
Asthma onset and relapse in adult life: the British 1958 birth cohort study

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Background: Few studies have investigated adult-onset wheezing because of difficulties identifying childhood asthma or wheeze retrospectively.

Objective: To investigate risk factors for the incidence and recurrence of wheezing illness in adulthood.

Methods: British children born during 1 week in 1958 (N = 18,558) were followed up periodically. Information on wheezing illness was obtained via parental interviews at ages 7, 11, and 16 years and via cohort member interviews at ages 23, 33, and 42 years. At ages 44 to 45 years a subset (N = 12,069) was targeted for biomedical survey, and total IgE and specific IgE responses to grass, cat, and dust mite were measured.

Results: Incidences of wheezing illness at ages 17 to 33 and 34 to 42 years were positively associated with atopy (any specific IgE ≥ 0.3 kU/L) and cigarette smoking. For ages 17 to 42 years, proportions of incident "asthma" and incident "wheeze without asthma" associated with atopy, adjusted for sex and smoking, were estimated to be 34% (95% confidence interval [CI], 26%–42%) and 5% (95% CI, 1%–9%), respectively, whereas proportions associated with cigarette smoking, adjusted for sex and atopy, were estimated to be 13% (95% CI, 0%–26%) and 34% (95% CI, 27%–40%), respectively. Among participants with no reported wheezing illness at ages 17 to 23 or 33 years, wheeze prevalence at the age of 42 years was positively associated with symptoms in childhood.

Conclusions: Onset and relapse of wheezing illness in adult life seem to be similarly affected by atopy and cigarette smoking, although the nature of these effects may differ between asthma and wheeze without asthma. Children who apparently "outgrow" early wheezing illness remain at increased risk for relapse or recurrence during midlife.

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INTRODUCTION

Wheezing illness takes on different forms, from "transient early wheezing" in very early childhood to persistent wheezing associated with atopy and raised total IgE levels in children of all ages.¹ In adults, the balance was thought to shift with age away from symptoms associated with allergy,² ie, away from atopic (extrinsic) asthma toward nonatopic (intrinsic) asthma. However, in 1989 this distinction between intrinsic and extrinsic disease was challenged by Burrows et al,³ who concluded, based on data from the Tucson Study, that physician-diagnosed asthma at any age is predominantly an allergic condition mediated by IgE. However, more recently Pearce et al⁴ conducted a review of the epidemiologic literature and suggested that the importance of atopy as a cause of asthma may have been overemphasized.

Using longitudinal data from the British 1958 birth cohort study, we aim to investigate the nature of adult wheezing illness⁵ and its associations with atopy, total IgE, sex, and smoking while differentiating between wheezing with and

without origins in childhood and between "asthma" and "wheezing without a reported diagnosis of asthma."

METHODS

Children born in Britain during 1 week in 1958 and immigrants younger than 17 years at entry and sharing the same birth date (N = 18,558) were followed up at the ages of 7, 11, 16, 23, 33, and 42 years.⁶ Information on asthma and wheezy bronchitis ever and in the past 12 months was obtained via parental interviews at the ages of 7, 11, and 16 years. At the age of 23 years cohort members were asked whether they had ever had asthma or wheezy bronchitis since the age of 16 years, and at the age of 33 years⁵ they were asked whether they had ever been told that they had asthma and whether they had had "wheezing or whistling in the chest" ever and in the past 12 months. At the age of 42 years they were asked the same questions on wheezing as at the age of 33 years, and they were also asked whether they had ever had or been told that they had asthma and whether they had had asthma in the past 12 months.

By the age of 44 years the total number of cohort members considered eligible (ie, still alive and living in Britain) for further follow-up was 16,078. Of these, only 12,069 had a good response history (still in contact with the cohort study team and capable of interview without proxy) and were targeted for the biomedical survey. Response among the targeted sample was 9,377 (78%). Further information on response in the 1958 cohort has been reported elsewhere.^{6,7} As part of the biomedical survey, blood samples collected by nurses in the home were sent to Newcastle for measurement

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of total IgE levels using the HYTEC automated enzyme immunoassay.⁸ Specific IgE levels to dust, cat, and grass were also measured if the total IgE level was greater than 30 kU/L. Those with at least 1 measurement of specific IgE greater than 0.3 kU/L were classified as atopic and those with at least 1 high level of specific IgE (>1.0 kU/L) as strongly atopic. The restricted measurement of specific IgE (ie, only if total IgE >30 kU/L) may have led to some cohort members being mistakenly classified as nonatopic rather than atopic. In a validation subset of 356 cohort members with a full set of measurements, 148 had a total IgE level of 30 kU/L or less, and of these, 19 (13%) were weakly atopic and a further 2 (1%) were strongly atopic. Ethical approval for the 2002 to 2004 biomedical survey was obtained from the South East England Multi-center Regional Ethics Committee.

Logistic regression models were fitted to the data using a software program (STATA versions 8 and 9; StataCorp, College Station, TX) to calculate odds ratios and 95% confidence intervals (CIs). Prevalence ratios were calculated using EpiTab in STATA. Various outcome variables were considered, including the incidence of wheezing illness at the ages of 0 to 7, 8 to 16, 17 to 33, and 34 to 42 years; the prevalence of wheezing illness at the age of 42 years; and, among those with incident disease, the presence or absence of a reported asthma diagnosis. Four main explanatory variables were investigated: sex, atopy, total IgE level, and smoking. Statistical significance was evaluated using the likelihood ratio test. Total IgE concentration was divided into 4 groups (<10, 10–30, 31–99, and ≥100 kU/L) for the calculation of odds ratios and for ease of presentation, but for all significance tests and when adjusting for its effects as a potential confounder, a log₁₀ transformation of the continuous variable was used. Total IgE results (n = 24) recorded as being below the level of detection (<1 kU/L) were recoded to 0.5 kU/L before transformation.

Population-attributable risks were calculated using methods described by Bruzzi et al⁹ having obtained strata-specific relative risks and Mantel-Haenszel combined relative risks for incidence at the ages of 17 to 42 years using EpiTab in

STATA. Bootstrapping (2,000 samples) in STATA was then used to estimate bias-corrected 95% CIs. The fact that population-attributable risks depend on the prevalence of “exposure” may limit generalizability.

RESULTS

Sample Attrition

Information on asthma and wheezy bronchitis was provided by the parents of 14,525 cohort members at the 7-year follow-up. However, only 3,646 of these went on to have complete information on wheezing illness during the life course plus information on atopy and total IgE level from the biomedical survey at the ages of 44 to 45 years (Table 1). Comparing those with and without this level of subsequent follow-up, the former group contained a lower proportion of men (48% vs 53%), a slightly lower proportion with a father in a manual occupation in 1958 (70% vs 73%), and a lower proportion of immigrants (0.9% vs 2.1%). Nevertheless there was little difference between the 2 groups in terms of the proportion with a report of hay fever (5.4% vs 5.6%) or eczema (7.7% vs 7.1%) by the age of 7 years. Table 1 presents incidence data for wheezing illness from birth to the age of 42 years.

Lifetime incidence rose from 18% (919/5,168) by the age of 7 years to 24% (1,251/5,168) by the age of 16 years and nearly 50% (2,580/5,168) by the age of 42 years. These estimates remained relatively stable whether or not we restricted the analysis to cohort members with complete wheezing information across all surveys or to those from the biomedical survey with a total IgE measurement.

Independent Effects of Total vs Specific IgE

Thirty-four percent of males and 24% of females were categorized as atopic, but an additional 21% of males and 18% of females were nonatopic but with a total IgE level greater than 30 kU/L. We, therefore, investigated whether total IgE contained information additional to specific IgE that was important in predicting new wheezing illness. Table 2 illustrates that when considered separately and having adjusted for sex

Table 1. Comparing the Incidence of Wheezing Illness in Different Subsets of the Data*

Period	All available data		Complete information on wheezing illness over life course	
	No other restrictions	Cohort members with information on total IgE and atopy	No other restrictions	Cohort members with information on total IgE and atopy
Birth to age 7 y	18.3 (2,665/14,525)	17.4 (1,168/6,721)	17.8 (919/5,168)	17.5 (639/3,646)
Age 8–16 y	7.8 (560/7,143)	7.9 (299/3,762)	7.8 (332/4,249)	8.0 (240/3,007)
Age 17–33 y	24.5 (1,073/4,387)	24.0 (682/2,837)	24.3 (950/3,917)	24.0 (663/2,767)
Age 34–42 y	12.8 (379/2,967)	12.5 (263/2,104)	12.8 (379/2,967)	12.5 (263/2,104)
Birth to age 42 y	49.9 (2,580/5,168)	49.5 (1,805/3,646)	49.9 (2,580/5,168)	49.5 (1,805/3,646)

* Incidence by the age of 7, 8 to 16, 17 to 33, and 34 to 42 years is based on (1) asthma or wheezy bronchitis ever, reported at the ages of 7, 11, and 16 years; (2) asthma or wheezy bronchitis since the age of 16 years, reported at the age of 23 years; and (3) asthma or wheezing or whistling in the chest ever, reported at the ages of 33 and 42 years. Data are given as percentage (number of cohort members reporting a positive history of wheezing illness during the period specified/total number with complete information on wheezing illness for the period specified and with no history of wheezing illness reported at previous follow-ups).

Table 2. Investigating Atopy and Total IgE Level as Predictors of Wheeze Incidence*

Atopy†	Total IgE, kU/L	Incidence of wheezing illness by age, % (No./total No.)			
		0–7 y	8–16 y	17–33 y	34–42 y
No atopy	<10	15.5 (215/1,386)	6.4 (51/803)	18.4 (118/641)	9.3 (48/514)
	10–30	15.1 (320/2,119)	6.7 (82/1,225)	20.2 (188/932)	10.7 (78/728)
	31–99	15.5 (153/986)	5.9 (34/581)	22.9 (101/442)	14.4 (47/326)
	≥100	14.7 (43/292)	9.2 (15/163)	29.5 (33/112)	17.9 (14/78)
Weak atopy	31–99	20.0 (123/614)	11.2 (38/338)	32.9 (79/240)	14.0 (22/157)
	≥100	20.9 (94/449)	8.9 (19/213)	27.8 (42/151)	15.1 (16/106)
Strong atopy	31–99	23.7 (66/279)	7.1 (10/141)	31.9 (36/113)	14.5 (11/76)
	≥100	25.8 (154/596)	16.8 (50/298)	41.3 (85/206)	22.7 (27/119)
Adjusting for sex and smoking as appropriate‡					
OR (95% CI) for strong atopy vs no atopy		1.83 (1.54–2.17)	2.19 (1.60–2.99)	3.07 (2.36–4.00)	1.96 (1.32–2.91)
χ^2 test for association with atopy		$P < .001$	$P < .001$	$P < .001$	$P = .005$
OR (95% CI) for IgE ≥100 vs <10 kU/L		1.46 (1.20–1.78)	1.96 (1.36–2.83)	2.52 (1.89–3.37)	2.09 (1.37–3.20)
χ^2 test for trend with log IgE		$P < .001$	$P < .001$	$P < .001$	$P < .001$
Adjusted for sex, smoking,‡ and atopy					
OR (95% CI) for IgE ≥100 vs <10 kU/L		0.99 (0.77–1.28)	1.25 (0.77–2.02)	1.44 (0.99–2.08)	1.92 (1.13–3.27)
χ^2 test for trend with log IgE		$P = .40$	$P = .82$	$P = .17$	$P = .02$

Abbreviations: CI, confidence interval; OR, odds ratio.

* Incidence of wheezing illness by age is based on (1) asthma or wheezy bronchitis ever, reported at the ages of 7, 11, and 16 years; (2) asthma or wheezy bronchitis since the age of 16 years, reported at the age of 23 years; and (3) asthma or wheezing or whistling in the chest ever, reported at the ages of 33 and 42 years.

† Atopy is defined as a specific IgE level greater than 0.30 kU/L for grass, cat, or dust. Strong atopy is defined as a specific IgE level greater than 10.00 kU/L for grass, cat, or dust.

‡ Associations with incidence in childhood were not adjusted for smoking.

and smoking (as appropriate), total IgE and atopy were positively associated with the incidence of wheezing illness in all 4 age groups. However, when associations with total IgE were additionally adjusted for atopy, only the relationship with onset in early midlife (ages 34–42 years), although slightly weakened, remained significant ($P = .02$). When we restricted analyses to nonatopic individuals and adjusted for sex and smoking, we found positive associations between total IgE and incident wheeze not only for those aged 34 to 42 years but also for those aged 17 to 33 years ($P = .04$ for both). Odds ratios comparing the highest and lowest IgE categories were 1.97 (95% CI, 1.22–3.19) for incidence in early adult life (ages 17–33 years) and 2.02 (95% CI, 1.03–3.95) for incidence in early midlife (ages 34–42 years).

Adult-Onset Wheezing by Asthma Label

Incident wheezing in early adult life (Table 3) and early midlife were strongly and positively associated with current cigarette smoking even after adjustment for sex, atopy, and total IgE level, and the risk of new disease in early midlife seemed particularly high in those who resumed or took up regular smoking between the ages of 33 and 42 years (Table 4). However, associations with smoking seemed to differ between asthma and wheeze without asthma. Among adult-onset

wheezers in both age groups (17–33 years and 34–42 years), the asthma label was significantly less common in current cigarette smokers than in ex-smokers and those with no history of regular cigarette smoking ($P = .002$ and $P = .001$, respectively, adjusted for sex, atopy, and total IgE level).

The incidence of wheezing illness at the ages of 17 to 33 years was significantly lower in men (0.63; 95% CI, 0.52–0.76 adjusted for smoking, atopy, and total IgE level), but the incidence at the ages of 34 to 42 years was similar for both sexes. However, again associations seemed to differ between asthma and wheeze without asthma, and among incident wheezers in both age groups, the asthma label was significantly less common in men than in women ($P < .001$ and $P = .01$, respectively, after adjustment). Associations between adult-onset wheezing illness and atopy and total IgE level seemed to be stronger for asthma than for wheeze without asthma. Among cases of early adult-onset and early midlife onset, the asthma label was positively and significantly associated with stronger atopy ($P < .001$ and $P = .03$, respectively) and higher total IgE ($P < .001$ and $P = .002$, respectively) after adjustment for sex and smoking.

Population-Attributable Risks

For the ages of 17 to 42 years, the proportions of incident asthma and incident wheeze without asthma estimated as being associ-

Table 3. Investigating the Incidence of Wheezing Illness Between the Ages of 17 and 33 Years and Its Possible Determinants

Variable	Cohort, No.*	Incidence of wheeze without asthma, ages 17–33 y, % (No.)	Incidence of asthma with or without wheeze, ages 17–33 y, % (No.)	Incidence of asthma or wheezing, ages 17–33 y (n = 2,811*†)	
				OR (95% CI)	Mutually adjusted OR (95% CI)
Cigarette smoking‡					
Never	2,207	11.4 (251)	3.9 (86)	1.00§	1.00§
Ex-smoker	862	20.6 (178)	5.3 (46)	1.61 (1.27–2.04)	1.73 (1.36–2.21)
Current smoker	1,289	35.3 (455)	3.8 (49)	3.15 (2.58–3.85)	3.44 (2.79–4.25)
Sex					
F	2,355	21.3 (501)	5.4 (128)	1.00§	1.00§
M	2,032	19.2 (390)	2.7 (54)	0.69 (0.58–0.83)	0.63 (0.52–0.76)
Atopy¶					
No atopy	2,127	18.2 (387)	2.5 (53)	1.00§	1.00§
Weak atopy	391	25.3 (99)	5.6 (22)	1.70 (1.34–2.17)	1.63 (1.22–2.17)
Strong atopy	319	23.8 (76)	14.1 (45)	2.36 (1.84–3.04)	2.67 (1.92–3.71)
Total IgE, kU/L					
<10	641	16.5 (106)	1.9 (12)	1.00§	1.00
10–30	932	17.2 (160)	3.0 (28)	1.15 (0.89–1.48)	1.15 (0.88–1.50)
31–99	798	22.7 (181)	4.5 (36)	1.69 (1.31–2.19)	1.31 (0.97–1.76)
≥100	470	24.5 (115)	9.6 (45)	2.33 (1.77–3.08)	1.44 (0.99–2.08)

Abbreviations: CI, confidence interval; OR, odds ratio.

* Cohort members with no report of asthma or wheezy bronchitis ever at the ages of 7, 11, and 16 years and no report at the age of 23 years of asthma or wheezy bronchitis since the age of 16 years but with complete information on asthma or wheeze or whistling in the chest ever as reported at the age of 33 years.

† Cohort members with complete information on sex, smoking status at the age of 33 years, and total and specific IgE levels.

‡ Those currently smoking fewer than 1 cigarette per day (occasional smokers) were coded as ex-smokers. Occasional past smokers were coded as never smokers.

§ $P < .001$.

¶ Atopy is defined as a specific IgE level greater than 0.30 kU/L for grass, cat, or dust. Strong atopy is defined as a specific IgE level greater than 10.00 kU/L for grass, cat, or dust.

ated with atopy vs no atopy, adjusted for sex and cigarette smoking, were 34% (95% CI, 26%–42%) and 5% (95% CI, 1%–9%), respectively, increasing to 46% (95% CI, 28%–63%) and 13% (95% CI, 2%–25%) when we used an alternative definition of allergic propensity, ie, total IgE levels of 10 kU/L or greater. However, the proportions estimated as being associated with cigarette smoking (ever vs never), adjusted for sex and atopy, exhibited the reverse pattern of 34% (95% CI, 27%–40%) for wheeze without asthma and 13% (95% CI, 0%–26%) for asthma. Overall, the proportions estimated as being associated with atopy and cigarette smoking, adjusted for sex, were similar for the 2 wheezing phenotypes at 42% (95% CI, 35%–50%) and 48% (95% CI, 33%–61%), respectively.

Wheezing With Origins in Childhood

Among cohort members who seemed to be symptom free between the ages of 17 and 33 years—that is, with no report at the age of 23 years of asthma or wheezy bronchitis since the age of 16 years and no report of wheezing or whistling in the chest in the past 12 months at the age of 33 years—the prevalence of any wheeze in the past 12 months as reported at the age of 42 years was significantly higher among those with a history of wheezing in childhood (prevalence ratio, 1.49; 95% CI, 1.23–1.79). This

association with childhood symptoms was of a similar magnitude for asthma at the age of 42 years (1.69; 95% CI, 1.11–2.58) as for wheeze without asthma at the age of 42 years (1.43; 95% CI, 1.16–1.78).

The prevalence ratio for all wheeze did not differ substantially when adjusted for any 1 of smoking history (1.48; 95% CI, 1.23–1.78), sex (1.47; 95% CI, 1.22–1.77), atopy (1.42; 95% CI, 1.13–1.79), or total IgE (1.41; 95% CI, 1.12–1.77) and remained significant when adjusted for all 4 together ($P = .003$). Figure 1 compares wheezing at the age of 42 years without previous symptoms (incidence) and wheezing at the age of 42 years after prolonged remission of childhood symptoms (relapse) in terms of associations with potential risk factors. Associations of wheeze prevalence with sex and smoking and trends in prevalence across atopy categories and with log total IgE seemed similar for those with and without childhood symptoms and did not differ significantly between the 2 groups (tests for statistical interactions: sex, $P = .61$; smoking, $P = .67$; atopy [trend], $P = .97$; and log total IgE [trend], $P = .97$).

DISCUSSION

The lifetime incidence of wheezing illness increased from 18% by the age of 7 years to 24% by the age of 16 years⁵ and

Table 4. Investigating the Incidence of Wheezing Illness Between the Ages of 34 and 42 Years and Its Possible Determinants

Variable	Cohort, No.*	Incidence of wheeze without asthma, ages 34–42 y, % (No.)	Incidence of asthma with or without wheeze, ages 34–42 y, % (No.)	Incidence of asthma or wheezing ages 34–42 y (n = 2085*†)	
				OR (95% CI)	Mutually adjusted OR (95% CI)
Cigarette smoker‡					
Never	1,520	7.2 (110)	1.9 (29)	1.00§	1.00§
Ex-smoker, ages 33 and 42 y	677	9.0 (61)	3.0 (20)	1.46 (1.05–2.04)	1.47 (1.05–2.06)
Ex-smoker, at 42 not 33 y	203	11.8 (24)	3.9 (8)	2.13 (1.33–3.42)	2.11 (1.31–3.40)
Current smoker, at 42 not 33 y	80	25.0 (20)	2.5 (2)	4.44 (2.41–8.15)	4.28 (2.32–7.92)
Current smoker, 33 and 42 y	467	20.0 (94)	1.7 (8)	2.10 (1.47–3.00)	2.05 (1.43–2.95)
Sex					
F	1,563	9.3 (145)	2.8 (44)	1.00	1.00
M	1,404	11.9 (167)	1.6 (23)	1.07 (0.82–1.38)	0.98 (0.75–1.28)
Atopy¶					
No atopy	1,646	9.6 (158)	1.8 (29)	1.00	1.00
Weak atopy	263	10.6 (28)	3.8 (10)	1.32 (0.91–1.93)	0.98 (0.63–1.53)
Strong atopy	195	13.8 (27)	5.6 (11)	1.84 (1.25–2.72)	1.41 (0.86–2.29)
Total IgE, kU/L					
<10	514	8.0 (41)	1.4 (7)	1.00§	1.00#
10–30	728	9.1 (66)	1.6 (12)	1.16 (0.79–1.70)	1.12 (0.76–1.64)
31–99	561	12.3 (69)	2.1 (12)	1.59 (1.09–2.33)	1.49 (0.98–2.27)
≥100	304	12.5 (38)	6.3 (19)	2.24 (1.48–3.39)	1.92 (1.13–3.27)

Abbreviations: CI, confidence interval; OR, odds ratio.

* Cohort members with no report of asthma or wheezy bronchitis ever at the ages of 7, 11, and 16 years, no report at the age of 23 years of asthma or wheezy bronchitis since the age of 16 years and no report of asthma or wheezing or whistling in the chest ever at the age of 33 years but with complete information on asthma or wheeze ever as reported at the age of 42 years.

† Cohort members with complete information on sex, smoking status at the ages of 33 and 42 years, and total and specific IgE levels.

‡ At 33 and 42 years old those currently smoking fewer than 1 cigarette per day (occasional smokers) were coded as ex-smokers. Occasional past smokers were coded as ex-smokers at the age of 42 years and never smokers at the age of 33 years.

§ $P < .001$.

¶ Atopy is defined as a specific IgE level greater than 0.30 kU/L for grass, cat, or dust. Strong atopy is defined as a specific IgE level greater than 10.00 kU/L for grass, cat, or dust.

|| $P < .01$.

$P < .05$.

nearly 50% by the age of 42 years. The large increase between the ages of 16 and 42 years may be due in part to a change in the definition of wheezing illness between follow-ups at the ages of 23 and 33 years from asthma or wheezy bronchitis to asthma or wheezing/whistling in the chest. However, it still suggests that by midlife approximately half of the cohort had developed wheezing illness.

In line with the findings of other studies investigating disease prevalence^{3,10,11} and incidence,^{12,13} new wheezing illness was strongly and positively associated with atopy, total IgE level, and current cigarette smoking. We also found a higher incidence in women, but this was only apparent with early adult incidence. Associations with atopy and total IgE level persisted after adjustment for sex and cigarette smoking (Table 2), and associations with cigarette smoking seemed to be invariant to adjustment for sex, atopy, and total IgE level.

The idea that all asthma has an allergic basis was first argued by Burrows et al³ based on the Tucson Study, where they found that the prevalence of physician-diagnosed asthma was associated with total IgE concentration even in nonatopic individuals. Sears et al¹⁴ and Sunyer et al¹⁵ provided further evidence sup-

portive of an association between the prevalence of reported asthma and total IgE level in nonatopic individuals in different populations and settings. However, Pearce et al,⁴ from a review of the epidemiologic literature, estimated that the proportion of asthma (physician-diagnosed, self-reported, or asthma symptoms) associated with atopy (defined in terms of skin prick testing) in predominantly adult populations ranged from 8% to 55%, with a weighted average of only 37%.

In the present study we found weak evidence of an association between total IgE level and the incidence of wheezing illness at the ages of 34 to 42 years having adjusted for specific IgE level in addition to sex and smoking. Similarly, we found associations between total IgE concentration and adult incident wheeze in nonatopic individuals, which, although only just significant after adjustment for sex and smoking, were of comparable magnitude to those reported for the data set as a whole. However, in line with the findings of Pearce et al,⁴ the proportion of adult-onset (ages 17–42 years) wheezing illness in the cohort associated with a total IgE level of at least 10 kU/L was estimated to be only 21% (95% CI, 12%–31%), and the proportion associated with cigarette

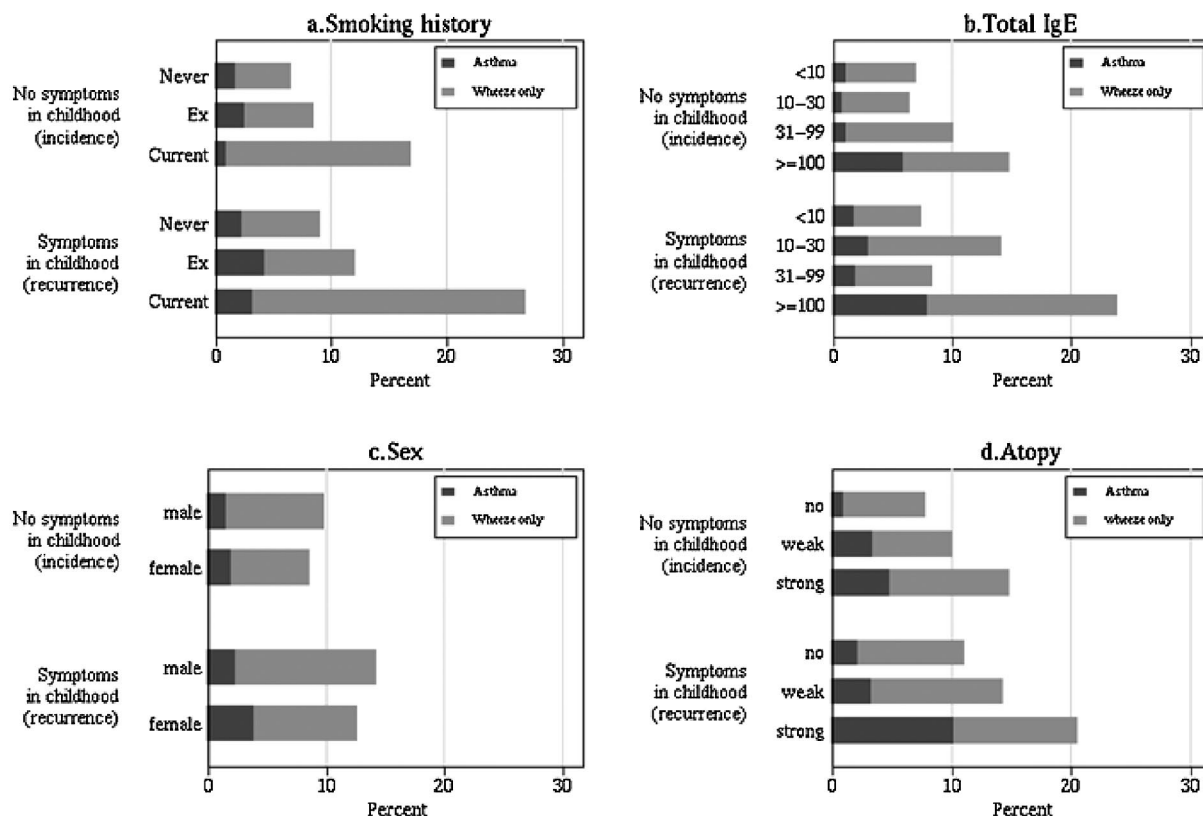


Figure 1. Prevalence of wheezing illness at the age of 42 years by symptoms in childhood (yes/no) and restricted to cohort members with no asthma or wheezy bronchitis since the age of 16 years as reported at the age of 23 years and no wheezing or whistling in the chest in the past 12 months as reported at the age of 33 years. For smoking history reported at the age of 42 years, current smoker is defined as smokes 1 or more cigarettes per day; ex-smoker is defined as past or occasional (<1 cigarette per day) smoker.

smoking (ever vs never) was estimated to be 29% (95% CI, 23%–34%) (data not shown).

The difference in findings between the present study and those of Burrows et al,³ Sears et al,¹⁴ and Sunyer et al¹⁵ may in part be due to our broader definition of disease. Sears et al,¹⁴ in their study of 11-year-old New Zealand children, found a strong association between total IgE level and the prevalence of reported asthma but a much weaker and nonsignificant association between total IgE level and current wheezing not diagnosed as asthma. A more pronounced association with current asthma than with current wheezing only was also found by Sunyer et al¹⁵ in their population study of young Spanish adults aged 20 to 44 years. We, therefore, considered incident wheeze without asthma and incident asthma with or without wheeze separately in Tables 3 and 4. Patterns of association seemed to differ between the 2 disease definitions. In particular, for both age groups (17–33 years and 34–42 years), wheeze without asthma was more common in current smokers than in ex-smokers (intermediate) or nonsmokers, whereas asthma was more common in ex-smokers. Also, positive associations with atopy and total IgE concentration seemed to be of greater magnitude for inci-

dent asthma than incident wheeze without asthma, suggesting that incident wheezing illness with a reported diagnosis of asthma has more of an allergic basis than wheezing illness without such a diagnosis. Indeed, the proportions of incident asthma (ages 17–42 years) and incident wheeze without asthma in the cohort associated with total IgE levels of 10 kU/L or greater were estimated at 46% (95% CI, 29%–63%) and 13% (95% CI, 2%–25%), respectively, and for cigarette smoking (ever vs never) the pattern was reversed at 13% (95% CI, 0%–26%) and 34% (95% CI, 27%–40%), respectively.

Of participants who had apparently remained symptom free since the age of 16 years, asthma or wheezy bronchitis reported in childhood seemed to be a strong predictor of wheezing illness in the past 12 months as reported at the age of 42 years. This suggests that children who apparently “outgrow” early wheezing remain at increased risk for relapse or recurrence during midlife. Furthermore, the patterns observed in Figure 1 for incidence and recurrence in terms of their associations with markers of allergy (ie, atopy and total IgE level) and cigarette smoking suggest, in common with the findings of a previous study,⁵ that allergy and smoking are

important risk factors for wheeze, for the onset of new symptoms in adult life, and also for the return of childhood symptoms after prolonged remission.

The present study has some limitations. The only measurements of total and specific IgE were made at the age of 44 to 45 years and may not adequately reflect allergic status earlier in life, particularly in childhood. Findings relating to the incidence of wheezing illness at the ages of 0 to 7 and 8 to 16 years (Table 2) should, therefore, be viewed with caution. There is also the problem of sample attrition. Although substantial, this seems to have had only a marginal effect on estimates of disease incidence (Table 1), and those with and without complete information on wheezing, atopy, and total IgE level differed little with respect to early indicators of allergic disposition, namely, hay fever and eczema by the age of 7 years. Another potential source of bias was the inclusion of immigrants given their higher levels of total IgE (median, 41 vs 28 kU/L). However, they constituted such a small proportion of the fully restricted data set (0.9%) that they are unlikely to have exerted any substantial effect on the results. Finally, the restricted measurement of specific IgE will have biased population-attributable risks for atopy toward the null. Approximations based on information from the validation subset suggest that this downward bias may be as large as 11 percentage points for asthma and 2 percentage points for wheeze without asthma. Consequently, results using an alternative definition of allergic propensity based entirely on total IgE concentration (IgE $\geq$ 10 kU/L) were also presented in the study.

In conclusion, therefore, of the estimated 50% of cohort members reporting wheezing illness during the life course, as many as half may have symptoms of true adult onset, and although such disease does not seem to fit the Burrows et al model and be wholly explained by markers of allergy, allergy is clearly an important risk factor for wheeze along with current cigarette smoking. There is also some suggestion that these factors have a similarly important role in the recurrence of childhood symptoms in adult life after prolonged remission. However, associations with smoking and allergy do not seem to be the same for asthma as for wheeze without asthma, and although this may be a consequence of the diagnostic process itself, it may indicate that we are dealing with different diseases.

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