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C-reactive protein, obesity, atopy and asthma symptoms in middle-aged adults

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ABSTRACT: **Recent research has suggested an association between circulating C-reactive protein (CRP) and adult asthma, confined to those without evidence of allergic predisposition. The current authors investigated the role of smoking and obesity as possible explanations for this relationship.**

At 44–45 yrs of age, members of the British 1958 birth cohort participated in a biomedical survey involving the measurement of the following: CRP; the specific immunoglobulin E to grass, cat and dust mite; standing height; and weight. Information on asthma and related symptoms was collected by computer-aided interview when the subjects were 42 yrs of age. Complete data were available for a total of 6,490 subjects.

CRP levels were positively correlated with the body mass index (BMI) and were found to be higher among females when compared with males, and higher among heavy smokers ($\geqslant$20 cigarettes·day^{-1}) when compared with never-smokers. After adjustment for sex and region, the odds ratios, comparing asthma prevalence in subjects above the fourth CRP quartile with subjects below the first quartile, were 1.85 (95% confidence interval 1.15–2.99) for nonatopics and 0.94 (0.62–1.41) for atopics, changing to 1.36 (0.80–2.32) and 1.07 (0.67–1.69), respectively, when additionally adjusted for smoking and BMI.

Any association between C-reactive protein and asthma prevalence confined to nonatopics may be due to confounding factors. Alternatively, it may reflect a more general association of C-reactive protein with smoking-related obstructive airways disease.

KEYWORDS: **Asthma, atopy, body mass index, C-reactive protein**

C-reactive protein (CRP) is an acute phase protein produced in the liver in response to infection and tissue damage under the control of interleukin-6, tumour necrosis factor-α and other cytokines [1, 2]. With the introduction of highly sensitive assays, CRP has been used in epidemiological studies as a marker for low-grade systemic inflammation [1, 2]. Positive associations of CRP levels with chronic obstructive pulmonary disease (COPD) [3–6], wheezing illness and asthma [1, 7], and an inverse association with lung function (forced expiratory volume in one second) [2, 8, 9], suggest that systemic inflammation may play a role in the pathogenesis of respiratory illness. However, a recent analysis of Icelandic and Scandinavian data from the second European Community Respiratory Health Survey, which reported a positive association between CRP and nonallergic asthma, found no evidence of a similar association with allergic asthma [1]. This argues against a general role for CRP and implies that these two asthma phenotypes may differ in terms of causal factors and pathogenesis [1]. However, confounding and reverse causation are possible alternative explanations for the association of CRP with nonatopic asthma. The current authors investigated these issues using data from the British 1958 birth cohort, adjusting for sex, body mass index (BMI), smoking and socioeconomic status in childhood and comparing the association of CRP with asthma prevalence at 42 yrs of age between atopic and nonatopic subjects.

MATERIALS AND METHODS

Study subjects

The British 1958 birth cohort (n=18,558) consisted of children born in Britain during one week in 1958 plus immigrants born at the same time and entering the country before their 17th birthday.

Study design

The cohort has been followed up at various ages [10, 11]. At 42 yrs of age, 11,419 cohort members [10] were interviewed and information was collected on smoking history and respiratory symptoms. Each cohort member was asked if they had ''ever had any wheezing or whistling in

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your chest in the past 12 months'', whether they had ''ever had or been told you had asthma'' and if so whether they ''had asthma in the last 12 months'' [12]. Information on the subject's father's social class was collected at birth by the midwife and later supplemented, where missing, with the father's social class as reported by parents at the 7-yr follow-up [13].

By August 2002, there were 14,737 cohort members living in Great Britain, after excluding permanent refusals. With the exclusion of a further 2,668 subjects for reasons including poor response history, the need for interview by proxy, no current valid address, past threatening behaviour and serving in the armed forces, a final 12,069 cohort members were invited to participate in a biomedical survey at 44–45 yrs of age [14]. This survey received ethical approval from the South East Research Ethics Committee (formally known as the South East England Multicentre Regional Ethics Committee; Aylesford, Kent, UK; ref. 01/1/44). The response rate among those targeted was 78% (n=9,377) [14]. Further details of sampling and possible bias are detailed elsewhere [10, 11, 14]. Nurses measured height and weight (estimated if measurement refused) and average systolic blood pressure (mean of three readings) [13] and collected blood samples for biochemical analysis, which included total cholesterol, CRP or and immunoglobulin (Ig) E. Information on current medication, chest infection (''any respiratory infections *e.g.* influenza, pneumonia, bronchitis or severe cold'') in the previous 3 weeks, and asthma medication use (''used an inhaler, puffer or any medication for your breathing'') in the last 24 h, was collected contemporaneously as part of a nurse-led computer-assisted personal interview [14].

Methods

The blood samples were separated into tubes and posted from the field, at ambient temperature, to the laboratory at the Royal Victoria Infirmary (Newcastle, UK), where the total IgE concentration was assayed using the HYTEC automated enzyme immunoassay (Hycor Biomedical Ltd, Penicuik, UK) [14, 15]. Specific IgE to cat, mixed grasses and house dust mite were also measured if the total IgE was >30 kU·L^{-1}, but automatically coded zero if total IgE was $\leqslant 30$ kU·L^{-1} [16]. Atopy was defined as a minimum of one specific IgE level >0.3kU·L^{-1}. Citrated plasma produced in the Royal Victoria Infirmary was frozen at -70°C and transported, frozen, to the Dept of Medicine at the University of Glasgow (Glasgow Royal Infirmary, Glasgow, UK), where CRP was measured using nephelometric analysis of latex particles coated in CRP monoclonal antibodies (BN ProSpec protein analyzer; Dade Behring, Marburg, Germany). The quality of CRP measurement was monitored over time using Levey–Jennings plots [14].

Analysis

The CRP distribution was positively skewed. The 365 values of CRP that were below the detection level of the assay (0.15 mg·L^{-1}) were arbitrarily assigned half this value (0.075 mg·L^{-1}) before being log transformed. CRP was classified as missing for those cohort members who reported a chest infection in the 3 weeks prior to giving a blood sample.

A series of logistical regression analyses, adjusted for sex and region of residence at 44–45 yrs of age, were used to investigate the association of log CRP with the prevalence of asthma in the previous 12 months, as reported at 42 yrs of age (primary outcome) and the prevalence of ''wheeze without asthma'' over the same period. Wheeze without asthma was defined as a report of wheezing or whistling in the chest in the past 12 months without a report of asthma in the previous 12 months. Models including and excluding a CRP/atopy interaction term were compared using the likelihood ratio test to detect differences in association between atopic and nonatopic subjects. Potential confounding by BMI, smoking history and father's social class was adjusted for by including these variables in the model, along with their atopy interaction terms. However, when investigating the association of BMI with the prevalence of asthma and wheeze without asthma, models were fitted that adjusted for father's social class and smoking history (including their interactions with atopy), sex and region but not CRP.

The association of log CRP with BMI, smoking history, father's social class and sex was modelled using mixed effects regression in the statistical system used, adjusting for the postal delay in processing blood samples and the hour in which the blood was taken as fixed effects and CRP batch as a random effect [17].

For ease of presentation, CRP and BMI were sometimes tabulated as four level factors, defined by their respective quartiles. However, the continuous variables, or in the case of CRP the log of the continuous variable, were always used for significance tests and when adjusting for their effects as potential confounders, unless otherwise stated.

RESULTS

Sample attrition

The self-reported prevalence of asthma at 42 yrs of age in the 11,376 subjects investigated was 684 (6%). Out of these 11,376 subjects a total of 6,490 had complete data on the following: atopy, CRP, sex, smoking, BMI, region and father's social class. Among those with complete data (n=6,490), the self-reported prevalence of asthma and wheeze without asthma was 5.6 and 12.2%, respectively. Among the remaining subjects (n=4,886), prevalence of asthma and wheeze without asthma was 6.5 and 14.9%, respectively. After the 871 individuals, who had reported a chest infection in the 3 weeks prior to giving a blood sample, were excluded these values fell to 5.7 and 14.4%, respectively.

Asthma

Asthma prevalence as reported at 42 yrs of age was higher in females than in males among atopic (16.1 *versus* 9.7%) and nonatopic subjects (4.7 *versus* 2.4%). In preliminary analyses adjusted for sex, atopy and region, asthma prevalence was significantly and positively associated with CRP and BMI. In both cases the association differed significantly between those with and without atopy (table 1).

Smoking

For smoking there was no evidence of an overall association with asthma prevalence. However, among nonatopics, prevalence appeared to increase with the amount currently smoked, while among atopics it appeared to decrease and this difference was highly, statistically significant. A similar, although less marked, contrast was observed for father's social class.

TABLE 1 The prevalence of asthma at 42 yrs of age among atopics and nonatopics by C-reactive protein (CRP) and other variables of interest

	Nonatopic		Atopic		Test for association with asthma adjusted for atopy #	Test for difference in association atopics *versus* nonatopics #
	Subjects n	Asthma prevalence %	Subjects n	Asthma prevalence %		
CRP mg·L^{-1}						
<0.454	1209	2.2	440	12.5		
0.454–0.937	1161	2.7	463	10.4	p=0.024¶	p=0.018¶
0.938–2.12	1150	3.9	470	12.1		
>2.12	1165	4.3	455	11.6		
BMI kg·m^{-2}						
<23.99	1410	3.1	462	12.6		
23.99–26.69	1349	2.9	548	13.0	p=0.014¶	p=0.012¶
26.69–29.92	1300	3.2	558	12.0		
>29.92	1245	5.2	565	12.0		
Smoking history at 42 yrs of age						
Never-smoker	2399	2.8	1008	13.0		
Ex-smoker						
<1 cigarette·day^{-1}	287	2.8	132	15.2		
⩾1 cigarette·day^{-1} >5 yrs ago	855	3.5	335	14.9		
⩾1 cigarette·day^{-1} ⩽5 yrs ago	242	4.1	80	16.3	p=0.60+	p<0.001+
Current smoker						
<1–9 cigarette·day^{-1}	385	3.9	164	9.8		
10–20 cigarette·day^{-1}	483	5.4	188	8.5		
⩾20 cigarette·day^{-1}	659	5.6	227	7.5		
Father's social class at birth						
Professional I	251	2.4	114	20.2		
Managerial or technical II	701	3.6	336	10.1		
Other nonmanual IIInm	517	3.3	212	13.2		
Skilled manual IIIm	2571	3.5	996	13.1	p=0.68+	p=0.042+
Partly skilled IV	672	4.0	226	10.6		
Unskilled manual V	421	4.8	156	7.7		
Other or unknown or unemployed	182	3.8	98	13.3		
Medication for breathing taken 24 h prior to giving a blood sample						
Yes	156	50.0	211	67.8	p<0.001¶	p=0.19¶
No or missing	5159	2.2	1927	6.3		

BMI: body mass index; #: likelihood ratio tests from logistic regression additionally adjusted for sex and region of residence at 44–45 yrs of age; ¶: one degree of freedom; +: six degrees of freedom.

C-reactive protein

CRP levels were independently positively associated with being female, higher BMI, current smoking, poorer socioeconomic status in childhood and self-reported use of an inhaler, puffer or other medication for breathing in the 24 h prior to giving a blood sample (table 2).

Asthma and C-reactive protein

Table 3 shows the effect of adjusting the CRP–asthma association for correlates of CRP. Following adjustment for smoking history and BMI, in addition to sex and region of residence, the association between CRP and asthma prevalence lost significance, as did the difference in association between atopics and nonatopics. Further analyses suggested that BMI and smoking history were equally important confounders in this respect (data not shown). Further adjustment for father's social class had little effect (table 3), as did the inclusion of a sex–atopy interaction term along with correlates of ischaemic heart disease (*i.e.* average systolic blood pressure, total cholesterol and reported use of medication for blood pressure or heart problem and their atopy interactions (data not shown)).

Confounding by smoking

Figure 1 shows the prevalence of asthma stratified by atopy and smoking. This illustrates the much higher prevalence of asthma among atopics than nonatopics but of particular

TABLE 2 Mutually adjusted percentage change[#] in C-reactive protein (CRP) associated with change in potential risk factors for asthma[¶]

Risk factor	Change in geometric mean of CRP	p-value
BMI per 5 kg·m^{-2} higher	73 (69–78)	p<0.001
Female *versus* male	15 (9–21)	p<0.001
Smoking history at 42 yrs *versus* never smoked		
Ex-smoker		
<1 cigarette·day^{-1}	8 (-32–1)	
⩾1 cigarette·day^{-1} >5 yrs ago	5 (-3–12)	
⩾1 cigarette·day^{-1} ⩽ 5 yrs ago	11 (-2–26)	
Current smoker		p<0.001
<1–9 cigarette·day^{-1}	21 (9–33)	
10–20 cigarette·day^{-1}	50 (37–65)	
⩾20 cigarette·day^{-1}	78 (64–94)	
Father's social class at birth *versus* professional I		
Managerial or technical II	-2 (-14–11)	
Other nonmanual IIInm	6 (-8–21)	
Skilled manual IIIm	14 (2–29)	p=0.002
Partly skilled IV	8 (-6–23)	
Unskilled manual V	13 (-2–30)	
Other or unknown or unemployed	13 (-5–34)	
Medication for breathing taken 24 h prior to giving a blood sample yes *versus* no or missing	19 (5–35)	p=0.005

Data are presented as per cent (95% confidence interval), unless otherwise stated. BMI: body mass index. [#]: also adjusted for delay in processing bloods, the hour in which the blood sample was taken and CRP batch (as a random effect); [¶]: n=6,718.

interest is the lack of a positive association between prevalence and CRP in the never-smokers.

In terms of sensitivity analyses the present authors also investigated the effect on the final model shown in table 3 using a simpler form of smoking variable (never-smoker, ex-smoker, current smoker) and using a more complex form of adjustment for smoking that included linear terms for both the number of cigarettes smoked by current smokers and the age of quitting, as reported by ex-smokers. In both cases the current results changed little. The odds ratios (OR (95% confidence interval)) comparing those greater than the fourth CRP quartile with those below the lower quartile for atopics and nonatopics, respectively, were 1.07 (0.67–1.70) and 1.39 (0.82–2.38) using the simple adjustment and 1.07 (0.67–1.70) and 1.39 (0.81–2.38) using the more complex adjustment.

TABLE 3 Adjusted odds ratios describing the association of C-reactive protein (CRP) with the prevalence of asthma at 42 yrs of age among those with[#] and without[¶] atopy

	Model 1[+]		Model 2[§]		Final model[f]	
	Nonatopic	Atopic	Nonatopic	Atopic	Nonatopic	Atopic
CRP mg·L^{-1}						
<0.454	1.00 (baseline)	1.00 (baseline)	1.00 (baseline)	1.00 (baseline)	1.00 (baseline)	1.00 (baseline)
0.454–0.937	1.25 (0.74–2.10)	0.87 (0.57–1.31)	1.16 (0.68–1.96)	0.91 (0.59–1.39)	1.19 (0.70–2.01)	0.90 (0.59–1.38)
0.938–2.12	1.79 (1.10– 2.90)	1.07 (0.71–1.59)	1.51 (0.91–2.49)	1.17 (0.77–1.78)	1.54 (0.93–2.56)	1.16 (0.76–1.77)
>2.12	1.85 (1.15–-2.99)	0.94 (0.62–1.41)	1.36 (0.80–2.32)	1.07 (0.67–1.69)	1.40 (0.82–2.38)	1.07 (0.67–1.69)
Test for association with asthma adjusted for atopy	p=0.030		p=0.11		p=0.12	
Test for difference in association atopics *versus* nonatopics	p=0.023		p=0.49		p=0.44	

Data are presented as odds ratio (95% confidence intervals), unless otherwise stated. [#]: n=1,820; [¶]: n=4,670; [+]: adjusted for atopy, sex and region of residence; [§]: adjusted as in model 1 with additional adjustment for smoking history and body mass index; [f]: adjusted as in model 2 with additional adjustment for father's social class.

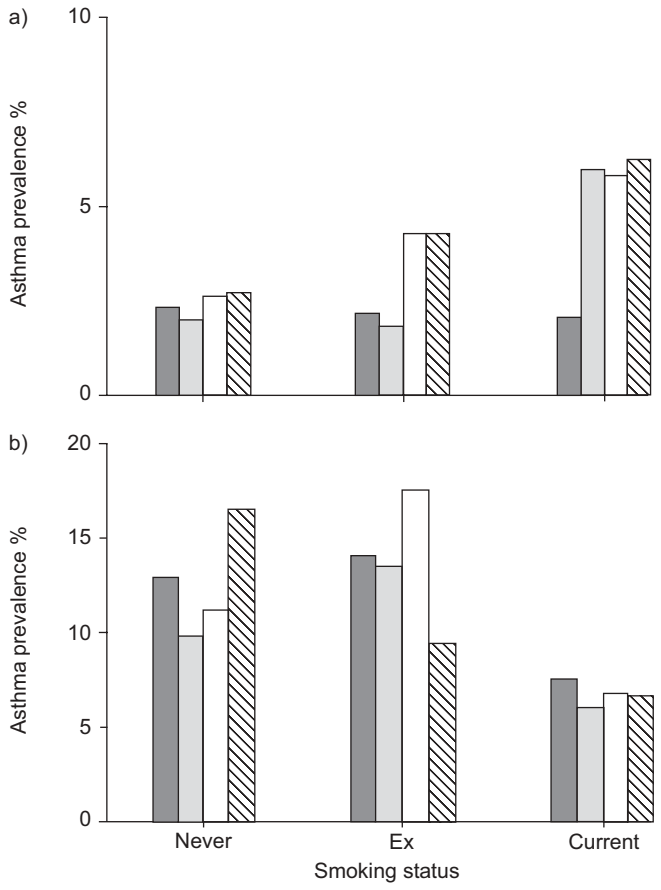

FIGURE 1. The association between asthma prevalence in a) nonatopic and b) atopic subjects at 42 yrs of age, their smoking status and the concentration of C-reactive protein ($mg \cdot L^{-1}$): ■: <0.454; ■: 0.454–0.937; □: 0.938–2.12; ▨: >2.12.

Confounding by BMI

In contrast, when the current authors added a quadratic term in BMI to the final model in table 3, to allow for nonlinearity in the BMI asthma prevalence association, the OR comparing those above the upper quartile with those below the lowest quartile of CRP changed little for atopics (1.05 (0.66–1.67)) but increased for nonatopics (1.50 (0.87–2.58)). However, both an overall association between CRP and asthma prevalence and any difference in association between atopics and nonatopics remained nonsignificant, p=0.104 and p=0.378, respectively. Similar results were obtained (p=0.081 and p=0.244, respectively) when BMI was adjusted for as a 10 level factor (defined by deciles). ORs contrasting those above the upper quartile with those below the lowest were 1.05 (0.66– 1.67) for atopics and 1.56 (0.91–2.67) for nonatopics.

Asthma and BMI

The overall positive association between BMI and asthma prevalence observed in table 2 persisted after the additional adjustment for smoking history and father's social class (p=0.010), as did evidence of a difference in this association between atopic and nonatopic subjects (p=0.015). The adjusted ORs contrasting those above the highest BMI quartile with those below the lowest were 1.06 (0.72–1.56) for atopics and 1.90 (1.27–2.82) for nonatopics.

Wheeze without asthma

When the present authors repeated the analyses for wheeze without asthma, a different pattern of association was observed (table 4).

Having adjusted for sex, atopy and region, the prevalence of wheeze without asthma was significantly higher among current cigarette smokers compared with ex-smokers and the never-smokers and among those from a lower compared with a higher social class background in childhood. There were also significant positive associations with CRP and BMI. However, only the association with BMI differed significantly between atopic and nonatopic subjects. When adjusted for smoking history (the more complex form of adjustment), BMI and father's social class, the association with CRP was considerably weakened and only just remained statistically significant (p=0.04). In contrast, the association with BMI persisted after adjustment for smoking history and father's social class (p<0.001), as did evidence of a difference in association between atopics and nonatopics (p=0.018). The adjusted ORs contrasting those above the highest quartile of BMI with those below the lowest quartile were 0.99 (0.71–1.39) for atopics and 1.93 (1.50–2.49) for nonatopics.

Response bias

The mean±SD BMI was higher among those with missing information on atopy 28.0±5.7 *versus* those with usable information on 27.3±4.9 $kg \cdot m^{-2}$. When the present authors included rather than excluded such subjects, the crude ORs contrasting those above the upper quartile of BMI with those below the lower quartile were 1.47 for asthma (increased from 1.38), and 1.48 for wheeze without asthma (decreased from 1.59). This suggested that although the current analyses tended to underestimate the overall association between BMI and asthma prevalence and overestimate the overall association between BMI and wheeze without asthma, these biases were relatively small.

DISCUSSION

In common with other studies, the present authors found that CRP was positively associated with obesity [1, 2, 5, 6, 9, 18, 19] and smoking [1, 2, 6]. Levels of CRP were also found to be higher among females than males [19] and among those with fathers in manual rather than nonmanual occupations [2, 6]. In preliminary analyses, adjusted only for sex, atopy and region of residence, there was evidence of a positive association between CRP and the prevalence of asthma at 42 yrs of age, an association which appeared to be confined to nonatopics. This was in keeping with the recent findings by ÓLAFSDOTTIR *et al.* [1], who suggested, based on data from the European Community Respiratory Health Study, that CRP was positively associated with nonallergic asthma but not with allergic asthma. However, when the current authors further adjusted for BMI and smoking, both the overall association between CRP and asthma prevalence and any difference in association between atopics and nonatopics lost statistical significance. No evidence of an atopy–CRP interaction was observed for wheeze without asthma.

The importance of smoking as a potential confounder was highlighted in the current data by the lack of evidence for an association between CRP and asthma prevalence among

TABLE 4 The prevalence of wheeze without asthma at 42 yrs of age among atopics and nonatopics by C-reactive protein (CRP) and other variables of interest

	Nonatopic		Atopic		Test for association adjusted for atopy[#]	Test for difference in association atopics *versus* nonatopics[#]
	Subjects n	Wheeze without asthma prevalence %	Subjects n	Wheeze without asthma prevalence %		
CRP mg·L^{-1}						
<0.454	1209	7.2	440	13.9		
0.454–0.937	1161	10.7	463	14.3	p<0.001[¶]	p=0.54[¶]
0.938 to 2.12	1150	10.0	470	14.0		
>2.12	1165	15.8	455	20.4		
BMI kg·m^{-2}						
<23.99	1410	8.7	462	18.6		
23.99–26.69	1349	10.0	548	13.5	p<0.001[¶]	p=0.02[¶]
26.69–29.92	1300	12.2	558	14.3		
>29.92	1245	15.8	565	18.6		
Smoking history at 42 yrs						
Never-smoker	2399	5.7	1008	10.6		
Ex-smoker						
<1 cigarettes·day^{-1}	287	6.6	132	15.2		
⩾1 cigarettes·day^{-1} >5 yrs ago	855	7.8	335	12.2		
⩾1 cigarettes·day^{-1} ⩽5 yrs ago	242	16.1	80	16.3	p<0.001[+]	p=0.28[+]
Current smoker						
<1–9 cigarettes·day^{-1}	385	13.8	164	18.9		
10–20 cigarettes·day^{-1}	483	20.5	188	27.1		
⩾20 cigarettes·day^{-1}	659	30.5	227	36.6		
Father's social class at birth						
Professional I	251	8.8	114	10.5		
Managerial or technical II	701	7.6	336	14.6		
Other nonmanual IIInm	517	9.5	212	13.7		
Skilled manual IIIm	2571	11.8	996	15.6	p<0.001[+]	p=0.24[+]
Partly skilled IV	672	13.8	226	23.9		
Unskilled manual V	421	17.6	156	17.9		
Other unknown or unemployed	182	11.5	98	19.4		
Medication for breathing taken 24 h prior to giving a blood sample						
Yes	156	19.2	211	19.0	p=0.007[¶]	p=0.16[¶]
No or missing	5159	11.3	1927	15.9		

BMI: body mass index. [#]: likelihood ratio tests from logistic regression additionally adjusted for sex and region of residence at 44–45 yrs of age; [¶]: one degree of freedom; [+]: six degrees of freedom.

lifelong nonsmokers (fig. 1). Furthermore, an increasing trend in asthma prevalence with the amount smoked was only found among nonatopics, whereas there was a decreasing trend with the amount currently smoked among atopics. Evidence for a positive association between smoking and asthma confined to nonatopics comes from a large study of young Spanish adults [20] that investigated the relationship between smoking and bronchial hyperresponsiveness.

Of equal importance, in terms of confounding was BMI, the exact nature of the association between BMI and asthma prevalence is not clear [21–22], although the present study's analyses suggested that any association was confined to nonatopics and that within this group, asthma prevalence was highest among the obese (table 1). Similar associations were observed for wheeze without asthma. This is in keeping with the findings of SCHACHTER *et al.* [21], who reported positive associations between severe obesity and recent asthma but no evidence of a similar relationship with atopy. However, these findings are in contrast with those of ÓLAFSDOTTIR *et al.* [1], who reported positive associations between obesity and both allergic and nonallergic asthma, the latter losing significance after adjustment for CRP. In addition the findings of SCHACHTER *et al.* [21] also contrast with large studies of Swedish male conscripts where a positive relationship with obesity was reported for both asthma with and asthma without rhinoconjunctivitis [23]. Nevertheless, the similarity of associations with BMI that the present authors observed for both asthma and wheeze without asthma does suggest that, should BMI have a role in the development or persistence of wheezing illness, this role may be confined to a type of disease that is unassociated with allergy. Whether pro-inflammatory cytokines mediate any association between BMI and wheezing illness requires further investigation [24].

The role of asthma medication (inhaler, puffer or any medication for breathing) in explaining any association between CRP and wheezing illness is difficult to assess. SIN *et al.* [25] and PINTO-PLATA *et al.* [3] found inverse associations between CRP and corticosteroids in patients with COPD; in contrast, the present authors detected a positive association between CRP and reported the use of asthma medication in subjects 24 h prior to giving a blood sample. These findings may suggest that any steroid-related suppression of CRP levels is being outweighed by a strong association between medication use and more severe forms of respiratory disease, including severe asthma and COPD. Alternatively, it is possible that medication may simply be acting as a marker for minor infections, such as mild-to-moderate colds.

In the current study's final analysis, having adjusted for sex, atopy, region, BMI, smoking history and father's social class, there was still some suggestion of a graded relationship between asthma prevalence and CRP and a pattern of higher OR among nonatopics, although associations were no longer statistically significant. Based on the study's sensitivity analyses, residual confounding by ischaemic heart disease or by amount currently smoked seems an unlikely explanation of any remaining pattern and the misspecification of the BMI and asthma association in the model may have resulted in some over-adjustment for confounding rather than any under-adjustment. However, the current authors found no evidence of a CRP-asthma association among lifelong never-smokers. Thus, the possibility of residual confounding by length of time smoked among current smokers cannot be totally discounted. Given that such residual confounding may be more important in a study covering a wide age group compared with a study involving a birth cohort, it could help explain the difference between the current findings and those of ÓLAFSDOTTIR *et al.* [1].

An alternative explanation for any observed pattern between asthma prevalence and C-reactive protein among nonatopics is possible comorbidity with chronic obstructive pulmonary disease, a disease known to be associated with raised C-reactive protein [3–6], or the misdiagnosis of smoking-related chronic obstructive pulmonary disease as asthma among older subjects [26]. Further studies should explore whether or not a C-reactive protein-atopy interaction exists for asthma in children and young adults, where smoking-related chronic bronchitis is less likely to occur or to overlap with nonatopic asthma.

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