%)	37 (31..1%)
Any 2	9 (10.0%)	22 (11.3%)	2 (9.6%)	1 (4.2%)	12 (8.4%)	14 (11.8%)
3 or more	5 (5.6%)	8 (4.1%)	0 (0%)	2 (8.3%)	6 (4.2%)	6 (5.0%)
Sum of measles and pertussis						
None	60 (63.2%)	118 (57.8%)	19 (82.6%)	17 (63.0%)	95 (63.8%)	74 (58.3%)
Either	33 (34.7%)	76 (37.3%)	3 (13.0%)	10 (37.0%)	50 (33.6%)	47 (37.0%)
Both	2 (2.1%)	10 (4.9%)	1 (4.4%)	0 (0%)	4 (2.6%)	6 (4.7%)
Sum of rubella, mumps and varicella						
None	69 (76.7%)	152 (77.5%)	17 (81.0%)	20 (83.4%)	112 (77.2%)	94 (79.0%)
Any of the 3	15 (16.7%)	36 (18.4%)	4 (19.0%)	2 (8.3%)	27 (18.6%)	18 (15.1%)
2 or more	6 (6.6%)	8 (4.1%)	0 (0%)	2 (8.3%)	6 (4.2%)	7 (5.9%)

Table 3 Serological tests in cases with adult onset wheeze and in subjects regrouped according to atopic status

	Wheeze (n=85)	*Controls (n=190)*	*Wheeze + asthma (n=19)*	*Wheeze + cough/phlegm (n=26)*	*Atopy positive (n=150)*	*Atopy negative (n=125)*
Seropositive to:						
Hepatitis A	56 (65.9%)	110 (57.9%)	8 (42.1%)	21 (80.8%)*	98 (65.3%)	68 (54.4%)
H pylori	49 (57.6%)	93 (48.9%)	6 (31.6%)	20 (76.9%)*	77 (51.3%)	65 (52.0%)
T gondii	16 (18.8%)	26 (13.7%)	2 (10.5%)	6 (23.1%)	18 (12.0%)	24 (19.2%)
Sum of seropositivity						
None positive	15 (17.6%)	35 (18.4%)	5 (26.3%)	2 (7.7%)	25 (16.7%)	25 (20.0%)
One positive	28 (32.9%)	88 (46.3%)	12 (63.2%)	6 (23.1%)	64 (42.7%)	52 (41.6%)
Two positive	33 (38.8%)	60 (31.6%)	2 (10.5%)	13 (50.0%)	54 (36.0%)	39 (31.2%)
Three positive	9 (10.7%)	7 (3.7%)	0 (0%)	5 (19.2%)*	7 (4.7%)	9 (7.2%)

*$p \leq 0.05$ (χ^2 tests of independence).

Table 4 Risk of adult onset wheeze and atopy according to sibship structure: adjusted odds ratios (95% confidence intervals)

	Wheeze (n=94)*	*Wheeze + asthma* (n=22)*	*Wheeze + cough/phlegm* (n=27)*	*Atopy positive† (n=150)*
Number of older siblings				
1	1.0 (0.5 to 2.0)	2.2 (0.6 to 7.9)	1.1 (0.4 to 3.6)	0.9 (0.5 to 1.6)
2	1.1 (0.5 to 2.3)	2.3 (0.5 to 9.9)	0.7 (0.2 to 2.8)	0.8 (0.4 to 1.5)
3 or more	0.6 (0.3 to 1.4)	1.1 (0.2 to 5.9)	0.4 (0.1 to 1.9)	0.8 (0.4 to 1.8)
Number of younger siblings				
1	1.0 (0.6 to 1.9)	0.9 (0.3 to 2.6)	1.0 (0.3 to 3.4)	0.9 (0.5 to 1.6)
2	0.7 (0.3 to 1.5)	0.1 (0.03 to 0.8)‡	1.0 (0.2 to 3.9)	2.3 (1.1 to 5.1)
3 or more	0.7 (0.3 to 1.8)	p for trend = 0.029	2.1 (0.5 to 8.4)	1.2 (0.5 to 2.6)
Total number of siblings				
1	1.1 (0.4 to 3.4)	0.7 (0.1 to 3.0)	1.6 (0.1 to 23.1)	1.1 (0.4 to 3.0)
2	0.6 (0.2 to 2.1)	0.4 (0.1 to 2.1)	1.6 (0.1 to 23.6)	1.3 (0.5 to 3.7)
3	0.6 (0.2 to 1.9)	0.2 (0.03 to 1.4)	1.4 (0.1 to 20.4)	1.1 (0.4 to 3.1)
4 or more	0.6 (0.2 to 2.1)	0.3 (0.04 to 2.0)	1.1 (0.1 to 15.9)	1.5 (0.5 to 4.2)

*Odds ratios are adjusted for sex, social class based on subject's own occupation, smoking habit, atopy, and family history of atopic disease.
†Odds ratios are adjusted for sex, social class based on subject's own occupation, smoking habit, and family history of atopic disease.
‡Due to small numbers, "younger siblings" was recoded as 0, 1, 2 or more in this model.

Table 5 Risk of adult onset wheeze and atopy according to childhood infections and sum of infections before the age of three: adjusted odds ratios (95% confidence intervals). The reference category included subjects who had not acquired the infections before age 10–15 years

Infection history to age 10–15 years	*Wheeze* (n ⩽95)*	*Wheeze + asthma* (n ⩽22)*	*Wheeze + cough/phlegm* (n ⩽28)*	*Atopy positive† (n ⩽151)*
Measles				
⩽ age 3	0.5 (0.2 to 1.2)	0.2 (0.03 to 0.8)	0.4 (0.1 to 2.1)	1.3 (0.6 to 3.0)
> age 3	0.6 (0.2 to 1.3)	0.4 (0.1 to 1.6)	0.6 (0.1 to 2.7)	1.5 (0.7 to 3.2)
Rubella				
⩽ age 3	1.2 (0.4 to 3.9)	‡	1.7 (0.3 to 10.5)	2.0 (0.7 to 6.1)
> age 3	1.7 (0.9 to 3.0)	1.0 (0.4 to 2.8)	1.2 (0.4 to 3.6)	0.7 (0.4 to 1.2)
Pertussis				
⩽ age 3	0.6 (0.2 to 1.7)	0.5 (0.1 to 5.0)	0.3 (0.03 to 2.4)	0.4 (0.2 to 1.0)
> age 3	0.9 (0.4 to 2.2)	2.4 (0.7 to 8.7)	1.0 (0.2 to 5.8)	0.9 (0.4 to 2.0)
Mumps				
⩽ age 3	2.7 (0.9 to 8.4)	1.3 (0.1 to 13.0)	1.5 (0.1 to 19.1)	0.8 (0.3 to 2.2)
> age 3	0.9 (0.5 to 1.7)	1.0 (0.4 to 2.9)	1.8 (0.6 to 5.0)	1.2 (0.7 to 2.1)
Varicella				
⩽ age 3	1.0 (0.4 to 2.2)	1.9 (0.3 to 11.8)	1.2 (0.3 to 5.8)	1.1 (0.5 to 2.4)
> age 3	0.9 (0.5 to 1.6)	3.5 (0.9 to 13.5)	0.7 (0.2 to 1.9)	1.1 (0.6 to 1.8)
Sum of all infections to age 3				
Any one	0.9 (0.5 to 1.7)	0.3 (0.1 to 1.1)	1.1 (0.3 to 3.5)	1.2 (0.7 to 2.1)
Any two	0.9 (0.4 to 2.5)	0.4 (0.1 to 2.4)§	0.4 (0.04 to 4.2)	0.7 (0.3 to 1.6)
Three or more	1.3 (0.3 to 5.0)		3.0 (0.4 to 22.1)	0.9 (0.3 to 3.4)
Sum of measles and pertussis to age 3				
Either	0.8 (0.4 to 1.4)	0.2 (0.1 to 0.9)§	0.7 (0.2 to 1.8)§	0.8 (0.5 to 1.4)
Both	0.4 (0.1 to 2.3)			0.6 (0.2 to 2.4)
Sum of rubella, mumps, varicella to age 3				
Any of the three	1.1 (0.5 to 2.3)	0.8 (0.2 to 2.8)§	0.8 (0.1 to 4.8)	1.4 (0.7 to 2.8)
Two or more	1.8 (0.5 to 6.0)		3.5 (0.5 to 24.0)	0.7 (0.2 to 2.3)

*Odds ratios are adjusted for sex, social class based on subject's own occupation, smoking habit, atopy, and family history of atopic disease.
†Odds ratios are adjusted for sex, social class based on subject's own occupation, smoking habit, and family history of atopic disease.
‡None of the cases with doctor diagnosed asthma had had rubella on or before age 3.
§Due to small numbers, the final two categories of the variable were combined.

ported by parents were acquired before or after the age of three (table 2). Seropositivity was similar in all the cases and controls, but the subgroup of cases with chronic cough and phlegm were more likely to be seropositive to hepatitis A and *H pylori* (table 3). Seropositivity was similar in atopic and non-atopic subjects and these similarities did not vary with wheezing status.

In multivariate analyses, having two or more younger siblings was independently associated with a lower risk of doctor diagnosed asthma (table 4). The occurrence of measles before the age of three was also independently associated with a lower risk of doctor diagnosed asthma (table 5). Both the effect of having two or more younger siblings (p = 0.033) and of acquiring measles up to the age of three (p = 0.028) were significantly related to a lower risk of asthma when included simultaneously in the adjusted analyses. Subjects who had measles or pertussis, or both, up to the age of three were significantly less likely to have been diagnosed with asthma in adulthood and, again, having two or more younger siblings was negatively associated with asthma after adjustment for the sum of measles and pertussis. There were no independent effects of the serological tests in terms of wheeze or atopy (table 6). However, there was a significant trend of increased risk in the odds ratios with an increasing number of infections in cases with a productive cough.

Sibship structure was not found to be associated with childhood infections or seropositivity (data not shown). Manual workers were significantly more likely than non-manual workers to be positive for hepatitis A, *H pylori*, and *T gondii* and there was a significant interaction between social class and *H pylori* positivity, with manual workers who were seropositive being at increased risk of wheeze (adjusted odds ratio (OR) 3.63; 95% confidence interval (CI) 1.05 to 12.48). Current smokers were significantly more likely than never smokers to be positive for *H pylori* and there was a significant interaction between smoking and *H pylori* positivity, with former smokers (not current smokers) who were seropositive being at increased risk of wheeze (adjusted OR 8.93; 95% CI 1.87 to 42.49).

Discussion

Our observation that individuals with two or more younger siblings have a lower risk of being diagnosed with asthma in adulthood extends the findings of recent studies relating sibship size to allergic disease in younger populations.[3 6–11] In several British studies the number of siblings was inversely related to self-reported allergy,[10] skin test positivity,[9] specific IgE,[11] and to symptoms suggestive of asthma.[11] The absence of an association between sibship structure and atopic status in the present study may be related to differences in the expression of atopy in older subjects (aged 39–45 years) who had no childhood wheeze compared with that in younger adults (aged 20–44 years)[9 11] and pregnant women (14–45 years)[10] in the general populations examined in these other studies.

With the exception of measles, there was no protective association between childhood infections and any form of adult onset wheeze or atopy in subjects who had no childhood wheeze in the present study. This is consistent with our previous observations made in the complete cohort at age 10–14 years[14] in which children who had had common childhood infections—including rubella, pertussis, mumps and varicella—rather than being protected, tended to be more likely to have childhood asthma, eczema, and hayfever when their parents were

Table 6 Risk of adult onset wheeze and atopy according to serological tests: adjusted odds ratios (95% confidence intervals)

	Wheeze (n=84)*	*Wheeze + asthma* (n=19)*	*Wheeze + cough/phlegm* (n=26)*	*Atopy positive† (n=146)*
Seropositive to:				
Hepatitis A	1.1 (0.6 to 2.0)	0.5 (0.2 to 1.6)	2.4 (0.7 to 7.5)	1.6 (0.9 to 2.6)
H pylori	1.2 (0.7 to 2.2)	0.5 (0.2 to 1.5)	2.5 (0.8 to 7.7)	0.9 (0.6 to 1.6)
T gondii	1.6 (0.7 to 2.5)	0.8 (0.2 to 4.1)	1.8 (0.5 to 6.3)	0.7 (0.3 to 1.4)
Sum of seropositivity:				
One positive	0.7 (0.3 to 1.5)	0.9 (0.3 to 3.3)	0.9 (0.1 to 5.4)	1.4 (0.7 to 2.8)
Two positive	0.9 (0.4 to 2.2)	0.2 (0.04 to 1.4)‡	1.9 (0.3 to 10.9)	1.5 (0.7 to 3.3)
Three positive	2.3 (0.6 to 8.4)		7.8 (0.98 to 62.4)	0.9 (0.3 to 2.8)
			p for trend = 0.027	

*Odds ratios are adjusted for sex, social class based on subject's own occupation, smoking habit, atopy, and family history of atopic disease.
†Odds ratios are adjusted for sex, social class based on subject's own occupation, smoking habit, and family history of atopic disease.
‡Due to small numbers, the final two categories of the variable were combined.

interviewed in 1964. These negative findings concord with the observation that common infections in the first month of life were not associated with hayfever in adolescents in Sheffield, UK[8] and with a more recent report that serious early childhood infections were not associated with increased risk of atopy at school age in German children.[20]

It remains possible that measles may have a protective effect since the occurrence of measles in this Aberdeen cohort was related to a reduced risk of asthma both in childhood[14] and adulthood. These findings, together with the inverse association between measles and skin test reactivity in a study in Guinea-Bissau,[12] imply that a single measles episode might influence the immune response for years ahead, the mechanism of any such effect being currently unexplained. However, in contrast to other studies,[8 13 4] our data do not support the concept that a series of infectious events involving repeated contacts with various pathogens may influence risk by shifting the pattern of immunological memory in a Th1 direction, nor do they suggest that infections spread by the faecal-oral route, such as hepatitis A and toxoplasmosis, are more likely to influence the risk of asthma or atopy than those spread by other routes. In the present study the sum of infections occurring before three years of age and the serological results showed no relation to adult onset wheezing or atopy. Rather, there was evidence of an increasing trend in the risk of wheeze associated with the sum of the positive serological tests in the subgroup of cases reporting chronic productive cough.

The interaction of social class and smoking with seropositivity suggests that seropositivity may be an indicator of greater exposure to risk factors for wheeze which are common to the manual class—for example, smoking, occupational factors, and dietary habits. While serological tests have been used by others to provide a measure of repeated exposure to infection in childhood,[4 15] it is important to note that the temporal relations between exposure to hepatitis A, *H pylori*, and *T gondii* and events leading to wheeze and atopy cannot be directly shown in our study.

While it is not possible to draw conclusions about atopy in the target population as a whole from these findings, the relationships observed between atopy and the independent variables in this study provide additional interesting information based on a well characterised population. There was no consistent trend observed in the current data to support the infection hypothesis, but it is possible that larger studies may be needed to detect any protective effect of larger families or infections.

In conclusion, this study suggests that exposure to infections as measured by parental reports obtained at age 10–14 years and by serological tests obtained in adulthood does not influence the development of wheeze or atopic status in adulthood. Measles may be associated with a lower risk of adult onset doctor-diagnosed asthma. The relationship between the number of younger siblings and adult onset asthma was not explained on the basis of childhood infections. Although further research may clarify the relationships between various infections and atopic disease, it is possible that the explanation for the sibship effect reported by others[2 6–11] may lie elsewhere.[14]

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Conflicts of interest: None

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