

Cardiovascular disease risk associated with asthma and respiratory morbidity might be mediated by short-acting β_2 -agonists

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Background: Studies examining the asthma-related risks of cardiovascular disease (CVD) events have generally used selected samples or did not control for the effects of β_2 -agonist use, itself associated with CVD events.

Objectives: We assessed the relationship between incident CVD/stroke and asthma and the effect of atopy while controlling for β_2 -agonist use in a representative adult population cohort free of CVD at baseline.

Methods: The North West Adelaide Health Study (stage 1, $n = 3812$; stage 2, $n = 3113$) assessed spirometry, anthropometry, atopy, blood pressure, and lipid levels. Questionnaires assessed doctor-diagnosed asthma and CVD (myocardial infarction and angina)/stroke, smoking status, and demographics. Asthma was defined by self-report or FEV₁ reversibility. Current short- and long-acting β_2 -agonist use was identified at follow-up.

Results: Results are expressed as odds ratios (ORs) and 95% CIs. By using multivariable logistic regression, after adjustment for risk factors, in female subjects incident CVD/stroke events were associated with asthma (OR, 3.24; 95% CI, 1.55-6.78), with no effect modification by atopy (P for interaction = .61), and with as-required short-acting β_2 -agonist use (OR, 2.66; 95% CI, 1.06-6.61). In male subjects events were associated with daily cough/sputum (OR, 1.92; 95% CI, 1.05-3.50) and FEV₁ of less than 80% of predicted value but an FEV₁/forced vital capacity ratio of greater than 0.70 (OR, 2.15; 95% CI, 0.91-5.09; $P = .08$). Although few CVD/stroke events occurred in male subjects with asthma, a significant interaction with atopic status was found ($P = .05$).

Conclusions: Studies are required to elucidate how asthma exposes older women to excess macrovascular risk and prospectively determine the short-acting β_2 -agonist-related risk in persons without existing CVD. CVD risk in relation to atopic

status of asthma also requires further investigation. (*J Allergy Clin Immunol* 2009;123:124-30.)

Key words: Adrenergic β -agonists, asthma, cardiovascular system, epidemiology, lung diseases, obstructive

Asthma and atherosclerosis occur on a background of inflammation. An association between these 2 disorders might be mediated by obesity^{1,2} and molecules, including TNF- α ^{3,4} and 12/15 lipoxygenase.^{5,6} Studies in selected samples show longitudinal associations of asthma with cardiovascular disease (CVD),⁷⁻⁹ but there is conflict in the literature surrounding the asthma-related risk of CVD identified in large, longitudinal epidemiologic studies. Schanen et al,¹⁰ reported an increased risk of stroke, but not coronary heart disease (CHD), associated with asthma. This contrasts with findings showing an increased risk of incident CHD among women but not among men.¹¹⁻¹³ Although Onufrak et al^{11,12} adjusted for the potential cardiotoxic effects of β_2 -adrenoceptor agonists,¹⁴ the effects were not quantified, and studies specifically examining the risk of CVD events associated with β_2 -agonist prescription have only done so in persons with a history of CVD.¹⁵⁻¹⁷ The role of asthma phenotype has been considered by very few studies, but these suggest that age of asthma onset modifies the association of asthma with CVD events.^{11,12}

We have previously reported a cross-sectional association of asthma and CVD at stage 1 of the North West Adelaide Health Study (NWAHS)¹⁸ after adjustment for risk factors and predictors. The primary aim of the present study was to determine the longitudinal association of asthma with incident CVD/stroke events (CVDSEs) in this large adult population sample and whether the association is modified by sex and atopic status. Given the concerns that have been expressed about long-acting β_2 -agonists (LABAs) as monotherapy for asthma^{19,20} and short-acting β_2 -agonist (SABA)-related asthma deaths,²¹ our secondary aim was to determine whether the relationship between asthma and CVD is mediated by β_2 -agonist use.

METHODS

Sample population and study method

The NWAHS is a representative biomedical population cohort study of adults aged 18 years or older randomly selected from the electronic White Pages telephone directory and living in the northwestern suburbs of Adelaide, South Australia (regional population, 0.6 million). The methods of the NWAHS²² and the validity of these methods of selection to achieve an unbiased sample have been described previously.²³

At stage 1 (conducted in 2 phases between December 1999 and December 2000 [$n = 2523$] and from August 2002 to July 2003 [$n = 1537$]), 4060

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Abbreviations used

BMI:	Body mass index
CATI:	Computer-assisted telephone interview
CHD:	Coronary heart disease
COPD:	Chronic obstructive pulmonary disease
CVD:	Cardiovascular disease
CVDSE:	Cardiovascular disease/stroke event
FVC:	Forced vital capacity
ICS:	Inhaled corticosteroid
LABA:	Long-acting β_2 -agonist
LTC ₄ :	Leukotriene C ₄
NWAHS:	North West Adelaide Health Study
OR:	Odds ratio
ROS:	Reactive oxygen species
SABA:	Short-acting β_2 -agonist
SBR:	Significant bronchodilator responsiveness

adults underwent biomedical examination (computer-assisted telephone interview [CATI] response rate, 69%). Follow-up of the cohort occurred between May 2004 and February 2006 by using the same stage 1 methodology and questions. Follow-up CATI and clinic data were obtained for 88% ($n = 3566$) and 79% ($n = 3206$) of the stage 1 NWAHS population, respectively. Of those unavailable for follow-up, 100 subjects were deceased, and the remaining subjects were unable to be contacted or refused further participation in the study. Mean participant follow-up time was 3.5 years (SD, 0.5 years; range, 1.7-5.8 years). At stage 2, self-reported CVDSE data were obtained for 3488 subjects. Subjects reporting a previous CVDSE at stage 1 ($n = 248$) and incident asthma cases ($n = 126$) were excluded from this analysis, leaving 3113 subjects. Incident asthma cases identified at follow-up ($n = 52$ doctor-diagnosed asthma and $n = 74$ participants with significant bronchodilator responsiveness [SBR] in the absence of a doctor's diagnosis) were excluded because it was unknown whether the asthma preceded the incident CVDSE (4 female patients and 1 male patient in the group with diagnosed asthma and 2 male patients in the SBR group) and to eliminate the possibility of respiratory medication use recorded at follow-up being related to new asthma cases.

At baseline and follow-up, CATI was used to investigate self-reported health status (including asthma, myocardial infarction, stroke, and angina) and demographic variables. Studies from community populations have found self-reported cardiac events and stroke to be accurate.^{24,25} A self-completed questionnaire comprised items on risk factors (smoking, family history of CVD, or stroke in a first-degree relative), respiratory symptoms, and use of blood pressure and lipid-lowering therapies. Clinic assessment included spirometry, skin prick testing (to rye grass, cat dander, house dust mite, *Alternaria* species, feather, and cockroach), and measurement of height, weight, blood pressure, and fasting plasma lipid, glucose, and glycated hemoglobin levels. High (uncontrolled) blood pressure was defined as a systolic pressure of 140 mm Hg or greater, a diastolic pressure of 90 mm Hg or greater, or both. Low-density lipoprotein cholesterol was classified according to the Adult Treatment Panel III criteria (borderline high low-density lipoprotein, ≥ 3.36 mmol/L or 130 mg/dL).²⁶ Body mass index (BMI) was categorized according to the World Health Organization criteria²⁷; however, underweight subjects (BMI < 18.5 kg/m², $n = 49$) were combined with those in the normal BMI category (18.5-24.9 kg/m²) because the event rates in these groups were not significantly different.

Asthma and respiratory morbidity

Asthma was identified based on a positive response to all 3 of the following questions: (1) "Have you ever had asthma?," (2) "Was your asthma confirmed by a doctor?," and (3) "Do you still have asthma?" Asthma was also identified by means of postbronchodilator spirometry (Microlab 3300 spirometer; Micro Medical LTD, Kent, United Kingdom) conducted according to American Thoracic Society criteria²⁸ and identifying FEV₁ reversibility (increase of at least 12% and 200 mL after inhalation of 400 μ g of salbutamol). Subjects demonstrating significant bronchodilator reversibility in the absence

of a doctor's diagnosis have significant respiratory morbidity, which is likely to be asthma.²⁹ Airways obstruction was identified based on a postbronchodilator FEV₁/forced vital capacity (FVC) ratio of less than 70%.³⁰ Low FEV₁ was defined as percent predicted FEV₁ of less than 80%. Respiratory symptoms were assessed at both time points with the validated Chronic Lung Disease Index.³¹ Cough with or without sputum was also identified by using 2 of the 6 Chronic Lung Disease Index subscales and defined as cough with or without sputum (several tablespoons per day) on most or every day in the past 3 months. Current SABAs (salbutamol and terbutaline) and LABAs (salmeterol/formoterol) alone or in combination with an inhaled corticosteroid (ICS) were identified at the follow-up, when subjects brought all medications that they were currently taking to their clinic appointments. Specific information on SABA use at the time of any CVDSE was not available. Frequency of SABA use was categorized as follows: no use, as required (less than daily use), and at least once per day. Most (99%, $n = 107$) LABA use occurred in combination with ICSs.

Statistical analysis

Statistical analysis was performed with SPSS 14.0 for Windows (SPSS, Inc, Chicago, Ill). Fisher exact or χ^2 tests were used to test differences in proportions of those with incident CVDSEs in relation to demographics, risk factors, asthma variables, and medication use. The t test was used to test differences in mean continuous variables (blood pressure, lipids, and lung function). Logistic regression analysis was used to model the asthma-related risks of having experienced an incident CVDSE (yes/no) with adjustment for variables that were significant (or $P < .25$) at the univariate level. Additional analysis was performed to determine whether there was a modifying effect of respiratory medication on the association of asthma and events. To assess whether the association between asthma and CVD differed significantly by sex, smoking, BMI, and atopic status, we tested the significance of the cross-product interaction terms in a logistic regression model. Sex-specific logistic regression models were conducted because of the significant interaction between sex and asthma ($P = .04$). Results are expressed as odds ratios (ORs) and 95% CIs. Cox regression models were not used because we were unable to identify the time to CVDSE.

The study was approved by the institutional ethics committees of the NWAHS, and all subjects provided written informed consent.

RESULTS

At follow-up of the cohort, an incident CVDSE was reported by 3.9% ($n = 122$) of participants free of CVDSEs at baseline. The incidence of self-reported myocardial infarction, angina, stroke, and transient ischemic attack were 1.3% ($n = 42$), 1.2% ($n = 38$), 0.5% ($n = 16$), and 1.1% ($n = 35$), respectively. Of 122 subjects reporting an event, 93% reported a single event. Subjects reporting an incident event or events were older and demonstrated higher mean levels of blood pressure, BMI, mean plasma glucose (but not lipid levels), and respiratory morbidity than those reporting no events (see Table E1 in this article's Online Repository at www.jacionline.org).

In the population free of CVDSEs at baseline, the prevalence of asthma was 12.2% ($n = 433$; male subjects: 10.7%, $n = 176$; female subjects: 13.5%, $n = 257$). The prevalence of asthma cases that were identified based solely on the questionnaire was 64% ($n = 281$). SBR was demonstrated in 15% ($n = 48$) of those with self-reported doctor-diagnosed asthma, and 36% ($n = 102$) of asthma cases were identified based on SBR. There was no difference in the current smoking rates in subjects with (22.2%) compared with those without (22.9%) asthma ($P = .42$). In contrast, subjects with asthma were significantly more likely to be ex-smokers (37.5%) than those without asthma (30.4%, $P < .01$). The prevalences of current and former smokers in the overall population were 22.8% and 31.2%, respectively.

Table I shows the prevalence of incident CVDSE in relation to stage 1 demographics, CVD risk factors, and respiratory disease variables for the overall population and by sex. We observed significant univariate associations of incident events in both male and female subjects with traditional risk factors, including age, low income, hypertension, and use of a SABA, along with baseline use of antihypertensive medication and statins. Incident events were also associated with asthma and LABA use with or without an ICS in female subjects and with low FEV₁, former smoking, and airways obstruction in male subjects. Cardiovascular system medications (statins, or antihypertensives, antianginals, anticoagulants, antiarrhythmic medications, or inotropes) were used by 87% of subjects reporting an incident event at follow-up compared with 30% of subjects without events ($P < .001$).

Because of the significant interaction between sex and asthma ($P = .04$), but not smoking and asthma ($P = .13$), BMI and asthma ($P = .37$), or atopy and asthma ($P = .31$), sex-specific multivariable logistic regression models were conducted to explain incident events. In female subjects, after adjusting for age and CVD risk factors (including hypertension, smoking, obesity, and family history), asthma was significantly associated with incident events (Table II). This significant association persisted after addition of SABA and LABA use in the final model. Events were positively associated with as-needed SABA use (OR, 2.66; 95% CI, 1.06-6.61; $P = .036$) but not at least once-daily use (OR, 0.81; 95% CI, 0.17-3.92; $P = .79$), and there was an inverse and nonsignificant association of LABA use alone or in combination with ICSs (OR, 0.58; 95% CI, 0.19-1.78; $P = .34$). The association of event with asthma was not modified by atopic status in female subjects (P for interaction = .61).

Few CVDSEs occurred in male subjects with asthma ($n = 7$). As shown in Table II, incident events were not associated with all asthma; however, the presence of daily cough and sputum (OR, 1.92; 95% CI, 1.05-3.50; $P = .03$), but not generalized respiratory symptoms, including dyspnea and wheeze, and as-needed SABA use (OR, 2.52; 95% CI, 0.72-8.88; $P = .15$), were associated with events, in addition to older age and hypertension, in the fully adjusted model. No significant association of events was seen with chronic obstructive pulmonary disease (COPD; obstruction and FEV₁ <80% of predicted value; OR, 1.43; 95% CI, 0.43-4.73; $P = .56$) or in those with obstruction but normal FEV₁ percent predicted (OR, 0.52; 95% CI, 0.07-4.03). However, in those with low FEV₁ (<80% of predicted value) and FEV₁/FVC ratios of greater than 0.70, the association approached statistical significance (OR, 2.15; 95% CI, 0.91-5.09; $P = .08$). In male subjects we observed a significant interaction between atopic status and asthma ($P = .05$) in the multivariable models. When asthma was stratified by atopic status, a borderline unadjusted association ($P = .06$) of nonatopic asthma with incident events was observed that did not persist in a limited multivariable model adjusted for age, hypertension, and smoking (nonatopic asthma: OR, 1.56; 95% CI, 0.51-4.74), most likely because of the small number of subjects. Similar to the results for female subjects, in male subjects there was no association of events with smoking (former or current) or LABA use alone or in combination with ICSs.

DISCUSSION

In this longitudinal analysis of a representative population of adults free of CVDSEs at baseline, asthma was independently associated with incident macrovascular disease in female subjects

after adjusting for CVD risk factors, was not modified by atopy, and persisted after adding SABA use to the model. Furthermore, CVDSE were significantly associated with as-needed SABA use. Of note, this association was seen after the short follow-up period of this study (mean time, 3.5 years). In male subjects events were associated with respiratory symptoms, SABA use, and reduced lung function but not with asthma. This is consistent with studies identifying an association between respiratory morbidity and ischemic heart disease-related mortality^{32,33} independent of smoking. In male subjects few events were seen in those with asthma, and even so, a significant effect modification by atopy was observed. In male and female subjects LABA use (alone or in combination with an ICS) was not associated with incident macrovascular events.

This study attempted to address gaps in the literature regarding the CVD risk associated with asthma and the effects of atopic status and β_2 -agonists in subjects free of CVD at baseline. In relation to the effect of atopic status on the relationship between asthma and CVD, we found no effect modification in female subjects. In male subjects, however, a significant effect modification by atopic status was found. The small number of incident events precluded further investigation of this phenomenon, but this is clearly an area for further research. Previous findings of female-specific associations of asthma with CVD might be explained by the failure of previous studies to assess effect modification by atopy. A recent study examining the cross-sectional associations of asthma with heart disease, stroke, and high blood pressure reported that men, but not women, with nonatopic asthma were significantly more likely to report events than their atopic counterparts based on self-reported allergy.³⁴ Given the significant potential of mast cells to contribute to atherogenesis,⁹ it is important to consider the atopic phenotype in relation to CVD. It is difficult to compare studies that have done so; IgE levels were associated with the progression of atherosclerosis in a selected sample with a low asthma prevalence (2.4%),⁹ and the contribution of atopy to CVD-related mortality has been shown to be affected by concurrent CVD risk factors.³⁵ In our population sample the absence of an overall association of atopy with incident events might be due to the high prevalence of atopy (61%) in our population.

Onufrak et al^{11,12} controlled for the effects of but did not report the hazard ratios for β -agonist use in models explaining events. An association between first-time use of β_2 -agonists (from prescription data)^{15,16} and incident myocardial infarction and unstable angina has been previously described in subjects with a history of CVD, and this is analogous to the association of events with as-required use described presently. In addition, tachyphylaxis to the bronchodilating effects of SABAs during methacholine challenge, which has been previously described,³⁶ provides plausibility for our association of CVDSEs with as-needed rather than daily use. Cardiotoxic effects of β_2 -agonists¹⁴ might, however, be attenuated by ICS use in patients with asthma^{37,38} and COPD.^{39,40} Concerns have been expressed about the potential adverse effects of LABAs²⁰; however, we found an inverse, although nonsignificant, association of LABA/ICS combination therapy with incident events. This is consistent with the view that corticosteroids in the combination therapy might offset the potential effects of LABAs because most subjects using LABAs did so in combination with ICSs. Our findings provide some reassurance that LABAs, when used in combination with ICSs, do not appear to be associated with significant cardiac events.

TABLE I. Prevalence of incident CVDSEs in relation to participant baseline demographics, CVD risk factors, respiratory disease, and medication use by sex

		CVDSEs, % (n)					
Baseline characteristic*		Overall	P value	Male subjects	P value	Female subjects	P value
Demographics							
Sex	Male	4.5 (64)	.13				
	Female	3.4 (58)					
Age (y)	≤54	1.6 (33)	<.01	2.1 (19)	<.01	1.3 (14)	<.01
	55-69	5.5 (42)		5.7 (20)		5.4 (22)	
	≥70	13.7 (47)		15.3 (25)		12.2 (22)	
Secondary school education only	Yes	4.5 (64)	.12	5.5 (27)	.23	4.0 (37)	.18
	No	3.4 (58)		4.0 (37)		2.8 (21)	
Annual household income ≤\$AUD 20,000	Yes	7.5 (58)	<.01	8.1 (23)	.01	7.1 (35)	<.01
	No	2.7 (64)		3.6 (41)		1.9 (23)	
CVD risk factors							
High blood pressure† (mm Hg)	Yes	7.4 (66)	<.01	8.1 (38)	<.01	6.7 (28)	<.01
	No	2.5 (56)		2.7 (26)		2.4 (30)	
LDL cholesterol ≥3.36 (mmol/L)	Yes	3.5 (46)	.44	4.1 (26)	.39	3.0 (20)	.75
	No	4.3 (74)		5.1 (37)		3.7 (37)	
BMI (kg/m ²)	≤24.9	3.2 (33)	.14	3.4 (13)	.38	3.1 (20)	.20
	25.0-29.9	3.8 (46)		4.7 (31)		2.8 (15)	
	≥30.0	4.9 (44)		5.3 (20)		4.7 (23)	
Smoking status	Current	2.8 (18)	.08	4.0 (13)	.05	1.5 (5)	.10
	Former	4.9 (49)		6.3 (32)		3.4 (17)	
	Never	3.7 (54)		3.3 (19)		4.1 (35)	
Family history (event in first-degree relative)	Yes	3.0 (31)	.06	4.7 (41)	.67	4.2 (50)	.01
	No	4.4 (91)		4.2 (23)		1.6 (8)	
Respiratory disease variables							
Asthma	Overall	6.8 (25)	<.01	4.7 (7)	.83	8.2 (18)	<.01
	Atopic	5.8 (15)		2.7 (3)		8.2 (12)	
	Nonatopic	9.3 (10)		11.1 (4)		8.3 (6)	
	No asthma	3.5 (94)		4.3 (55)		2.7 (39)	
FEV ₁ /FVC <70%‡	Yes	6.9 (9)	.07	9.2 (8)	.03	2.3 (1)	.67
	No	3.8 (111)		4.1 (55)		3.5 (56)	
Atopic	Yes	4.0 (76)	.77	4.6 (41)	.73	3.4 (35)	1.00
	No	3.8 (45)		4.2 (22)		3.4 (23)	
Predicted FEV ₁ <80%‡	Yes	8.6 (19)	<.01	11.1 (14)	<.01	5.3 (5)	.30
	No	3.5 (101)		3.8 (49)		3.3 (52)	
Medication use							
SABA	Yes	9.0 (18)	<.01	9.5 (7)	.03	8.7 (11)	<.01
	No	3.6 (104)		4.2 (57)		3.0 (47)	
SABA	≥Daily	3.4 (2)	<.01	0.0 (0)		5.0 (2)	<.01
	As needed	11.5 (16)		13.0 (7)		10.6 (9)	
LABA alone/+ ICS	None	3.4 (104)		4.2 (57)		3.0 (47)	
	Yes	7.8 (8)		6.3 (3)		8.5 (5)	
Baseline antihypertensives	No	3.8 (114)	<.01	4.4 (61)	<.01	3.3 (53)	<.01
	Yes	12.0 (47)		12.9 (21)		11.4 (26)	
Baseline statins	No	2.8 (75)	<.01	3.4 (43)	<.01	2.2 (32)	<.01
	Yes	14.8 (34)		17.9 (20)		11.9 (14)	
	No	3.0 (87)		3.4 (44)		2.7 (43)	
	Yes						

LDL, Low-density lipoprotein.

*Free of existing CVDSEs.

‡Postbronchodilator.

†High (uncontrolled) blood pressure: systolic pressure of 140 mm Hg or greater, diastolic pressure of 90 mm Hg or greater, or both.

Our findings in female subjects are generally consistent with those from large cross-sectional³⁴ and longitudinal^{11,13} epidemiologic studies. It is presently unclear why the association of macrovascular disease with asthma is confined to female subjects. That CVD risk is differentially affected by sex is consistent with other findings in our cohort with an increased risk of incident events related to increased glycated hemoglobin levels in female subjects but not in male subjects.⁴¹ Asthma-related inflammation might contribute more strongly to the atherosclerotic process in

female subjects compared with male subjects. A role for female hormones in allergy and asthma⁴² is supported by data showing that menstrual irregularity⁴³ and the menopausal transition⁴⁴ were associated with an increased asthma risk and lower lung function. These epidemiologic findings^{43,44} are supported by recent evidence that estradiol induces mast cells to undergo partial degranulation and enhances IgE-induced degranulation and secretion of leukotriene C₄ (LTC₄).⁴⁵ The cysteinyl leukotrienes derived from leukocytes and vascular smooth muscle cells are

TABLE II. Crude and adjusted ORs for the association of incident CVDSEs with asthma (all and by atopic status) by sex

	Crude OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI): CVD risk factors	Adjusted OR (95% CI): Risk factors + asthma medication*
Female subjects				
No asthma	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Asthma	3.22 (1.81-5.74)		3.33 (1.79-6.19)†	3.24 (1.55-6.78)‡
Atopic		3.20 (1.64-6.25)		
Nonatopic		3.27 (1.34-8.00)		
Male subjects				
No asthma	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Asthma	1.09 (0.49-2.44)		0.59 (0.23-1.50)§	0.45 (0.15-1.38)
Atopic		0.61 (0.19-1.97)		
Nonatopic		2.75 (0.94-8.00)		

*SABA frequency and LABA use alone or in combination with ICS.

†Adjusted for age, hypertension, smoking, family history of CVDSEs, obesity.

‡Adjusted for age, hypertension, family history of CVDSEs, SABA frequency (as needed, at least daily vs no use), and LABA use alone/in combination with an ICS (nonsignificant variables removed because of sample size constraints).

§Adjusted for age, hypertension, smoking, postbronchodilator FEV₁/FVC ratio less than 70%, FEV₁ of less than 80% of predicted value, and respiratory symptoms.

||Adjusted for age, hypertension, smoking, postbronchodilator FEV₁/FVC ratio of less than 70%, FEV₁ of less than 80% of predicted value, respiratory symptoms, SABA use (all as needed vs no use), and LABA use alone/in combination with an ICS.

important proinflammatory mediators in asthma, being potent bronchoconstrictors and vasoconstrictors, and induce reactive oxygen species (ROS) production. A pathway linking hormones, asthma, and atherosclerosis is undoubtedly complex, but Mueller et al⁴⁶ have recently shown that the release of LTC₄ from vascular smooth muscle cells has proatherosclerotic effects and that monteleukast, a cysteinyl leukotriene receptor antagonist, inhibited ROS production and reduced atherosclerotic plaques. It is possible that estradiol-induced LTC₄ production⁴⁵ might augment this pathway, leading to increased ROS production and atherosclerosis in women compared with men with asthma. These findings suggest that monteleukast might attenuate the asthma-related risk of CVD, and this is an area for further investigation. Montelukast use was rare (*n* = 1) in our cohort, preventing an analysis in relation to CVDSEs.

The female-specific association between asthma and incident CVDSEs is unlikely to be due to the diagnostic misclassification of COPD as asthma because the objectively determined prevalence of persistent airways obstruction in female subjects with asthma was only 13%, and importantly, CVDSEs occurred largely (98%) in those without persistent airways obstruction. In male subjects with asthma, the prevalence of persistent airways obstruction was 27%, and 22% demonstrated COPD (FEV₁/FVC <70% and a predicted FEV₁ <80%). The possibility of diagnostic misclassification in men is less important given that we have objective measures of COPD, and in this study, CVDSEs were associated not with asthma but with low lung function. Furthermore, studies that have conducted subanalyses in those who have never smoked¹¹ and in subjects without COPD³⁴ so as to minimize the possibility of misdiagnosis have found the association of asthma with CVD events to persist in these populations.

Our previous cross-sectional analysis found a strong association of events with traditional CVD risk factors, including smoking (current and former), in the NWAHS population¹⁸; however, this was not the case in relation to incident events when adjusted for other risk factors. Over a short follow-up time, the effects of age and hypertension might have overwhelmed the effects of smoking, particularly former smoking. Given that the mean age of those reporting incident events was 64 years and that of current and former smokers was 42 and 56 years,

respectively, we hypothesize that current smokers might simply be too young to have had events. In relation to former smokers, it is possible that a short smoking history in early age might explain the lack of an adjusted association with later incident events. Furthermore, in men it is possible that smoking is working through an effect on lung function and that events are observable not in smokers *per se* but those sensitive to the effects of smoking, as evident from cough and sputum and low lung function.

Self-reported doctor-diagnosed asthma and CVDSEs might be considered a limitation of this study. However, self-report is used widely and has been shown to be a valid measure of asthma,⁴⁷ and we also included those with significant bronchodilator reversibility. Self-reports of cardiac and stroke events have been reported to be accurate.^{24,25} In addition, the prevalence of cardiovascular system medication use was high in this group. We were unable to ascertain cause-of-death data at follow-up of the cohort, and therefore fatal macrovascular events that would have increased statistical power have been excluded from this analysis. β_2 -Agonist use was recorded at follow-up rather than at baseline, which precludes us from identifying whether the medication use preceded the incident events; however, we believe that follow-up SABA use at the time of a clinic visit (57% of subjects with asthma) is likely to reflect usual use. We were unable to assess CVDSE risk in relation to asthma severity, which might be a significant modifier of events and requires further assessment in unselected asthma samples. To date, 2 studies have reported an increased risk of CHD mortality in subjects with severe asthma (ie, subjects with asthma admitted to the hospital⁷ and those treated daily with oral corticosteroids for >1 year⁸). These studies did not, however, control for the effects of SABA use. We did not collect age of asthma onset data, but it is unclear how important this is in our cohort given that we observed an association with all asthma in women, whereas incident CHD events in the Atherosclerosis Risk in Communities cohort female subjects were not associated with asthma overall¹⁰ but were after stratification by age of onset,¹¹ suggesting a possible association with nonatopic asthma.⁴⁸ Given the small number of incident events in total (*n* = 123), we were also unable to test the association by type of event with adequate statistical power and were also limited as to the number of explanatory variables entered into the models

and therefore cannot exclude the possibility of confounding by socioeconomic factors. In relation to β_2 -agonist use, there is little evidence of a significant differential use of these medications by social class in Australia.⁴⁹ Our survey was limited to households with telephones, but because 97% of the households in the region have telephones²³ and the demographic characteristics were representative of the population of profile of Adelaide overall,⁵⁰ the extent of any bias is likely to be small. The strengths of our study include our large randomly recruited population sample and that we have also considered events in the younger population, who demonstrate an increasing burden of macrovascular disease.⁵¹

In conclusion, incident macrovascular events were strongly associated with asthma in female subjects but with respiratory impairment in male subjects after adjustment for traditional risk factors and SABA use. Further studies in subjects free of existing CVD are required to prospectively confirm the SABA-related risk of macrovascular events and a potential protective effect of LABA/ICS therapy. Further investigation of CVDSEs in relation to the atopic status of asthma in large population samples is important. Studies are required to elucidate the pathway by which asthma exposes older women to excess macrovascular risk in addition to identifying factors that might modify the increased risk of CVDSEs in women with asthma.

Clinical implications: Management of macrovascular disease risk in older female subjects with asthma is warranted to avoid additional significant morbidity burden.

REFERENCES

- Beuther D, Sutherland E. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med* 2007;175:661-6.
- Fantuzzi G. Adipose tissue, adipokines, and inflammation. *J Allergy Clin Immunol* 2005;115:911-9.
- Babu K, Davies D, Holgate S. Role of tumor necrosis factor alpha in asthma. *Immunol Allergy Clin North Am* 2004;24:583-97.
- Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation, and atherogenesis. *Endocrinology* 2003;144:2195-200.
- Andersson CK, Claesson H-E, Rydell-Tormanen K, Swedmark S, Hallgren A, Erjefalt JS. Mice Lacking 12/15-lipoxygenase have attenuated airway allergic inflammation and remodeling. *Am J Respir Cell Mol Biol* 2008;39:648-56.
- Huo Y, Zhao L, Hyman MC, Shashkin P, Harry BL, Burcin T, et al. Critical role of macrophage 12/15-lipoxygenase for atherosclerosis in apolipoprotein e-deficient mice. *Circulation* 2004;110:2024-31.
- Musk A, Ryan G, Perera D, D'Souza B, Hockey R, Hobbs M. Mortality from asthma in Western Australia. *Med J Aust* 1987;147:423-7.
- Toren K, Lindholm N. Do patients with severe asthma run an increased risk from ischaemic heart disease? *Int J Epidemiol* 1996;25:617-20.
- Knoflach M, Kiechl S, Mayr A, Willeit J, Poewe W, Wick G. Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies. *Arch Intern Med* 2005;165:2521-6.
- Schanen J, Iribarren C, Shahar E, Punjabi N, Rich S, Sorlie P, et al. Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study. *Thorax* 2005;60:633-8.
- Onufrak SJ, Abramson JL, Austin HD, Holguin F, McClellan WM, Vaccarino LV. Relation of adult-onset asthma to coronary heart disease and stroke. *Am J Cardiol* 2008;101:1247-52.
- Onufrak S, Abramson J, Vaccarino V. Adult-onset asthma is associated with increased carotid atherosclerosis among women in the Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis* 2007;195:129-37.
- Iribarren C, Tolstykh I, Eisner M. Are patients with asthma at increased risk of coronary heart disease? *Int J Epidemiol* 2004;33:743-8.
- Salpeter S, Ormiston T, Salpeter E. Cardiovascular effects of β -agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004;125:2309-21.
- Au DH, Curtis JR, Every NR, McDonnell MB, Fihn SD. Association between inhaled β -agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002;121:846-51.
- Au DH, Lemaitre RN, Randall Curtis J, Smith NL, Psaty BM. The risk of myocardial infarction associated with inhaled beta-adrenoceptor agonists. *Am J Respir Crit Care Med* 2000;161:827-30.
- Suissa S, Assimes T, Ernst P. Inhaled short acting β agonist use in COPD and the risk of acute myocardial infarction. *Thorax* 2003;58:43-6.
- Appleton S, Ruffin R, Wilson D, Taylor A, Adams R. Asthma is associated with cardiovascular disease in a representative population sample. *Obes Res Clin Pract* 2008;2:91-9.
- Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. *N Engl J Med* 2005;353:2637-9.
- Nelson H. Long-acting beta-agonists in adult asthma: evidence that these drugs are safe. *Prim Care Respir J* 2006;15:271-7.
- Pearce N, Hensley MJ. Epidemiologic studies of beta agonists and asthma deaths. *Epidemiol Rev* 1998;20:173-86.
- Grant J, Chittleborough C, Taylor A, Dal Grande E, Wilson D, Phillips P, et al. The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort for selected chronic diseases. *Epidemiol Perspect Innovations* 2006;3:4.
- Taylor A, Wilson D, Wakefield M. Differences in health estimates using telephones and door-to-door survey methods—a hypothetical exercise. *Aust N Z J Public Health* 1998;22:223-6.
- Rahman A, Gibney L, Person S, Williams O, Kiefe C, Jolly P, et al. Validity of self-reports of reasons for hospitalization by young adults and risk factors for discordance with medical records. The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Epidemiol* 2005;162:491-8.
- Kriegsman D, Penninx B, van Eijk J, Boeke A, Deeg D. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly: a study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol* 1996;49:1407-17.
- National Cholesterol Education Program, NHLBI. Third report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Full Report. Bethesda (Md): National Institutes of Health; 2002.
- World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: World Health Organization; 1997.
- American Thoracic Society. Lung function testing: selection of reference values and interpretive strategies. *Am Rev Respir Dis* 1991;144:1202-18.
- Appleton S, Adams R, Wilson D, Taylor A, Ruffin R. on behalf of the North West Adelaide Cohort Health Study Team. Spirometric criteria for asthma: adding further evidence to the debate. *J Allergy Clin Immunol* 2005;116:976-82.
- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Available at: www.goldcopd.com. Accessed July 15, 2003.
- Selim A, Ren X, Fincke G, Rogers W, Lee A, Kazis L. A symptom-based measure of the severity of chronic lung disease: results from the Veterans Health Study. *Chest* 1997;111:1607-14.
- Frostad A, Soyseth V, Haldorsen T, Andersen A, Gulsvik A. Respiratory symptoms and long-term cardiovascular mortality. *Respir Med* 2007;101:2289-96.
- Sin DD, Wu L, Man SFP. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005;127:1952-9.
- Dogra S, Arden C, Baker J. The relationship between asthma age of onset and cardiovascular disease in Canadians with asthma. *J Asthma* 2007;44:849-54.
- Hospers JJ, Rijcken B, Schouten JP, Postma DS, Weiss ST. eosinophilia and positive skin tests predict cardiovascular mortality in a general population sample followed for 30 years. *Am J Epidemiol* 1999;150:482-91.
- Hancox RJ, Aldridge RE, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, et al. Tolerance to beta-agonists during acute bronchoconstriction. *Eur Respir J* 1999;14:283-7.
- Suissa S, Assimes T, Brassard P, Ernst P. Inhaled corticosteroid use in asthma and the prevention of myocardial infarction. *Am J Med* 2003;115:377-81.
- Camargo CA Jr, Barr RG, Chen R, Speizer FE. Prospective study of inhaled corticosteroid use, cardiovascular mortality, and all-cause mortality in asthmatic women. *Chest* 2008;134:546-51.
- Lofdahl CG, Postma DS, Pride NB, Boe J, Thoren A. Possible protection by inhaled budesonide against ischaemic cardiac events in mild COPD. *Eur Respir J* 2007;29:1115-9.
- Huairt L, Ernst P, Ranouil X, Suissa S. Low-dose inhaled corticosteroids and the risk of acute myocardial infarction in COPD. *Eur Respir J* 2005;25:634-9.
- Adams R, Appleton S, Hill C, Wilson D, Taylor A, Chittleborough C, et al. Independent association of HbA1c and incident cardiovascular disease in people without diabetes. *Obesity* 2009. In press.
- Jensen-Jarolim E, Untersmayr E. Gender-medicine aspects in allergology. *Allergy* 2008;63:610-5.
- Real FG, Svanes C, Omenaas ER, Antò JM, Plana E, Janson C, et al. Menstrual irregularity and asthma and lung function. *J Allergy Clin Immunol* 2007;120:557-64.

44. Real FG, Svanes C, Omenaas ER, Antò JM, Plana E, Jarvis D, et al. Lung function, respiratory symptoms, and the menopausal transition. *J Allergy Clin Immunol* 2008;121:72-80.
45. Zaitis M, Narita S-I, Lambert KC, Grady JJ, Estes DM, Curran EM, et al. Estradiol activates mast cells via a non-genomic estrogen receptor-[alpha] and calcium influx. *Mol Immunol* 2007;44:1977-85.
46. Mueller C, Wassmann K, Widder J, Wassmann S, Chen C, Keuler B, et al. Multi-drug resistance protein-1 affects oxidative stress, endothelial dysfunction, and atherogenesis via leukotriene C4 export. *Circulation* 2008;117:2912-8.
47. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. *Chest* 1993;104:600-8.
48. Kitch B, Levy B, Fanta C. Late onset asthma. *Epidemiology, diagnosis and treatment. Drugs Aging* 2000;17:395.
49. Australian Centre for Asthma Monitoring. Asthma in Australia: findings from the 2004-05 National Health Survey. Canberra: Australian Institute of Health and Welfare; 2007.
50. Australian Bureau of Statistics. 2001 Census Basic Community Profile and Snapshot: 405 Adelaide (Statistical Division), Australia, South Australia. Canberra: Australian Bureau of Statistics; 2001.
51. O'Flaherty M, Ford E, Allender S, Scarborough P, Capewell S. Coronary heart disease trends in England and Wales from 1984 to 2004: concealed leveling of mortality rates among young adults. *Heart* 2008;94:178-81.

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Burks W, Jones SM, Berseth CL, et al. Hypoallergenicity and Effects on Growth and Tolerance of a New Amino Acid-Based Formula with Docosahexaenoic Acid and Arachidonic Acid. *J Pediatr* 2008;153:266-71.

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Malmström K, Lohi J, Lindahl H, et al. Longitudinal Follow-up of Bronchial Inflammation, Respiratory Symptoms, and Pulmonary Function in Adolescents after Repair of Esophageal Atresia with Tracheoesophageal Fistula. *J Pediatr* 2008;153:396-401.

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TABLE E1. Baseline mean (SE) biomedical characteristics of participants* reporting an incident CVDSE

Biomedical characteristic	Incident CVDSE		P value
	Yes (n = 122)	No (n = 2991)	
Age (y)	63.3 (1.21)	48.2 (0.27)	<.01
BMI	29.0 (0.56)	27.7 (0.10)	<.01
Systolic BP (mm Hg)	138.6 (1.84)	126.2 (0.32)	<.01
Diastolic BP (mm Hg)	83.7 (0.98)	80.4 (0.18)	<.01
Triglycerides (mmol/L)	1.53 (0.07)	1.44 (0.02)	.37
Total cholesterol (mmol/L)	5.20 (0.09)	5.28 (0.02)	.40
HDL cholesterol (mmol/L)	1.35 (0.03)	1.37 (0.01)	.50
LDL cholesterol (mmol/L)	3.15 (0.09)	3.26 (0.02)	.22
Glucose (mmol/L)	5.71 (0.19)	5.15 (0.02)	<.01
Glycated hemoglobin (%)	5.87 (0.09)	5.49 (0.01)	<.01
Lung function†			
Percent predicted FEV ₁	97.1 (1.69)	102.3 (0.29)	<.01
Percent predicted FVC	95.3 (1.46)	101.6 (0.27)	<.01
Respiratory symptoms: CLDI‡	27.9 (1.42)	23.2 (0.25)	<.01
Smoking status (%)			.08
Never	44.6 (54)	46.6 (1388)	
Former	40.5 (49)	32.0 (954)	
Current	14.9 (18)	21.3 (635)	

BP, Blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Free of existing CVDSEs.

†Postbronchodilator spirometry.

‡Chronic Lung Disease Index (CLDI): lower = less symptoms.³¹