

Sex Differences in the Relation between Body Mass Index and Asthma and Atopy in a Birth Cohort

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Rationale: Several studies have identified an association between asthma and obesity in women. It remains unclear if this association is due to genuine asthma or to symptoms caused by overweight, at what age the association develops, and whether it is confined to females. **Objective:** To explore the relations between body mass index, asthma, and atopy in a birth cohort of approximately 1,000 individuals. **Methods:** Information on asthma and measurements of lung function, airway responsiveness, and atopy were obtained on multiple occasions between ages 9 and 26. Associations between these outcomes and body mass index were analyzed using generalized mixed linear regression models. Further analyses adjusted for potential covariates including breastfeeding, birth order, parental asthma, and personal and family smoking history. **Main results:** Body mass index was positively associated with asthma, wheeze, asthma treatment, atopy, immunoglobulin E, and inversely with the FEV₁/FVC ratio in females. There was no significant association with airway responsiveness to methacholine or salbutamol. There was little evidence of an association between body mass index and asthma or atopy in males. Analyses adjusting for potential covariates showed similar findings. Asthma was not associated with a raised body mass index in childhood and childhood asthma did not lead to being overweight as an adult. **Conclusions:** A raised body mass index is associated with asthma and atopy in women but not men. Population attributable fraction calculations estimate that 28% (95% confidence interval 7–45) of asthma developing in women after age 9 is due to overweight.

Keywords: birth cohort; obesity; prevalence; respiratory epidemiology

In recent decades, many parts of the world have observed marked increases in the prevalence of asthma (1–6) and obesity (7). Both conditions result from complex interactions between genetic traits and environmental influences. Although the environmental changes leading to the increase in obesity appear obvious, the causes of the increased prevalence of asthma remain obscure. Several studies have indicated that there may be a link

between asthma and obesity (8). Although some commentators have questioned this association (9, 10), others have suggested biologically plausible mechanisms to explain it (8, 11).

An association between asthma and obesity has been observed in both children and adults. In several studies, the association has been stronger, or only observed, in females (12–21). A causal relation between asthma and obesity is supported by data from cohort studies. Camargo and colleagues (22) and Beckett and colleagues (16) found that an increase in body mass index (BMI) is associated with an increased risk of developing asthma in women. Castro-Rodríguez and colleagues (17) found that girls who became overweight between ages 6 and 11 were more likely to have new asthma symptoms, peak flow variability, and bronchodilator responsiveness at age 11 or 13. This association was not observed in boys. Similarly, Gold and colleagues (23) reported that a higher baseline BMI and a greater increase in BMI were associated with developing asthma in 6- to 14-year-old girls followed for 5 years. The association in boys was more complex, with both the smallest and greatest changes in BMI being associated with asthma.

However, our understanding of the issue remains incomplete (11). Many surveys have relied on responses to questionnaires to indicate asthma. This raises the possibility that respiratory symptoms caused by obesity, such as dyspnea, may have been mistaken for asthma. For example, Schachter and colleagues found significant associations between obesity and symptoms of wheeze and diagnosed asthma but not atopy, airflow obstruction, or airway responsiveness in adults (24). It is also uncertain if the association between overweight and asthma is confined to females. Gilliland and colleagues found that overweight boys had a higher risk of developing asthma over a 5-year follow-up than did overweight girls (25). Among the few studies to have used an “objective” marker of asthma, the European Community Respiratory Health Survey found an association between BMI and bronchial responsiveness to methacholine in males with only a weak and insignificant association in women (26), whereas Celedón and colleagues reported similar increases in symptomatic airway responsiveness to methacholine in both overweight and underweight Chinese men and women (27).

We have explored the relation between BMI and measures of asthma, lung function, airway responsiveness, and atopy in a birth cohort of approximately 1,000 New Zealanders followed into adulthood. Because the association between asthma and body weight could be confounded by a number of other factors (e.g., we have previously found in this cohort that breastfeeding during infancy is associated with a lower risk of overweight and a higher prevalence of asthma [28, 29]), we further examined whether the association was confounded by a number of potential covariates.

METHODS

The Dunedin Multidisciplinary Health and Development Study is a cohort study of 1,037 children (52% male) born between April 1972

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and March 1973 (30). Follow-up assessments have been conducted at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 years when 980 (96%) of 1,019 living study members participated. The Otago Ethics Committee approved the study. Written informed consent was obtained at each assessment.

At age 9, the accompanying adult was questioned about current and previous asthma, wheeze, and cough (31). This information was updated at subsequent assessments (32). Current asthma is defined as diagnosed asthma with symptoms within 12 months; asthma with airway hyperresponsiveness as both current asthma and airway hyperresponsiveness (see the following paragraph); current wheeze as more than two episodes of wheezing lasting more than 1 hour in the previous year; and asthma treatment as any bronchodilator, corticosteroid, or cromoglycate medication. Current smoking was defined as smoking daily for at least 1 month during the past year.

At each age, height and weight in light clothing without shoes were measured to calculate BMI in kg/m². Spirometry was performed at each assessment from age 9. Airway responsiveness was measured using methacholine at ages 9, 11, 13, 15, and 21 or salbutamol (albuterol) at ages 18 and 26 (33). A provocative concentration of methacholine to induce a 20% fall in FEV₁ of 8 mg/ml or less, or an increase in FEV₁ of 10% or greater, indicated airway hyperresponsiveness. Skin-prick testing at ages 13 and 21 included house dust mite (*Dermatophagoides pteronyssinus*), grass, cat, dog, horse, kapok, wool, *Aspergillus fumigatus*, *Alternaria*, *Penicillium*, and *Cladosporium* (34). A weal diameter 2 mm greater than saline control was considered positive, and atopy was defined as a positive response to one or more allergens. Total serum immunoglobulin E (IgE) was measured at ages 11 and 21 (35).

The adult accompanying the study member at age 7 was asked whether the natural mother or father had asthma (36). Self-reported height and weight was obtained for 81% of mothers and 77% of fathers at the age 11 assessment. Family smoking history was ascertained at age 9. Duration of breastfeeding was reported at the age 3 assessment and verified from a prospective record (29). Birth order was categorized according to the number of older siblings (none, one, two, three, or more).

Statistical Analysis

Associations between BMI and the dependent variables asthma, asthma with airway hyperresponsiveness, wheeze, treatment, atopy, FEV₁/FVC ratio, methacholine responsiveness, bronchodilator responsiveness, and log IgE levels were analyzed using generalized mixed linear and logistic regression models across ages 9–26 years (37). For the logistic regression models, the number of quadrature points was set to 24. There were significant sex–BMI interactions for asthma, wheeze, asthma treatment, and atopy. Males and females were therefore analyzed separately.

Further analyses adjusted for potential covariates: parental history of asthma, breastfeeding, birth order, personal and family smoking, and maternal smoking during pregnancy. Pregnant women were excluded from all analyses. Supplementary analyses calculated population-attributable fractions for asthma resulting from overweight at age 26. The association between asthma and BMI in parents of the study members was analyzed by logistic regression. *p* Values < 0.05 were considered significant. All analyses were performed using Stata 8.0 (Stata Corporation, College Station, TX). (Additional details on the METHODS are provided in the online supplement.)

RESULTS

The results of the generalized mixed model analyses are shown in Table 1. Asthma, wheeze, atopy, and log IgE were significantly associated with BMI in females, whereas there was a significant inverse association with the FEV₁/FVC ratio. There was no significant association between BMI and airway responsiveness to either methacholine or salbutamol. In males, there was an association between BMI and wheeze that was of borderline statistical significance, but there were no other significant associations with BMI.

The results of the analyses with adjustment for the potential covariates are shown in Table 2. These show a similar pattern of findings with little change in the magnitude of the odds ratios, coefficients, or *p* values. In this analysis, the trend to an inverse relation between BMI and airway hyperresponsiveness to methacholine in females was still present. However, there was a significant positive association between BMI and asthma combined with airway responsiveness in females.

Model fitting for the generalized mixed logistic regression analyses was checked using different numbers of quadrature points. At lower numbers of quadrature points (8–16), some of the coefficients varied significantly depending on the number of points chosen. At higher number of points (greater than 20), the results were more stable. Although the size of the coefficients varied according to the number of quadrature points, the findings were similar and the interpretation of the results did not change according to the number of quadrature points used.

Further exploration of the data using cross-sectional analyses at each age indicated that there was no association between BMI and any of the outcomes at age 9. Indeed, a diagnosis of asthma at age 9 was associated with a significantly lower BMI at age

TABLE 1. GENERALIZED MIXED LOGISTIC AND LINEAR REGRESSION ANALYSES OF ASTHMA AND ATOPY VARIABLES ON BMI

	Female			Male		
	n	OR	95% CI	n	OR	95% CI
Asthma	2,840	1.10*	(1.02–1.18)	3,093	1.06	(0.98–1.15)
Asthma with AHR	2,647	1.08	(0.92–1.28)	2,895	1.01	(0.90–1.14)
Wheeze	2,837	1.12*	(1.07–1.17)	3,090	1.05*	(1.00–1.10)
Treatment	2,840	1.06	(0.99–1.13)	3,093	1.02	(0.93–1.11)
PC ₂₀ ≤ 8	1,836	0.89	(0.79–1.02)	1,997	1.05	(0.92–1.19)
BDR ≥ 10	811	0.96	(0.87–1.04)	898	1.03	(0.94–1.13)
Atopy	765	1.14*	(1.01–1.30)	822	1.00	(0.84–1.19)
	n	Coefficient	95% CI	n	Coefficient	95% CI
FEV ₁ /FVC	2,738	−0.07*	(−0.14–−0.01)	2,990	−0.04	(−0.12–0.04)
Log IgE	597	0.04*	(0.01–0.08)	686	0.02	(−0.02–0.06)

Definition of abbreviations: AHR = airway hyperresponsiveness (either PC₂₀ ≤ 8 mg/ml, or ≥ 10% increase in FEV₁ after salbutamol); BDR ≥ 10 = 10% or greater increase in FEV₁ in response to salbutamol; BMI = body mass index; coefficient = change in outcome for each kg/m² unit increase in BMI; n = number of observations in the analysis (several observations made for each study member at different ages); OR = odds ratio (the change in odds of the outcome for each kg/m² unit increase in BMI); PC₂₀ ≤ 8 = provocative concentration of methacholine to induce a 20% fall in FEV₁ = 8 mg/ml or less.

Analyses are unadjusted for covariates.

**p* < 0.05.

TABLE 2. GENERALIZED MIXED LOGISTIC AND LINEAR REGRESSION ANALYSES OF ASTHMA AND ATOPY VARIABLES ON BMI ADJUSTED FOR COVARIATES

	Female			Male		
	n	OR	95% CI	n	OR	95% CI
Asthma	2,275	1.14*	(1.05–1.23)	2,550	1.03	(0.92–1.15)
Asthma with AHR	2,153	1.20*	(1.04–1.39)	2,408	0.96	(0.82–1.13)
Wheeze	2,275	1.12*	(1.07–1.18)	2,549	1.05	(1.00–1.10)
Treatment	2,275	1.06	(0.99–1.13)	2,550	1.03	(0.95–1.13)
PC ₂₀ ≤ 8	1,545	0.91	(0.78–1.06)	1,698	1.03	(0.88–1.19)
BDR ≥ 10	608	0.98	(0.90–1.08)	710	1.00	(0.89–1.12)
Atopy	618	1.10	(0.95–1.26)	683	1.06	(0.86–1.29)
FEV ₁ /FVC %	2,223	−0.11*	(−0.19–−0.04)	2,488	0.00	(−0.09–0.09)
Log IgE	478	0.04	(0.00–0.08)	564	0.03	(−0.02–0.08)

For definition of abbreviations, see Table 1.

Analyses are adjusted for breastfeeding, birth order, parental asthma, and personal and family smoking and smoking during pregnancy.

* $p < 0.05$.

26 (mean difference 1.47 kg/m², 95% confidence interval [CI] 0.33–2.6), with similar differences in males and females. There was a significant association between adult BMI and developing asthma after age 9 in females (Figure 1). Analyses of data at ages 9, 11, 13, 15, 18, 21, and 26 suggest that the association between BMI and asthma in females emerged during the late teens. There were trends to an association between wheeze and

BMI at all ages, although this was only significant from age 15 onward (Table 3). Population-attributable fraction calculations suggest that 18% (95% CI 2–32) of all asthma in 26-year-old women, and 28% (95% CI 7–45) of asthma developing since age 9, may be attributable to being overweight (BMI > 25) at 26. Attributable fractions were smaller and not significant in males.

The association between asthma and BMI in the parents of the study members was similar to that observed in the study members themselves. That is, asthma was significantly associated with BMI in the mothers of the study members ($n = 813$, odds ratio [OR] for each unit increase in BMI = 1.06, 95% CI 1.01–1.12), but not in the fathers ($n = 770$, OR = 0.99, 95% CI 0.93–1.05). (Additional RESULTS are provided in the online supplement.)

DISCUSSION

This study found that a high BMI is associated with asthma, wheeze, and asthma treatment in females. There were also associations between BMI and atopy on skin-prick testing and serum IgE, and a negative association with the FEV₁/FVC ratio. In males, there was an association between a high BMI and wheeze that was of borderline statistical significance, but otherwise the associations were weaker and not significant.

This association appears to be due to the development of asthma in females who become overweight during adolescence and early adulthood. Cross-sectional analyses indicate that there was no evidence of an association in girls at age 9. By age 26 the association between BMI and asthma was statistically significant.

Our findings confirm and extend those of a number of studies that have reported an association between BMI and asthma in women (13–19, 21). We found no association between a raised BMI and asthma in children; the association appeared to emerge in late adolescence (Table 3). It has been reported that an early onset of puberty and a high BMI are both risk factors for developing asthma during adolescence in females (17, 38). We did not find an association between asthma and age of menarche in this study, nor did it modify the relationship between BMI and asthma (data not shown). There was also no evidence that the association between asthma and adult BMI arose because girls with childhood asthma put on extra weight during puberty. In fact, those who had already developed asthma by age 9 tended to have lower BMIs as adults.

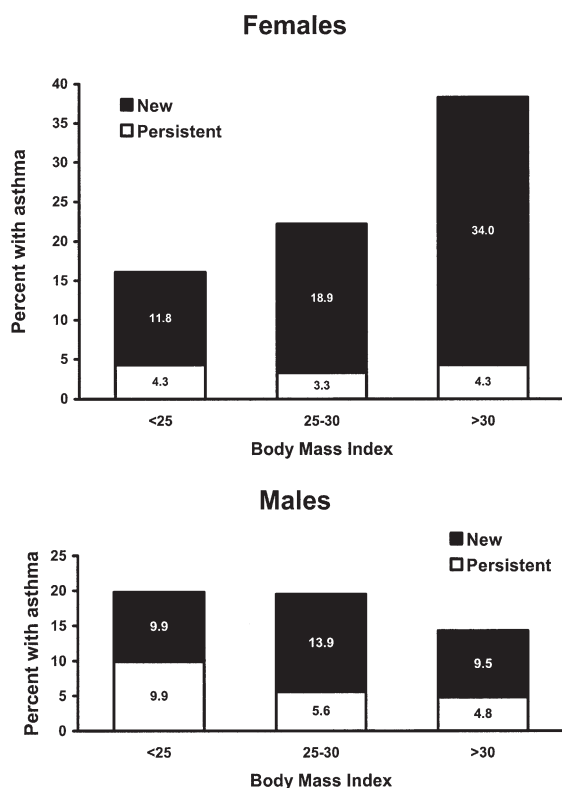


Figure 1. New and persistent asthma at age 26 according to body mass index category at age 26. Persistent asthma is defined as current asthma at both the age 9 and 26 assessments. New asthma is defined as current asthma at age 26, but not at age 9. The trends for both new asthma and all asthma (new and persistent) in females are significant; $p < 0.01$. No trend is significant in males.

TABLE 3. LOGISTIC REGRESSION OF ASTHMA AND WHEEZE ON BMI AT EACH AGE

	Age (yr)	Asthma			Wheeze		
		n	OR	95% CI	n	OR	95% CI
Female	9	383	0.91	(0.70–1.17)	383	1.06	(0.92–1.22)
	11	339	0.85	(0.69–1.04)	339	1.02	(0.89–1.17)
	13	355	0.96	(0.84–1.10)	355	1.06	(0.97–1.16)
	15	462	1.01	(0.91–1.12)	462	1.11*	(1.03–1.20)
	18	405	1.04	(0.96–1.12)	405	1.09*	(1.02–1.16)
	21	447	1.05	(0.98–1.11)	447	1.08*	(1.03–1.14)
	26	445	1.04*	(1.00–1.09)	442	1.04*	(1.00–1.08)
Male	9	426	0.90	(0.72–1.14)	426	1.12	(0.97–1.30)
	11	371	0.98	(0.86–1.12)	371	1.04	(0.93–1.16)
	13	380	1.00	(0.89–1.13)	380	1.05	(0.96–1.15)
	15	493	1.02	(0.93–1.10)	493	1.05	(0.98–1.12)
	18	437	1.01	(0.93–1.10)	437	1.08*	(1.01–1.15)
	21	482	1.00	(0.92–1.07)	482	1.02	(0.97–1.08)
	26	494	0.99	(0.94–1.06)	491	1.02	(0.97–1.07)

Definition of abbreviations: BMI = body mass index; n = number of observations in the analysis (several observations made for each study member at different ages); OR = odds ratio (the change in odds of the outcome for each kg/m² unit increase in BMI) and 95% confidence intervals from logistic regression.

*p ≤ 0.05.

The lack of association between BMI and asthma in prepubertal children is consistent with large surveys of 4- to 11-year-old Canadian and American children (17, 39). By contrast, the 1993–1994 survey of the UK National Study of Health and Growth found that BMI was associated with asthma in 4- to 11-year-old children of both sexes (15). An analysis of earlier samples of children in the same study suggested that the association between BMI and asthma is of recent onset (40). The authors speculated that this may reflect a recent change in nutrition or lifestyle increasing the prevalence of both obesity and asthma and thereby confounding the association. If similar changes occurred in New Zealand, this might explain why the association between BMI and asthma in the Dunedin Study was not apparent until the 1987–1988 assessment when the study members were age 15. However, such a sudden change in environmental or nutritional factors seems unlikely, and it is unclear how this explanation would account for the differences in the association between asthma and BMI in males and females. Furthermore, we are able to analyze the relationship between estimated BMI and reported asthma in the parents of the study members using data obtained between 1979 and 1984. This shows a significant association between asthma and BMI in the mothers of the study members, but not in their fathers. This indicates that the association between BMI and asthma has been stable across two generations of New Zealand women.

The question remains as to whether this association between BMI and asthma is real. It is possible that there is an apparent association because symptoms of overweight, such as exercise-induced dyspnea, are mistaken for asthma. The definition of asthma used in this study—a self-report of diagnosed asthma with symptoms in the previous year—does not exclude this possibility. In support of this explanation, BMI was not associated with airway responsiveness to either methacholine or salbutamol. In fact, there was a trend to an inverse association between BMI and methacholine responsiveness in females. However, a higher BMI was associated with a lower FEV₁/FVC ratio in females, indicating that overweight was associated with airflow obstruction and with respiratory symptoms. This inverse association between BMI and the FEV₁/FVC ratio in females was independent of an asthma diagnosis (coefficient −0.07, 95% CI −0.13–0.01). A recent study by Aaron and colleagues (41) found that weight loss in obese asthmatic women was associated

with improvements in lung function, including both the FEV₁ and FVC, but had no significant effect on airway responsiveness to methacholine. Because airway responsiveness is regarded as a hallmark of asthma (42), the lack of association between BMI and methacholine responsiveness suggests that obese women develop airflow obstruction and respiratory symptoms through nonasthmatic mechanisms. Schachter and colleagues also found that adult obesity was associated with asthma and wheeze, but not airway responsiveness (24). By contrast, the European Community Respiratory Health Survey found obesity to be associated with methacholine responsiveness, but paradoxically this association was stronger in men than women (26). The reason for these differences between studies is unclear.

Although the lack of association between BMI and airway responsiveness suggests that the association between obesity and asthma may be due to diagnostic or reporting bias, other findings indicate that this is unlikely to be the case. First, a more stringent definition of asthma requiring both current diagnosed asthma and significant airway responsiveness to either methacholine or salbutamol was positively associated with BMI in women. Second, there were significant associations between BMI and both atopy and serum IgE levels in females. Previous reports on obesity and atopy are conflicting. Neither Schachter and colleagues (24) nor Jarvis and colleagues (43) found an association between BMI and atopy in adults. By contrast, other surveys found a high BMI to be a risk factor for atopy in 7- to 12-year-old girls (20), both boys and girls ages 4–17 (44), and young adults of both sexes (45). Although we found that the associations between BMI and atopy/IgE were of borderline statistical significance after adjusting for potential confounding factors, these are well recognized risk factors for asthma and suggest that there may be an association between adiposity and the immunologic responses typical of allergic asthma.

Consistent with several other studies, we did not find a relation between BMI and asthma in males. Why the association between BMI and asthma is more often observed in females is unknown, but may be partially explained by the fact that for a given BMI, women have a greater percentage of body fat than men (46). Thus the relation between BMI and asthma/atopy may be weaker in males and this study may have had insufficient power to demonstrate it. It is possible that a relation between BMI and asthma will emerge as these men age and adiposity

increases. An alternative explanation is that the association between BMI and asthma is mediated by female sex hormones (8, 11, 47). Regardless of the underlying cause, these observations may help to explain the widely recognized but poorly understood sex difference in asthma epidemiology. Asthma is more prevalent among preadolescent boys than girls, but females are more likely to develop asthma after puberty. Our findings suggest that part of the explanation for this may be the increase in body fat in females after puberty. Population attributable fractions indicate that 28% (95% CI 7–45) of incident asthma between age 9 and 26 in women may be attributable to becoming overweight by age 26 (BMI > 25 kg/m²).

This study has a number of strengths for assessing the changing risks for asthma through the life course. These include frequent assessments during childhood to early adulthood, a low attrition rate, and direct measurement of objective variables including height, weight, lung function, atopy, and airway responsiveness. Even so, our main outcome measure—diagnosed asthma with symptoms in the past year—is self-reported and open to error. Undoubtedly there will be a few study members who misreport this, but we think it is unlikely that reporting errors would bias our findings. Furthermore, reporting error could not account for the findings of lower FEV₁/FVC ratios and increased atopy and serum IgE.

In summary, we have found a significant association between BMI and the development of asthma and atopy in females. A positive association with atopy and an inverse association with the FEV₁/FVC ratio suggest that this association may be due to “real” asthma, rather than a mislabeling of symptoms caused by overweight and obesity. We found little evidence for this association in males. There was no evidence of reverse causation because having asthma as a child was not a risk factor for becoming overweight as an adult.

Conflict of Interest Statement: R.J.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; B.J.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; R.P. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.R.T. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.M.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; C.R.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; J.O.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; E.M.F. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; G.P.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; M.R.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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Sex differences in the relation between body mass index and asthma and atopy in a birth cohort

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Online data supplement

METHODS

Participants

The Dunedin Multidisciplinary Health and Development Study is a longitudinal investigation of health and behaviour in a birth cohort^{E1}. Study members were born in Dunedin, New Zealand between April 1972 and March 1973 when obstetric, perinatal, neonatal and demographic data were systematically recorded. Of these, 1037 children (91% of eligible births; 52% male) participated in the first follow-up assessment at age 3, constituting the base sample for the remainder of the study. Cohort families represent the full range of socioeconomic status in the general population of New Zealand and are primarily white of European descent. Follow-up assessments occurred at ages 5, 7, 9, 11, 13, 15, 18, 21, and at age 26 years when we assessed 980 (96%) of 1019 study members still alive. The study was approved by the Otago Ethics Committee, and written informed consent was obtained at each assessment.

Outcome measures

Asthma, wheeze and cough. At age 9, the accompanying adult (usually mother) was asked questions on current wheezing and coughing symptoms and also about respiratory symptoms and illnesses since birth. The frequency, severity, trigger factors and treatment of symptoms were recorded, including whether a diagnosis of asthma had been made^{E2}. At age 11, 13, and 15, questions were asked regarding symptoms since the last assessment. At age 18, 21, and 26 a self-administered questionnaire^{E3} including selected questions from the American Thoracic Society questionnaire^{E4} and the ECRHS questionnaire^{E5} was completed by the study member before the interviewer-administered questionnaire.

Current asthma was defined as a diagnosis of asthma with symptoms in the previous year.

Current wheeze was defined as more than two episodes of wheezing lasting for at least one

hour in the previous year. Asthma treatment included any bronchodilator, corticosteroid or cromoglycate medication.

Lung function and airway responsiveness. Spirometry was performed at each assessment from age 9, recording the best of three acceptable forced expiratory manoeuvres without prior bronchodilator (within 6 hours). At 18 and 26, bronchodilator responsiveness was measured by repeating spirometry 10 minutes after nebulised or metered dose (200µg) salbutamol. At ages 9, 11, 13, 15 and 21, a methacholine challenge was performed using a modified Chai protocol^{E6} as previously described^{E7}. Five deep inhalations of methacholine 0.025 mg/mL were administered through a Hudson Updraft nebuliser. Spirometry was repeated after 30 seconds and 2 minutes. Provided the FEV₁ fell less than 20% further methacholine was administered at concentrations of 0.25, 2.5 and 25 mg/mL. The procedure was stopped when FEV₁ fell by 20%, if there were symptoms of concern or after the final concentration. The provoking concentration causing a 20% fall in FEV₁ (PC₂₀) was determined by linear interpolation. A PC₂₀ of 8mg/mL or less was regarded as indicating airway hyperresponsiveness to methacholine. Study members showing significant airflow obstruction at baseline (FEV₁/FVC < 75% at 9 and 11 years, or < 70% at older ages) were not challenged, but instead were retested after inhaling salbutamol as above. An increase in the FEV₁ of 10% of baseline or greater was regarded as indicating significant airway responsiveness to salbutamol.

Atopic status. Skin prick testing was undertaken at age 13 in 714 study members using house dust mite (*Dermatophagoides pteronyssinus*, Bencard, UK), grass, cat, dog, horse, kapok, wool, *Aspergillus fumigatus*, *alternaria*, *penicillium*, and *cladosporum* (Hollister-Stier, USA)^{E8}. These were repeated at age 21 in 885 study members with addition of cockroach allergen (Hollister-Stier, USA). A positive response was defined as a weal

diameter 2mm greater than the negative (saline) control. Total serum IgE was measured at ages 11 and 21 in 571 and 786 study members respectively ^{E9}.

Body Mass Index. At each age, height without shoes, and weight in light clothing, were measured to calculate Body Mass Index (BMI) in kg/m².

Control variables

Parental asthma and BMI. The adult attending with the study member at age 7 was asked whether the natural mother and father had asthma, hay fever or allergies^{E10}. This information was obtained again from the study member at age 18. Preference was given to the information obtained at age 7 if available. At the age 11 assessment, a report of the height and weight of the Study member's parents was obtained for 81% of mothers and 77% of fathers.

Cigarette smoking. Current smoking was defined as smoking daily for at least one month during the past year from age 15 onwards. Family smoking history was ascertained at age 9 from the accompanying parent, namely maternal and paternal smoking, smokers living with the study member, and maternal smoking during pregnancy.

Breastfeeding. At the assessment at age 3, parents were questioned about breastfeeding and its duration, and data were verified from a prospective record of infant milestones^{E11}. Study members were classified according to whether they had been breastfed for longer than 3 weeks.

Birth order was categorised according to whether the study member had no, one, two, or three or more older siblings.

Statistical Analysis

Associations between BMI and the dependent variables: asthma, asthma with airway hyperresponsiveness, wheeze, treatment, atopy, FEV₁/FVC ratio, methacholine responsiveness, bronchodilator responsiveness and log IgE levels, were analysed using generalised mixed linear and logistic regression models across ages 9 – 26 years^{E12}. This approach uses Gaussian quadrature to do the numerical integration by picking the optimal abscissas and weights for n quadrature points to obtain the best estimate of the integral. Initial analyses indicated that these statistical models were unstable at lower numbers of quadrature points. The number of quadrature points was therefore set to 24. Repeat analyses using 20 and 28 quadrature points provided similar results. There were significant sex*BMI interactions for asthma, wheeze and atopy, males and females were therefore analysed separately. Further analyses adjusted for potential covariates: parental history of asthma, breastfeeding, birth order, personal and family smoking and maternal smoking during pregnancy. Pregnant women were excluded from all analyses. Supplementary analyses calculated population attributable fractions for asthma due to overweight at age 26. The association between asthma and BMI in parents of the study members was analyzed by logistic regression. p values <0.05 were considered significant. All analyses were performed using Stata 8.0 (Stata Corporation, TX).

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Female						Male				
Age	n*	Mean (SD)BMI	% overweight	% asthma	% wheeze	n*	Mean (SD)BMI	% overweight	% asthma	% wheeze
9	387	16.4 (1.8)	7.2	6.2	19.1	428	16.3 (1.6)	4.7	8.9	20.6
11	382	17.6 (2.2)	7.1	8.1	13.4	420	17.5 (2.1)	8.1	14.8	21.2
13	355	20.0 (2.6)	16.1	9.9	28.5	380	19.3 (2.3)	11.0	15.8	33.2
15	472	20.9 (2.6)	12.5	12.9	29.7	496	20.0 (2.8)	9.0	15.5	29.0
18	419	22.9 (3.2)	19.5	15.5	37.0	449	22.7 (3.2)	17.5	14.0	26.9
21	468	23.7 (3.7)	28.9	17.7	44.7	489	23.9 (3.3)	30.5	14.5	37.0
26	481	24.9 (4.9)	38.2	19.8	37.3	499	25.1 (3.9)	44.3	18.4	36.0

Table E1 Percent of overweight, asthmatic and wheezy Study members at each age

Overweight during childhood was defined using the standards of the International Obesity Task Force¹³. At ages 18 – 26 overweight was defined as a BMI ≥ 25 . * n = number of Study members for whom information on asthma diagnosis is available. Pregnant women are excluded from the BMI and overweight analyses.

Female				Male				
	Methacholine*	Salbutamol	Atopy	FEV ₁ /FVC	Methacholine*	Salbutamol	Atopy	FEV ₁ /FVC
Age	% response	% response	%	mean (SD)	% response	% response	%	mean (SD)
9	15.4			89.9 (6.2)	18.4			87.2 (6.6)
11	8.9			90.1 (5.5)	12.7			86.6 (6.4)
13	6.2		37.1	89.4 (6.1)	10.2		51.8	84.7 (6.3)
15	7.8			90.2 (6.5)	9.5			85.7 (7.2)
18		6.3		88.8 (6.8)		9.9		85.8 (8.2)
21	8.6		62.3	86.0 (6.4)	8.0		67.1	83.3 (7.1)
26		6.4		83.2 (6.7)		9.9		80.0 (7.3)

Table E2 Percent of Study members with airway responsiveness, atopy and mean FEV₁/FVC ratio at each age

See methods for definitions. *For Study members with airflow obstruction, the response to salbutamol was tested instead of methacholine (see text for details).