

Sex Differences in Factors Associated with Childhood- and Adolescent-Onset Wheeze

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Rationale: Factors predicting the development of wheeze may differ between sexes and between childhood and adolescence. **Methods:** A New Zealand birth cohort of 1,037 children was followed to age 26. For this analysis, those reporting recurrent wheezing at two or more assessments were classified as "wheezers." We examined risk factors for development of wheeze before age 10 (childhood) and subsequently (adolescent-onset) for males and for females separately using Cox regression modeling. **Results:** Males more often developed childhood wheeze ($p = 0.002$) and females adolescent-onset wheeze ($p < 0.001$). Maternal atopy (asthma or hay fever) was a risk factor for childhood wheeze in both sexes (hazard ratio [HR], 1.48, $p < 0.05$ for males; HR, 2.37, $p < 0.001$ for females). Paternal atopy also influenced childhood wheeze, significantly for males (HR, 1.72; $p = 0.01$), and similarly but not significantly for females (HR, 1.70; $p = 0.08$). For adolescent-onset wheeze, neither maternal (HR, 1.41; $p = 0.19$) nor paternal history (HR, 0.73; $p = 0.42$) was a risk factor in males, but maternal history (HR, 2.08; $p < 0.01$) was a significant risk factor for females. When both age ranges were combined, providing greater power for analysis, paternal history was a stronger risk factor for wheeze in females (HR, 1.62; $p = 0.02$) than in males (HR, 1.35; $p = 0.12$). **Conclusion:** The influence of parental atopy on the development for wheeze differs between males and females and between childhood- and adolescent-onset wheeze.

Keywords: age of onset; asthma; parental history; risk factors; sex

Studies of the epidemiology and natural history of childhood asthma demonstrate changing sex prevalence with age. Until age 12 to 13 years, the incidence of asthma is greater in males than in females (1–3). During adolescence, the incidence of asthma increases in females such that, by age 20, the dominance of males with asthma is reversed (1, 4–6). A higher prevalence of asthma in females persists throughout adult life.

Risk factors for the development of asthma in childhood include the following: atopy, a family history of asthma or hay fever, and airway hyperresponsiveness. Studies of the natural history of asthma consistently find that female sex, atopy, and airway hyperresponsiveness are associated with the persistence of asthma from childhood to adulthood (2, 7–21). However, studies are conflicting regarding risk factors for predicting new asthma or wheeze during adolescence. One recent German study reported that atopy was not a risk factor for incidence of asthma in females during puberty (22), whereas an Australian longitudinal cohort study showed that, in addition to family history of asthma, atopy was a risk factor for the development of adolescent wheeze (23).

Population-based studies of asthma may include subgroups with different risk factors for asthma. If these different subgroups are not separated, the strength of a risk factor for asthma will be averaged across the different groups in both univariate and multiple variable analyses. Only those risk factors that are strong in one or a few subpopulations or moderate in most or all subpopulations will be identified. Examples of subpopulations in asthma include males and females, and those with and without a family history of asthma or atopic disease. By examining these subpopulations, the underlying mechanisms of disease may be better understood.

We have analyzed data from a longitudinal study of a New Zealand population-based birth cohort study followed to adulthood to examine factors associated with development of asthma or wheeze during childhood and during adolescence in male and female subpopulations. We have previously reported that, although there were no significant sex differences in the prevalence of recurrent wheeze by age 13, males were more likely to have been diagnosed with asthma than females (24). This finding is confirmed by several other studies (25–27). To eliminate gender bias in the diagnosis of asthma, we have used either recurrent wheeze or asthma as the outcome variable.

METHODS

Participants in the Dunedin Multidisciplinary Health and Development Research Study (7, 21, 24, 28–34) were born April 1972 through March 1973. A population-representative birth cohort of 1,037 children was assessed at age 3. Follow-up assessments occurred at ages 5, 7, 9, 11, 13, 15, 18, 21, and 26 years. The Otago Hospital Research Ethics Committee approved each assessment. Written, informed consent was obtained at each visit from the guardian or participant.

Comprehensive respiratory questionnaires were completed at all visits from age 9 (7, 29). Parental asthma or hay fever was recorded at the age 7 (30) and 18 visit. Breastfeeding was recorded at age 3 and validated from prospective records (31, 35, 36). Ownership of cats and dogs was recorded at each age (29), and smoking history from age 15 onward (7).

Spirometry was performed at each assessment from 9 to 26 years (7, 32). Methacholine challenge was performed by all consenting study members at ages 9, 11, 13, 15, and 21 using a validated abbreviated protocol (32). Allergen skin testing was performed at age 13 and 21 (33). Detailed methods are described in previous publications (7, 21, 28–34, 36) and in the online supplement.

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We included all study members seen at least once between ages 7 and 26 and whose age of first wheezing (if wheezing occurred) could be determined ($n = 1,022$).

Statistical Analysis

For this analysis, children with recurrent wheezing reported at two or more assessments were classified as “wheezers.” The youngest age at which wheezing was reported was used as the age of onset. The oldest age at which nonwheezers were seen was when data were censored. Males and females were analyzed separately. Analyses were repeated defining wheezers as those with recurrent wheezing at three or more assessments, and those who had persistent or relapsing symptoms, as previously described (7).

Kaplan-Meier analysis log-rank test was used with univariate analysis. For continuous variables, and to calculate univariate hazard ratios, Cox regression modeling was used; the proportional hazard assumption was tested using log minus log plots and by modeling a “time \times factor” interaction term.

We examined factors associated with onset of wheeze during childhood (to age 10) and adolescence (after age 10). To examine risk factors for adolescent-onset wheeze, individuals who developed wheeze before age 10 were excluded from the analysis. Age-dependent risk was noted if hazard ratios for childhood- and adolescent-onset wheeze differed significantly. To isolate the independent influence of maternal and paternal history on the development of wheeze, individuals with only a maternal or only a paternal history were identified and compared with study members where neither parent had a history of asthma or hay fever. Multiple variable analyses by Cox regression used a backward likelihood ratio ($p \leq 0.05$ in, $p > 0.1$ out). All multiple regression analyses for adolescent-onset wheeze were corrected for smoking at age 15. A secondary analysis identified factors associated with the development of wheeze at any age to last follow-up at age 26. Statistical analysis was completed using SPSS, version 12 (SPSS, Inc., Chicago, IL).

RESULTS

Sample Characteristics

Of the 1,022 study members included in this analysis, 474 were classified as wheezers (reported at two or more assessments) by age 26, of which 50.1% were males. Of the 220 study members

with onset of wheeze between ages 10 and 26, 210 (95.5%) developed symptoms between 10 and 18 years. Among males who developed wheeze by age 26, 63% did so before age 10 ($p = 0.002$ compared with females), whereas females were more likely to develop wheeze between ages 10 and 26 ($p < 0.001$; Figure 1).

Compared with nonwheezers, both males and females who developed wheeze by age 26 had a lower FEV₁/FVC ratio at all ages tested, were more likely to be atopic at age 13 and 21, to have a positive methacholine challenge at age 9, to have a maternal history of atopy, to be ever diagnosed with asthma, and to smoke at age 15 (Table 1). Differences between wheezers and nonwheezers for breastfeeding, having pets before age 9, being first-born, and smoke exposure as a child were not significant in this analysis (Table 1).

Females who developed wheeze at any age to 26 had a higher body mass index from age 9 onward and were more likely to have a paternal history of atopy, but were less likely to have owned a dog before age 9.

Univariate Analysis

Results using wheezing defined by reported symptoms at two or more assessments or three or more assessments, or adolescent-onset wheeze defined only between ages 10 and 18, or those with persistent or relapsing systems were consistent. Results using wheeze defined by symptoms at two or more assessments are presented. Unadjusted hazard ratios (HR) for childhood-onset wheeze (Table 2), adolescent-onset wheeze (Table 3), and wheeze at any age to 26 (Table 4) are presented. None of the variables violated the proportional hazards assumption. Several variables demonstrated an age-dependent risk.

Development of childhood-onset wheeze (by age 10). Both males and females who developed childhood-onset wheeze were more likely to have a positive methacholine challenge at age 9 (HR, 4.20 [2.88–6.12] for males; HR, 6.48 [4.14–10.14] for females; Figure 2), to be atopic at age 13 (HR, 2.89 [1.97–4.25] for males; HR, 2.62 [1.68–4.09] for females; Figure 3), and have a parental

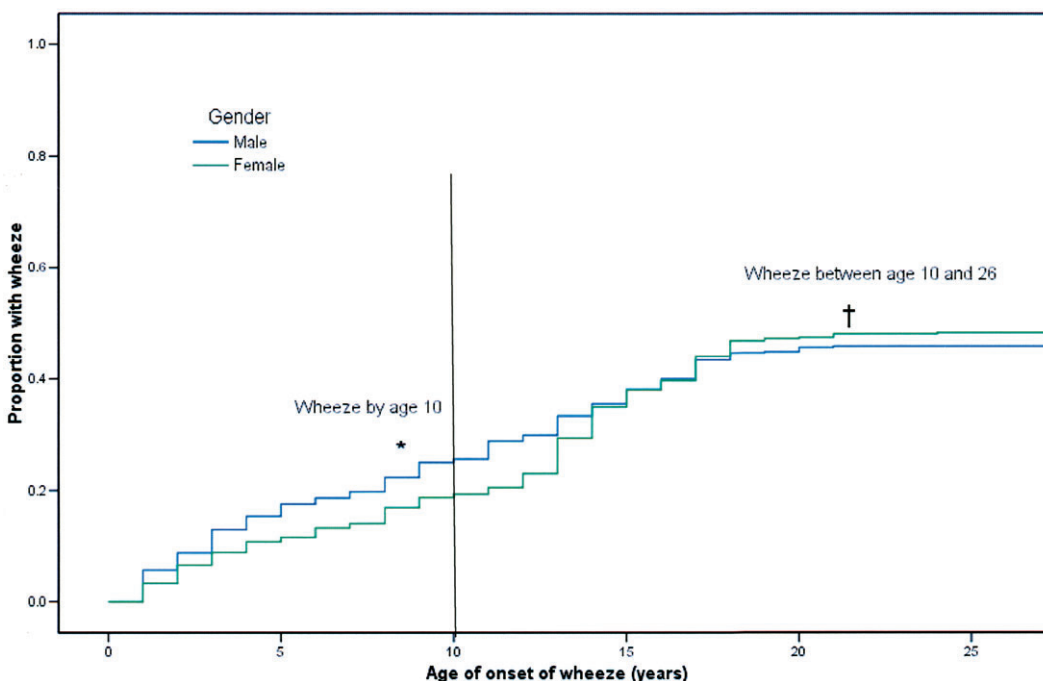


Figure 1. Proportion of males and females who develop wheeze by age 26, by age of onset. *Males, compared with females, are more likely to develop wheeze before age 10, $p = 0.002$; †females, compared with males, are more likely to develop wheeze after age 10, $p < 0.001$.

TABLE 1. SAMPLE CHARACTERISTICS OF MALE AND FEMALE STUDY MEMBERS REPORTING RECURRENT WHEEZING AT TWO OR MORE ASSESSMENTS BY AGE 26

	Males		Females	
	Wheezers by Age 26* (n = 238)	Nonwheezers by Age 26 (n = 297)	Wheezers by Age 26* (n = 236)	Nonwheezers by Age 26 (n = 266)
Age of onset of wheeze by age 10	151 (63%)	N/A	102 (43%)	N/A
FEV ₁ /FVC at age 26, %	79.2 [†] SD, 8.1	81.7 SD, 5.9	82.7 [†] SD, 6.5	85.4 SD, 5.4
BMI at age 26, kg/m ²	25.5 SD, 3.9	24.8 SD, 3.8	25.7 [†] SD, 5.7	24.3 SD, 4.0
Atopic at 13	123/187 [†] 65.8%	68/182 37.4%	78/170 [†] 45.9%	50/175 28.6%
Positive methacholine at 9 years (PC ₂₀ ≤ 8 mg/ml)	49/185 [†] 26.5%	13/216 6.0%	46/182 [†] 25.3%	3/185 1.6%
Any maternal history of atopy (asthma or hay fever)	80/227 [†] 35.2%	67/266 25.2%	92/221 [†] 41.6%	47/235 20.0%
Any paternal history of atopy (asthma or hay fever)	57/224 25.5%	53/259 20.5%	60/218 [†] 27.5%	41/232 17.7%
Diagnosis of asthma ever	126/237 [†] 53.2%	19/288 6.6%	121/236 [†] 51.3%	20/261 7.7%
Smoker at 15 yr	40/232 [†] 17.2%	23/260 8.9%	61/229 [†] 26.6%	36/241 14.9%
Breastfed ≥ 4 wk	122/237 51.5%	129/288 44.8%	118/236 50.0%	129/261 49.4%
Tobacco smoke exposure as a child	146/215 67.9%	141/234 60.3%	137/215 63.7%	126/204 61.8%
Dog ownership before age 9	109/206 52.9%	109/221 49.3%	80/194 [†] 41.2%	108/193 56.0%
Cat ownership before age 9	160/206 77.7%	176/221 79.6%	154/194 79.4%	149/193 77.2%
First-born	76/215 35.4%	86/234 36.8%	74/215 34.4%	86/204 42.2%

Definition of abbreviation: BMI = body mass index; NA = not applicable.

Except where otherwise indicated, figures are number with characteristic/number assessed.

* Defined as recurrent wheezing reported at two or more surveys.

[†] p < 0.05 comparing wheezers to nonwheezers.

history of atopy (HR, 1.61 [1.17–2.23] for males; HR, 2.22 [1.48–3.33] for females). Males and females with childhood-onset wheeze had a lower FEV₁/FVC ratio at all ages tested between 9 and 26 years compared with nonwheezers (p < 0.001; Table 2).

Males with only a paternal history were more likely to develop childhood wheeze (by age 10) than those with no parental history of atopy (HR, 1.72 [1.11–2.69]; Figure 4A). Because fewer females develop childhood wheeze, the same hazard ratio (HR, 1.70 [0.92–4.14]) for paternal history was not significant for females (p = 0.085; Figure 4B). However, although females with a mater-

nal history were more likely to develop childhood wheeze (by age 10) than those with no parental history (HR, 2.37 [1.48–3.81]), the influence of maternal history for males was only borderline significant (HR, 1.48 [0.99–2.22]).

Females who were breastfed were more likely to develop childhood-onset wheeze, with a less strong trend seen in males (HR, 1.34 [0.97–1.85] for males; HR, 1.58 [1.06–2.38] for females). When stratified by any parental history, the influence of breastfeeding was most strongly seen for childhood-onset wheeze in breastfed females with a parental history of atopy

TABLE 2. UNIVARIATE ANALYSES FOR FACTORS ASSOCIATED WITH DEVELOPMENT OF CHILDHOOD-ONSET WHEEZE (RECURRENT WHEEZE, ONSET BEFORE AGE 10, REPORTED AT TWO OR MORE ASSESSMENTS)

Risk Factor	Males			Females		
	p Value	HR	95% CI	p Value	HR	95% CI
Any family history	0.003	1.61	1.17–2.23	< 0.001	2.22	1.48–3.33
Maternal history only	0.055	1.48	0.99–2.22	< 0.001	2.37	1.48–3.81
Paternal history only	0.014	1.72	1.11–2.68	0.08	1.70	0.92–3.14
Breastfed ≥ 4 wk	0.07	1.34	0.97–1.85	0.021	1.58	1.06–2.35
Owned a dog before age 9	0.99	1.00	0.72–1.39	0.15	0.74	0.48–1.12
Owned a cat before age 9	0.79	0.95	0.64–1.41	0.96	0.99	0.60–1.63
Had childhood tobacco smoke exposure	0.55	1.11	0.78–1.58	0.92	1.02	0.67–1.56
FEV ₁ /FVC at 9 yr (HR is per 1 unit FEV ₁ /FVC)	< 0.001	0.93	0.91–0.95	< 0.001	0.91	0.88–0.93
Positive methacholine at age 9	< 0.001	4.20	2.88–6.12	< 0.001	6.48	4.14–10.14
BMI at age 9 (HR is per unit BMI)	0.150	1.08	0.97–1.19	0.50	1.04	0.93–1.16
Atopy at 13 yr	< 0.0001	2.89	1.97–4.25	< 0.001	2.62	1.68–4.09

Definition of abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio.

TABLE 3. UNIVARIATE ANALYSES FOR FACTORS ASSOCIATED WITH ADOLESCENT-ONSET WHEEZE (RECURRENT WHEEZE, ONSET AFTER AGE 10, ON TWO OR MORE ASSESSMENTS)

Risk Factor	Males			Females		
	p Value	HR	95% CI	p Value	HR	95% CI
Any family history	0.46	1.18	0.76–1.83	< 0.001	2.00	1.41–2.83
Maternal history only	0.19	1.41	0.83–2.40	< 0.001	2.08	1.34–3.22
Paternal history only	0.42	0.73	0.33–1.61	0.10	1.57	0.92–2.66
Breastfed \geq 4 wk	0.73	1.08	0.71–1.65	0.20	0.81	0.57–1.13
Owned a dog before age 9	0.24	1.34	0.82–2.20	0.021	0.64	0.44–0.95
Owned a cat before age 9	0.79	0.92	0.51–1.67	0.43	1.22	0.75–1.98
Had childhood tobacco smoke exposure	0.07	1.55	0.95–2.55	0.63	1.09	0.75–1.58
FEV ₁ /FVC at 9 yr (HR is per 1 unit FEV ₁ /FVC)	0.19	0.97	0.93–1.02	0.053	0.97	0.93–1.00
Positive methacholine at age 9	0.12	1.82	0.83–3.98	< 0.001	4.07	2.21–7.48
Change in BMI between age 9 and 11 (HR is per unit change in BMI)	0.24	1.20	0.88–1.64	0.07	1.18	0.99–1.42
Atopy at 13 yr	0.041	1.69	1.01–2.82	0.31	1.24	0.80–1.92
Smoked at 15 yr	< 0.001	2.57	1.56–4.22	0.005	1.71	1.16–2.53

For definition of abbreviations, see Table 2.

(HR, 1.44 [1.02–2.05]) versus breastfed females without a parental history (HR, 0.83 [0.56–1.24]). A similar trend was seen in males (Figure 5A, males; Figure 5B, females).

Development of adolescent-onset wheeze (after age 10 to age 26). Smoking at age 15 was a risk factor for adolescent-onset wheeze for both males and females (HR, 2.57 [1.56–4.22] for males; HR, 1.71 [1.16–2.53] for females). All other risk factors for adolescent-onset wheeze were different between the sexes (Table 3).

In males, any atopy at age 13 (HR, 1.69 [1.01–2.28]) and maternal smoking during the third trimester of pregnancy were associated with adolescent-onset wheeze (HR, 1.79 [1.02–3.14]).

In females, maternal history (HR, 2.08 [1.34–3.22]) was a significant risk factor and paternal history was again borderline significant (HR, 1.57 [0.92–2.66]). A positive methacholine challenge at age 9 (HR, 4.07 [2.21–7.48]) was also a risk factor for adolescent-onset wheeze. Females with adolescent-onset wheeze also had a lower FEV₁/FVC at age 9 ($p = 0.053$). Atopy was not a risk factor for adolescent-onset wheeze in females. Females whose families owned a dog before age 9 were less likely to develop wheeze at any age to 26, with the effect being most pronounced on the development of adolescent-onset wheeze (HR, 0.64 [0.44–0.95]). Change in body mass index between age

9 and 11 was a borderline significant risk factor for adolescent-onset wheeze in females (HR, 1.18 [0.99–1.42]).

Development of wheeze at any age to 26. To address the issue of reduced power resulting from subdivision of the sample into two age ranges, the relation of paternal history to wheeze at any age to 26 was examined (Table 4). Compared with study members with no family history of atopy, having only a paternal history was a risk factor for wheeze at any age to 26 for females (HR, 1.62 [1.09–2.42]) but was not a significant risk factor for males (HR, 1.35 [0.92–1.97]) across this broader age range, whereas maternal history was a predictor in both sexes.

Multiple Variable Analyses

Development of childhood-onset wheeze. To identify the strongest factors associated with wheeze by age 10, factors entered into the Cox regression included the following: any parental history of atopy, any atopy at age 13, PC₂₀ FEV₁ less than or equal to 8 mg/ml at age 9, owning either a cat or dog before age 9, FEV₁/FVC at age 9, maternal smoking during the third trimester, breastfeeding, birth order, maternal and paternal smoking during the childhood of the study member, and body mass index at all ages. If any parental history was found to be a factor associated with wheeze, to maintain the same reference population, both

TABLE 4. UNIVARIATE ANALYSES FOR FACTORS ASSOCIATED WITH DEVELOPMENT OF WHEEZE AT ANY AGE TO 26 (WHEEZE ON TWO OR MORE ASSESSMENTS)

Risk Factor	Males			Females		
	p Value	HR	95% CI	p Value	HR	95% CI
Any family history	0.005	1.44	1.11–1.87	< 0.001	2.09	1.60–2.72
Maternal history only	0.019	1.46	1.06–2.01	< 0.001	2.21	1.60–3.04
Paternal history only	0.12	1.35	0.92–1.97	0.016	1.62	1.09–2.42
Breastfed \geq 4 wk	0.10	1.24	0.96–1.60	0.57	1.08	0.83–1.39
Owned a dog before age 9	0.51	1.10	0.83–1.44	0.008	0.69	0.51–0.91
Owned a cat before age 9	0.71	0.94	0.68–1.31	0.58	1.10	0.78–1.56
Had childhood tobacco smoke exposure	0.12	1.25	0.94–1.67	0.67	1.06	0.80–1.40
FEV ₁ /FVC at 9 yr (HR is per 1 unit FEV ₁ /FVC)	< 0.001	0.94	0.92–0.96	< 0.001	0.93	0.91–0.95
Positive methacholine at age 9	< 0.001	3.45	2.48–4.81	< 0.001	5.44	3.83–7.72
BMI at age 26 (HR is per unit BMI)	0.056	1.03	1.00–1.06	0.003	1.04	1.01–1.06
Atopy at 13 yr	< 0.001	2.40	1.77–3.25	< 0.001	1.78	1.32–2.41
Smoked at 15 yr	0.021	1.48	1.05–2.08	< 0.001	1.64	1.22–2.19

For definition of abbreviations, see Table 2.

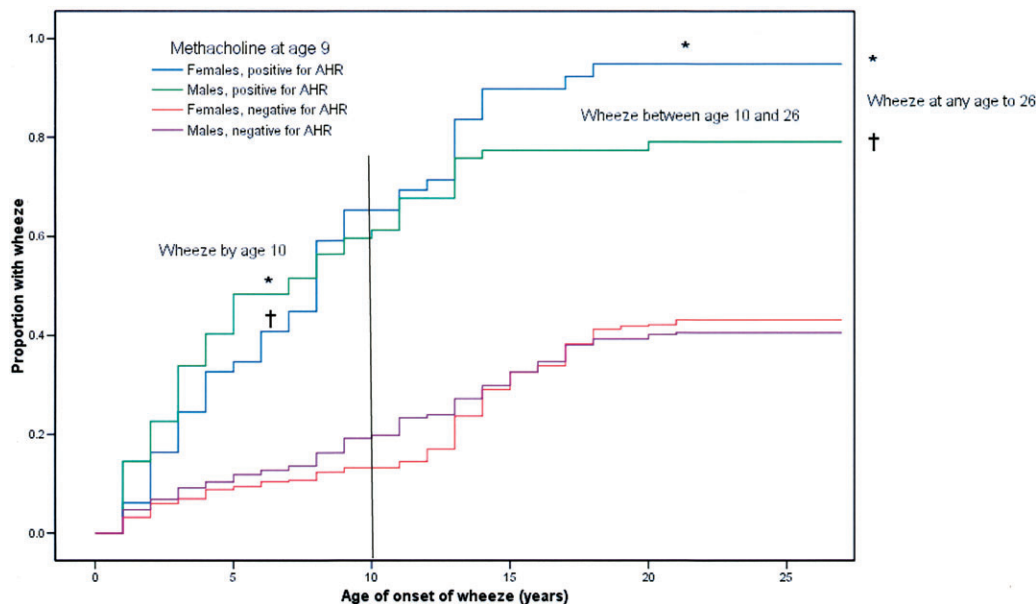


Figure 2. Proportion of individuals with and without a positive methacholine challenge ($PC_{20} \leq 8$ mg/ml) at age 9 who develop wheeze by age 26, by age of onset. *Females positive for airway hyperresponsiveness (AHR) at age 9 are more likely to develop wheeze by age 10, between ages 10 and 26, and at any age to 26 versus those females without AHR, $p < 0.001$ for all analyses; †males positive for AHR at age 9 are more likely to develop wheeze by 10, and at any age to 26 versus those males without AHR, $p < 0.001$ for both analyses.

maternal-only and paternal-only history were substituted into the model. Model 1 included all variables listed. Because atopy, lung function, and airway hyperresponsiveness were measured near or after the end of the period, it is less certain whether these factors are a result of wheeze or a risk factor for wheeze. Model 2 therefore excluded these variables from the regression.

For males, any atopy at age 13 and airway hyperresponsiveness at age 9 were associated with childhood-onset wheeze (Table 5). When airway hyperresponsiveness was excluded from the regression, lung function at age 9, in addition to atopy, was associated with development of wheeze by age 10. For Model 2, only parental history was found to be a risk factor for childhood wheeze in males. When any parental history was replaced by

maternal-only and paternal-only history, paternal history was the strongest predictor of childhood wheeze in males.

For females, any atopy at age 13, airway hyperresponsiveness at age 9, and lung function at age 9 were also found to be associated with childhood-onset wheeze (Table 6). When airway responsiveness was excluded, atopy and lung function remained significant risk factors. For Model 2, the interaction of any parental history of asthma or hay fever with breastfeeding was a risk factor for childhood wheeze. When any parental history was replaced by maternal-only and paternal-only history, only the interaction of breastfeeding by maternal history was a risk factor for childhood wheeze.

Development of adolescent-onset wheeze. To identify risk fac-

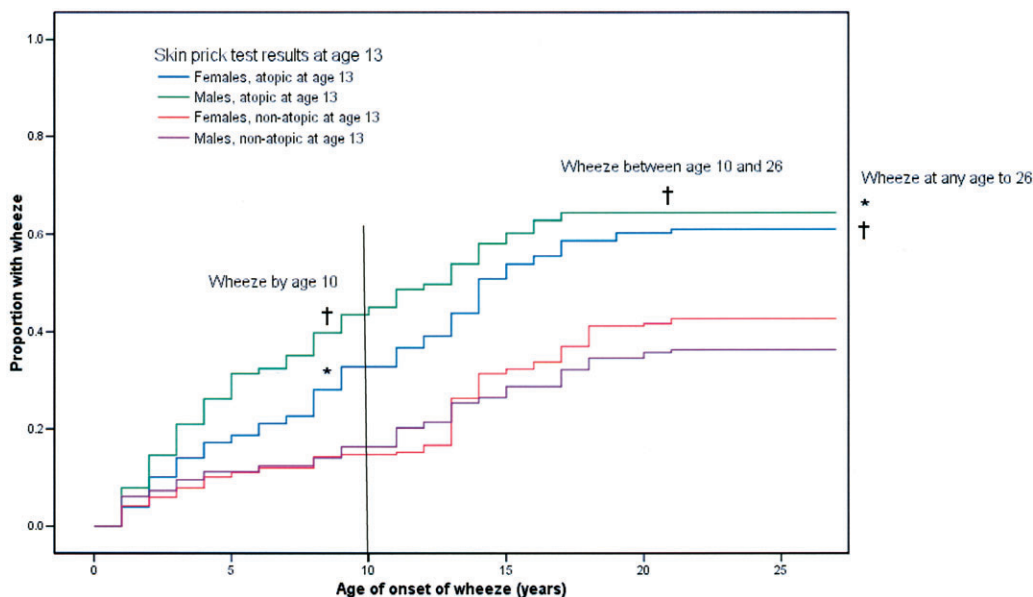


Figure 3. Proportion of individuals with and without any positive skin-prick test (≥ 2 -mm wheal) at age 13 and the development of wheeze by age 26, by age of onset. *Females positive for any atopy at age 13 are more likely to develop wheeze by age 10, and at any age to 26 versus nonatopic females, $p < 0.001$; †males positive for any atopy at age 13 are more likely to develop wheeze by 10, between ages 10 and 26, and at any age to 26 versus nonatopic males, $p < 0.001$.

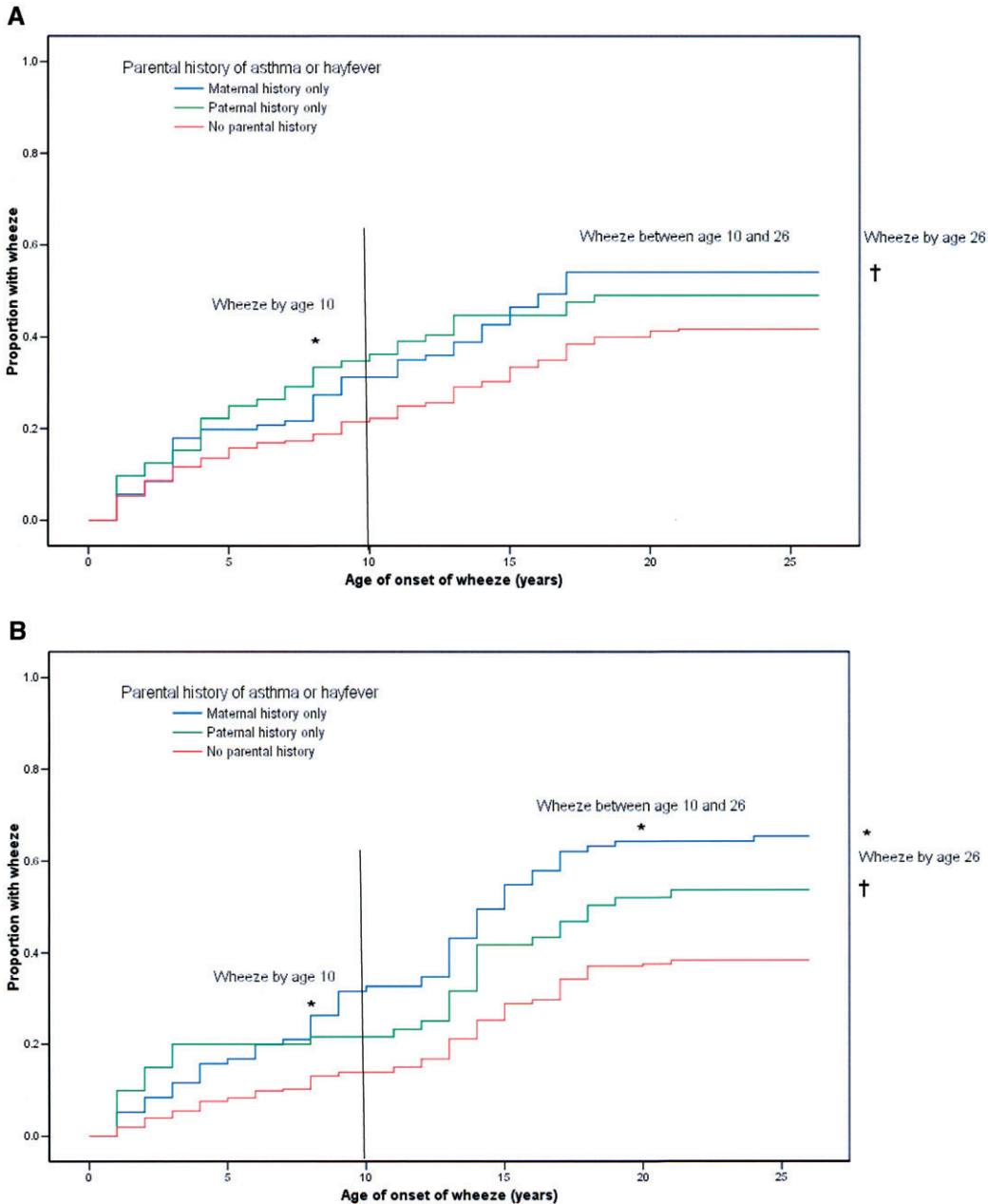


Figure 4. (A) Proportion of males with parental history of asthma or hay fever who develop wheeze by age 26, by age of onset. *Males with only a paternal history of atopy are more likely to develop wheeze by 10 versus males with no parental history of atopy: $p = 0.005$; †males with only a maternal history of atopy are more likely to develop wheeze at any age to 26 versus males with no parental history of atopy, $p = 0.005$. (B) Proportion of females with parental history of asthma or hay fever who develop wheeze by age 26, by age of onset. *Females with only a maternal history of atopy are more likely to develop wheeze by age 10, between age 10 and 26, at any age to 26 versus females with no parental history of atopy, $p < 0.0001$; †females with only a paternal history of atopy are more likely to develop wheeze at any age to 26 versus females with no parental history of atopy, $p = 0.015$.

tors associated with new wheeze after age 10, factors entered into the Cox regression included the following: any parental history of atopy, any atopy at age 13, PC_{20} FEV₁ less than or equal to 8 mg/ml at age 9, owning a cat or dog before age 9, FEV₁/FVC at age 9, maternal smoking during the third trimester, breastfeeding, birth order, maternal and paternal smoking during the childhood of the study member, and body mass index at age 9 and 11 for both males and females. If any parental history was found to be a factor associated with wheeze, to maintain the same reference population, both maternal-only and paternal-only history were substituted into the model. All multiple variable analyses are corrected for smoking at age 15.

For males, atopy at age 13 and maternal smoking in the third trimester of pregnancy were associated with adolescent-onset wheeze (Table 7). No difference was found when either variable was excluded from the regression. For females, airway hyperresponsiveness at age 9 was the strongest risk factor for adoles-

cent-onset wheeze (Table 8). When airway hyperresponsiveness was excluded from the multiple variable regression, lung function at age 9 and any parental history of asthma or hay fever were then found to be risk factors for adolescent-onset wheeze. When any parental history was replaced by maternal-only and paternal-only history, both maternal history and lung function were associated with adolescent-onset wheeze in females.

DISCUSSION

This analysis of data from a population-based birth cohort has identified significant differences between males and females for factors associated with childhood- and adolescent-onset wheeze. Atopy and airway hyperresponsiveness were associated with childhood wheeze in both sexes. However, although atopy continues to be a risk factor for developing wheeze through adolescence in males, atopy was not a risk factor for adolescent-onset wheeze in females.

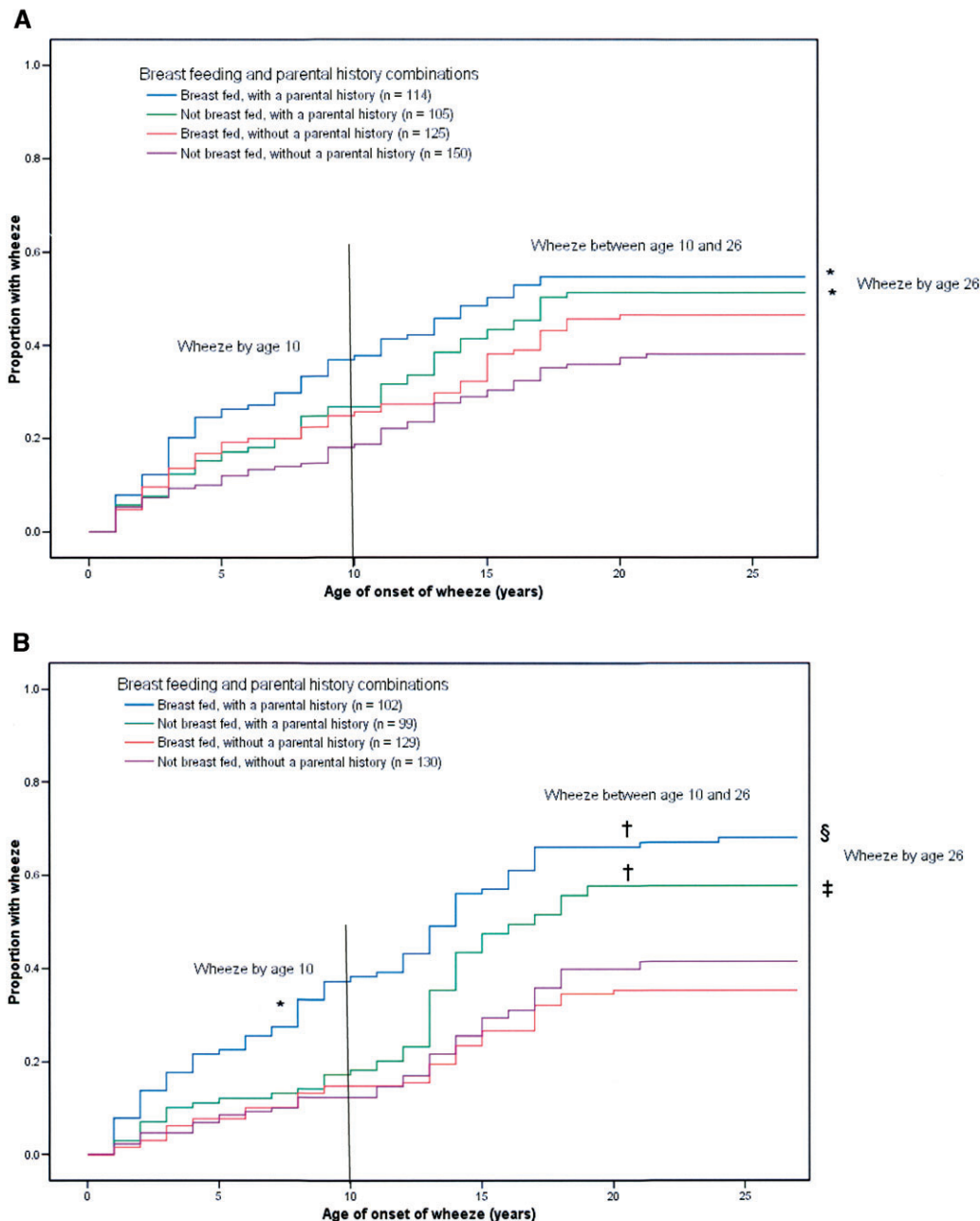


Figure 5. (A) Proportion of males, with and without a family history of asthma or hay fever, stratified by breastfeeding status, who develop wheeze by age 26, by age of onset. *Males with a family history of atopy, regardless of breastfeeding status, are more likely to develop wheeze at any age to 26 versus males with no family history of atopy and who were not breastfed, $p = 0.036$. (B) Proportion of females, with and without a family history of asthma or hay fever, stratified by breastfeeding status, who develop wheeze by age 26, by age of onset. *Females with a family history of atopy, who were breastfed, are more likely to develop wheeze by age 10 versus females with no family history of atopy and who were not breastfed, $p = 0.067$; †females with a family history of atopy, regardless of breastfeeding status, were more likely to develop wheeze between ages 10 and 26 compared with females without a family history of atopy, $p = 0.022$; ‡females with a family history of atopy, who were not breastfed, were more likely to develop wheeze at any age to 26 versus females with no family history of atopy and who were not breastfed, $p = 0.015$; §females with a family history of atopy, who were breastfed, were more likely to develop wheeze at any age to 26 than all other groups, including females with a family history of atopy only, $p = 0.042$.

The results from this study may clarify contradictory results from previous studies on the influence of atopy on the development of adolescent asthma. An Australian study has previously reported that atopy, defined by skin testing at age 8 through 10, was a risk factor for the development of wheeze in puberty (23). In contrast, a German study found that atopy at age 10 was not a risk factor for the development of adolescent asthma (22). Although the proportion of females included in the analysis is similar for both studies (55% females in the Australian study, 48.5% females in the German study; $p > 0.05$), the prevalence of atopy at baseline was significantly lower in the Australian study than in the German cohort and our cohort (22.3% in the Australian cohort, 45.6% in the German cohort, 44.7% in our cohort; $p < 0.001$). The lower prevalence of atopy in the Australian study may explain why atopy was a risk factor for adolescent-onset wheeze. Neither the Australian or German studies strati-

fied their analysis to evaluate if atopy was a sex-specific risk for adolescent-onset wheeze. Our analysis found that atopy was a risk factor for adolescent-onset wheeze in males but not in females.

One of the limitations of our study is that several factors associated with childhood-onset wheeze, including atopy and airway responsiveness, were measured near or after age 10. As a result, this study cannot establish whether these factors are causally related. Further studies with more detailed and prospective measurements of childhood atopy and airway responsiveness are needed to understand the relationship between these variables and asthma. The first comprehensive history of childhood wheezing was obtained when the children were age 9 (29). Those study members with childhood-onset wheeze likely represent children with either persistent or relapsing symptoms, symptoms significant enough to be reported by the mother.

TABLE 5. MULTIPLE VARIABLE ANALYSIS EXAMINING FACTORS ASSOCIATED WITH DEVELOPMENT OF CHILDHOOD-ONSET WHEEZE (BETWEEN BIRTH AND AGE 10) IN MALES

Factor	Significance	HR	95% CI for the HR	
			Lower	Upper
Model 1: all variables included				
Atopy at age 13	0.001	2.20	1.45	3.34
Positive methacholine at 9 yr	0.000	3.49	2.32	5.21
Excluding airway hyperresponsiveness				
FEV ₁ /FVC at 9 yr	< 0.001	0.94	0.91	0.96
Atopy at age 13	< 0.001	2.64	1.79	3.89
Model 2: excluding airway hyperresponsiveness, atopy, and lung function				
Any family history of asthma or hay fever	0.004	1.61	1.17	2.23
Replacing family history with maternal and paternal history of atopy*				
Maternal history of asthma or hay fever	0.05	1.49	0.99	2.22
Paternal history of asthma or hay fever	0.016	1.73	1.11	2.69

Definition of abbreviations: CI = confidence interval; HR = hazard ratio.

* Maternal only and paternal only, compared with reference group with no family history.

Early-childhood wheezing not recalled by the mother had probably been mild and had remitted; otherwise, one would expect these symptoms to be remembered. Therefore, the risk factors for childhood wheeze identified in this study are more likely to apply to children with persistent wheeze, and less to children with transient wheeze.

Paternal and maternal history of asthma and hay fever was obtained from the guardian (usually mother) at age 7 and the study member at 18. Both mother and study member may underreport or confuse symptoms for other family members (e.g., reporting hay fever rather than a diagnosis of asthma). Therefore, we chose to combine asthma and hay fever into a single variable. Despite the potential for recall bias for maternal and paternal atopy by mother and study member, a maternal history of atopy was a risk factor for wheeze for both males and females, consistent with other studies (37, 38). A paternal history of atopy was a significant predictor of wheeze in females but did not show an age-dependent effect. Previous studies have found that maternal history was a strong risk factor for asthma under age 5, with paternal history being a weak risk factor for early-childhood

wheeze and a stronger risk factor for wheeze after age 5 (39, 40). Both of these studies were analyzed cross-sectionally, without stratification by sex. If we analyze our study in a similar manner, paternal history is a risk factor for adolescent-onset wheeze. When analyzed longitudinally with stratification by sex, maternal and paternal history affects males and females differently.

Although dividing a sample into subgroups decreases the power of the study, subgroup analysis may still be sufficiently powered to see larger effects in at-risk subgroups within a study population (e.g., wheeze in females with a family history of atopy who are breastfed). One danger in stratification is if the subgroups are selected after a preliminary analysis has been completed. Such *post hoc* stratification may lead to biased results because the authors have prior knowledge of differences within the sample. In this report, all stratification decisions were made before undertaking the analyses.

We have considered several potential explanations for the finding of maternal history as a strong risk factor for wheeze in males and females, and paternal history as a strong risk factor for wheeze in females but a weak risk factor in males. Several

TABLE 6. MULTIPLE VARIABLE ANALYSIS EXAMINING FACTORS ASSOCIATED WITH DEVELOPMENT OF CHILDHOOD-ONSET WHEEZE (BETWEEN BIRTH AND AGE 10) IN FEMALES

Factor	Significance	HR	95% CI for the HR	
			Lower	Upper
Model 1: all variables included				
FEV ₁ /FVC at 9 yr	0.002	0.93	0.89	0.97
Atopy at age 13	0.027	1.88	1.14	3.10
Positive methacholine at 9 yr	0.001	3.14	1.81	5.44
Excluding airway hyperresponsiveness				
FEV ₁ /FVC at 9 yr	< 0.001	0.92	0.89	0.95
Atopy at 13 yr	0.003	2.18	1.38	3.46
Model 2: excluding airway hyperresponsiveness, atopy, and lung function				
Any parental history of asthma or hay fever	0.27	1.42	0.76	2.66
Breastfed \geq 4 wk	0.98	1.01	0.53	1.91
Breastfed \times parental history interaction	0.07	2.18	0.95	5.00
Replacing family history with maternal and paternal history of atopy				
Maternal history of asthma or hay fever	0.74	1.15	0.50	2.63
Paternal history of asthma or hay fever	0.96	0.97	0.33	2.87
Breastfed \geq 4 wk	1.00	1.00	0.53	1.89
Breastfed \times maternal history interaction	0.025	3.22	1.16	8.99
Breastfed \times paternal history interaction	0.18	2.49	0.66	9.36

For definition of abbreviations, see Table 5.

TABLE 7. RESULTS FOR THE MULTIPLE VARIABLE ANALYSIS EXAMINING FACTORS ASSOCIATED WITH DEVELOPMENT OF ADOLESCENT-ONSET WHEEZE (ONSET AFTER AGE 10) IN MALES

Factor (all variables included)	Significance	HR	95% CI for the HR	
			Lower	Upper
Maternal smoking during the third trimester	0.006	2.26	1.27	4.02
Atopy at 13 yr	0.016	2.03	1.14	3.60

For definition of abbreviations, see Table 5.

of these (maternal–fetal interactions, genomic imprinting) only provide an incomplete explanation. We suggest that asthma might possibly be partly explained as an X-linked recessive disorder in the context of a complex genetic disorder. In short, if asthma is an X-linked recessive disorder, males should have a higher incidence of disease because they only have one copy of the X chromosome, whereas females need an abnormal X chromosome from both parents to manifest disease. However, because of X inactivation, heterozygous females may still develop a milder form of disease. Maternal history would be a strong risk factor because it would affect both sons and daughters. Paternal history would be a risk factor for asthma in females, who receive an X chromosome from their father, but not for males, who do not.

This X-linked recessive disorder hypothesis alone cannot explain the increased incidence of wheeze among adolescent females. However, several studies have suggested that female sex hormones influence asthma (41). Atopy, measured by skin-prick test, changes during the menstrual cycle (42). When estrogen levels are high, wheal and flare responses increase (42–44). The proliferation of peripheral blood monocytes to pokeweed mitogen is increased in the presence of estrogen, whereas testosterone inhibits this response (45, 46).

This analysis of our longitudinal birth cohort study suggests different mechanisms for the development of asthma at different times between males and females. The possibility that asthma may in part be an X-linked recessive disorder, explaining the different effects of maternal and paternal history of atopy, and that the gene products on the X chromosome that cause asthma

TABLE 8. RESULTS FOR THE MULTIPLE VARIABLE ANALYSIS EXAMINING FACTORS ASSOCIATED WITH DEVELOPMENT OF ADOLESCENT-ONSET WHEEZE (ONSET AFTER AGE 10) IN FEMALES

Factor	Significance	HR	95% CI for the HR	
			Lower	Upper
All variables included				
Positive methacholine at 9 yr	< 0.001	3.69	2.00	6.81
Excluding airway hyperresponsiveness				
FEV ₁ /FVC at 9 yr	0.025	0.96	0.93	1.00
Any parental history of asthma or hay fever	0.006	1.75	1.18	2.50
Replacing family history with maternal and paternal history of atopy				
Maternal history of asthma or hay fever	0.009	1.89	1.17	3.06
Paternal history of asthma or hay fever	0.41	1.28	0.71	2.30
FEV ₁ /FVC at 9 yr	0.022	0.96	0.92	0.99

For definition of abbreviations, see Table 5.

are subsequently influenced by changes in sex hormones, needs to be further tested in genetic, epidemiologic, and clinical studies (47).

Conflict of Interest Statement: P.J.M. 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; J.O.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript; D.R.T. has no commercial interests that represent a conflict of interest regarding this study. He received airfare and accommodation expenses for speaking at a symposium sponsored by AstraZeneca in 2005. His department received an educational grant from GlaxoSmithKline annually until 2004, valued at N.Z. \$45,000 per annum; 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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