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Relation of Adult-Onset Asthma to Coronary Heart Disease and Stroke

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Abstract

Asthma has been associated with atherosclerotic disease in several studies with some evidence that this association may be limited to women. However, most previous studies have failed to account for the heterogeneity of asthma subtypes. We previously reported increased carotid intima medial thickness among women with adult-onset asthma. In this study, we examine the association of adult and child-onset asthma with incident coronary heart disease (CHD) and stroke. Subjects were classified according to self-report of physician diagnosed asthma and age of asthma onset. We used Cox proportional hazards models to test the association of adult and child-onset asthma with incident CHD and stroke, testing for gender interaction. Subanalysis was also performed using only neversmokers. Women with adult-onset asthma experienced a 2-fold increase in incident CHD and stroke which was independent of other risk factors including smoking, body mass index, and physical activity and persisted when the analysis was restricted to never-smokers. No significant association was found among women with child-onset asthma or among men. In conclusion, adult-onset asthma may be a significant risk factor for CHD and stroke among women but not men.

Keywords

ASTHMA; CORONARY DISEASE; STROKE; SEX FACTORS

Asthma has been associated with vascular disease, carotid atherosclerosis, coronary heart disease (CHD), or stroke in at least nine studies.[1–9] Among studies that present results stratified by gender, there is a suggestion that the association may be stronger among or entirely limited to women.[1–4] However, asthma is not a single disease but rather a collection of distinct underlying subtypes, with somewhat differing etiologies.[10,11] Child and adult-onset asthma differ in regards to asthma triggers[11], gender distribution[11], and systemic inflammation.[12] We previously reported an association between carotid intima medial thickness and adult-onset

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asthma among women in the Atherosclerosis Risk in Communities (ARIC) study.[4] This association was not observed among women with child-onset asthma or among men with either adult or child-onset asthma. In this study, we examined the association of asthma age of onset phenotypes with incidence of CHD and stroke according to gender within the ARIC cohort.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective study of the etiology of atherosclerotic, cardiovascular, and cerebrovascular disease in 4 U.S. communities in North Carolina, Mississippi, Minnesota, and Maryland.[13] The study population of 15,792 men and women ages 45 to 64 years includes both black and white participants. Subjects completed a baseline clinic visit during 1987 to 1989 and were followed for incidence of CHD and stroke events. We used publicly available data with follow-up available through 2001 for 15,732 participants. We excluded subjects missing data for asthma status (n=28) or who reported ever having asthma but did not report physician diagnosis of asthma (n=131). We also excluded subjects with self reported history of stroke (n= 320) or prevalent CHD (n=692), defined as history of MI, silent MI, or revascularization surgery at baseline. This left 14,567 subjects for analysis.

Baseline assessment of asthma status and other covariates

Based on self report of physician diagnosed asthma and age of asthma onset, subjects were classified as having “adult-onset asthma” if age of onset was 21 years or above, or “child-onset asthma” if onset was before age 21. Smoking was measured by self-reported smoking status (former, current, or never). Classification of diabetes was based on at least one of the following: fasting plasma glucose greater than 126 mg/dL, non-fasting plasma glucose greater than 200 mg/dL, self reported diabetes, or taking diabetes medications. Low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol were included in models as continuous variables. All laboratory tests were run at centralized chemical, hemostasis and lipid laboratories, and hematological tests were run at local laboratories. Hypertension was defined as a diastolic blood pressure greater than or equal to 90 mm Hg, a systolic blood pressure greater than 140 mm Hg, or self report of use of anti-hypertensive drugs.[14] Physical activity was assessed according to the Baecke scale based upon frequency, duration, and intensity of physical activity.[15] Education level was classified according to the number of years of school completed (<12 years, 12–16 years, or>16 years). Asthma medication use (beta adrenergic and oral glucocorticoids) was classified according to use during the 2 week period prior to the baseline clinic visit and was ascertained by having subjects bring all prescription and non-prescription medications used during this period to the clinic during their baseline visit. Forced expiratory volume in one second (FEV1) and forced expiratory vital capacity (FVC) were assessed using spirometry according to the ARIC study protocol. [16] This protocol includes strict quality control procedures to ensure recorded spirometry measurements are technically acceptable and reproducible.[16] FEV1 was categorized for use in multivariable analysis according to gender-specific quartiles. Chronic bronchitis and emphysema were classified based upon self report of physician diagnosis.

Ascertainment of incident CHD and stroke events

For our primary analysis, incident CHD was defined as definite or probable myocardial infarction (MI) or fatal CHD. We also performed subanalyses in which incident CHD events included revascularization procedures and silent MI detected through electrocardiogram (ECG). Incident strokes included both ischemic and hemorrhagic strokes. Potential CHD and stroke events were identified in cohort members through annual follow-up, survey of area hospital discharge lists, and state vital statistics. Where discharge summaries indicated

diagnosis codes for cardiovascular disease, diabetes, stroke, or included stroke related keywords, hospital records were abstracted by trained study personnel. Out-of-hospital deaths were investigated by means of death certificates, interview with one or more next of kin, and a physician questionnaire, coroner reports or autopsy reports. MI events were classified based upon chest pain, cardiac enzyme levels, and ECG results. Fatal CHD classification was based on chest pain symptoms, cause of death from the death certificate, and available hospital information and medical history, including ARIC clinic visits. For stroke events, records were reviewed in detail by a member of the ARIC study Stroke-Mortality and Morbidity Classification Committee and the patient was classified according to the type of stroke that occurred (ischemic or hemorrhagic). The outcome ascertainment process has been described in further detail by ARIC investigators.[17]

Analysis

Analysis was completed using SAS version 9. Baseline covariates were compared by asthma history among men and women separately using chi-square tests, Fisher exact tests, and pooled or unpooled t-tests. Missing covariate values, which occurred at <3% for any covariate, were imputed using multiple imputation methods.[18] Crude incidence density rates of CHD and stroke were calculated among men and women for non-asthmatics, child-onset asthmatics, and adult-onset asthmatics. Crude and multivariate hazard ratios comparing each asthma subtype to non-asthmatics were computed using Cox proportional hazards models. Multivariate models were adjusted for age, body mass index (BMI), black race, smoking status, diabetes, hypertension, education level, low and high density lipoprotein levels, and leisure physical activity. We tested for interaction between asthma and gender in crude and multivariate models using Wald chi-square tests. In subanalyses, we used an expanded definition of CHD to include revascularization and silent MI.

We also performed additional analyses to investigate the impact of asthma medications, lung function, and the respiratory comorbidities chronic bronchitis and emphysema on the association of asthma with cardiovascular outcomes. To further examine the possible confounding effect of smoking and the possible misclassification of chronic obstructive pulmonary disease (COPD) as asthma on our results, we repeated the analysis in the subgroup of individuals who never smoked in the past. Finally, we also performed age-adjusted analysis among women free of diabetes, hypertension, emphysema, and chronic bronchitis. In all of these additional analyses we used a combined outcome of incident CHD or stroke to maximize the number of events in the model.

Results

The distribution of asthma age of onset among men and women is shown in figure 1. The prevalence of child-onset asthma was higher among men (3.3%) than women (2.5%), while adult-onset asthma was more common among women (3.4%) compared to men (2.0%). Compared to their non-asthmatic counterparts, men and women with adult-onset asthma were older, had a higher prevalence of diabetes and hypertension, more pack-years of smoking, higher fibrinogen levels, and a higher prevalence of beta adrenergic and glucocorticoid steroid asthma medication use at baseline (table 1). Women with adult-onset asthma also had significantly higher body mass index (BMI), lower physical activity, and were more often post-menopausal than women without a history of asthma. Compared to nonasthmatics, FEV1, % expected FEV1, and FEV1/FVC were lower among men and women with either asthma subtype but were lowest among those with adult-onset asthma. Likewise, chronic bronchitis, emphysema, and use of asthma medications were more prevalent among all asthmatics but were most prevalent among adult-onset asthmatics (table 1).

Women, but not men, with adult-onset asthma experienced a 2-fold increase in rate of CHD compared to their non-asthmatic counterparts (table 2). This association was attenuated but remained significant after adjustment for age, BMI, black race, smoking status, diabetes, hypertension, education level, low and high density lipoprotein cholesterol levels, and physical activity (table 2). Child-onset asthma was not significantly associated with incident CHD among women or men. Tests of interaction between gender and adult-onset asthma were significant ($p<0.05$) in all CHD models, while interaction tests of child-onset asthma with gender were not. Results were similar in subanalyses where incident CHD also included revascularization procedures and silent MI, with an adjusted hazard ratio (HR) of 1.86 (95% Confidence Interval [CI]: 1.31 to 2.63) for women with adult-onset asthma and nonsignificant associations observed among all other asthma-gender subgroups.

Similar to the results for CHD, adult-onset asthma was associated with incident stroke among women but not men with a significant gender interaction ($p<0.05$) (table 3). The association of adult-onset asthma with stroke in women remained significant after adjustment for demographic variables and established CHD risk factors (table 3). The small numbers of stroke events precluded multivariate analysis among men. Child-onset asthma was not significantly associated with incident stroke among men or women and the interaction of child-onset asthma and gender was nonsignificant (table 3).

Because of the similarity of results for the CHD and the stroke outcomes, we performed additional analyses using a combined endpoint of incident cardiovascular disease, including CHD or stroke (figure 2). In the fully adjusted model including covariates for asthma medications, FEV1, chronic bronchitis, and emphysema, adult-onset asthma was significantly associated with this combined outcome among women (HR = 1.68, 95% CI: 1.21 to 2.35). Results remained robust in analyses restricted to never-smokers, which again confirmed a significant association of adult-onset asthma among women but not among men or among women or men with child-onset asthma (table 4). Finally, in age-adjusted analysis among women free of diabetes, hypertension, emphysema, and chronic bronchitis, adult-onset asthma was strongly associated with incidence of CHD or stroke (HR = 3.93, 95% CI: 2.01 to 7.02) while child-onset asthma was not significantly associated (HR = 1.80, 95% CI: 0.67 to 4.87).

Discussion

In this large, community-based follow-up study, women with adult-onset asthma experienced a nearly 2-fold increase in the rate of CHD and stroke, which was independent of other risk factors including smoking, BMI, and physical activity and persisted when the analysis was restricted to never-smokers. This result is consistent with our previous finding that women, but not men, with adult-onset asthma have increased carotid intima medial thickness compared to their nonasthmatic counterparts [4] and with other reports suggesting a role of asthma in atherosclerotic disease among women but not men.[1–3]

This is the first study to test the association of asthma age of onset subtypes with cardiovascular outcomes. It is recognized that “asthma” is not a uniform disease, but rather a constellation of distinct conditions.[10,11,19] Adult-onset asthma differs from childonset asthma in several aspects, including its distribution among men and women[11], and its immunological and inflammatory pathophysiology.[10,19] Nevertheless, previous studies of asthma and atherosclerotic outcomes have generally ignored asthma subtypes. Three previous studies have presented gender specific results for the association between asthma and CHD. Toren et al. reported an age-adjusted standardized mortality ratio for ischemic heart disease of 1.4 (95% CI: 0.8 to 2.0) among asthmatic men and 2.5 (95%CI: 1.7 to 3.3) among asthmatic women.[1] In a retrospective cohort study of a large insurance cohort, Iribarren et al. reported multivariate adjusted hazard ratios of 1.22 (95% CI: 1.14 to 1.31) among asthmatic women and 0.99 (95%

CI: 0.93 to 1.05) among asthmatic men.[2] Similarly, an earlier report from the ARIC study found an elevated risk of stroke in asthmatic women, but not men, compared to non-asthmatic subjects, although no association was found with CHD outcomes in either women or men.[3] None of these previous reports distinguish among asthma subtypes. Thus, the lack of association of asthma with CHD reported in the previous ARIC study probably reflects a mixing of the heterogeneous effects of adult and child-onset asthma subtypes. [3] By separating asthma subtypes, we have uncovered an important risk associated with adult-onset asthma among women.

The precise mechanisms underlying the association between adult-onset asthma and atherosclerotic vascular disease in women are unclear. Asthma may predispose to atherosclerosis through specific pathophysiologic pathways perhaps linked to the chronic inflammatory response of this disorder. Alternatively, the association between asthma and atherosclerosis may be due to an inherent joint susceptibility to both diseases through shared inflammatory pathways. For example, cysteinyl leukotrienes, potent inflammatory mediators, are implicated in the pathogenesis of both asthma[20] and atherosclerosis[21]. Why is the association between asthma and cardiovascular disease only observed in women with adult-onset asthma? Estrogen levels, which increase at puberty, modulate the release of proinflammatory cytokines from activated monocytes, macrophages[22], and vascular cells[23, 24] and also regulates the production of leukotrienes from mast cells.[25] The incidence rate of asthma among women is temporally associated with shifts in estrogen levels, with incidence increasing after puberty[26] and peaking during the onset of menopause [27] (figure 1). Thus, we may speculate that the women who develop asthma during these hormonal life events may be particularly susceptible to estrogen-modulated alterations in inflammatory cytokine and leukotriene regulation.

Our study has several strengths. Foremost, the ARIC cohort is large, multiracial and prospective, and includes rich and high quality subject data. We were able to control for potentially important confounding variables such as smoking, physical activity, and asthma medication use and we further addressed confounding by smoking and other confounders by performing sub-analyses restricted to never smoking subjects and subjects free of diabetes, hypertension, emphysema, and chronic bronchitis. The major weakness of our study is the fact that asthma status was based upon self-report of physician diagnosis. Although there is some evidence to suggest that self-reported asthma yields high specificity[28], there is also literature to suggest that misdiagnosis of COPD as asthma occurs frequently, and more so among women[29]. Because approximately 85% of COPD cases have a history of smoking, the persistence of the association of adult-onset asthma with CHD among never smoking women suggests that the observed association is not likely to be due to misdiagnosed COPD cases. Nonetheless, there remains the need for further research in which asthma classification is objectively determined through established clinical guidelines. Furthermore, we did not have information on IgE levels, asthma triggers, or presence of allergies to differentiate asthma according to allergic status. Other limitations include small numbers of events, particularly stroke, among men with adult-onset asthma and lack of data for inflammatory markers such as C - reactive protein. Finally, because our study is observational we cannot exclude the influence of unmeasured confounding factors or residual confounding because asthma is associated with many known cardiovascular risk factors.

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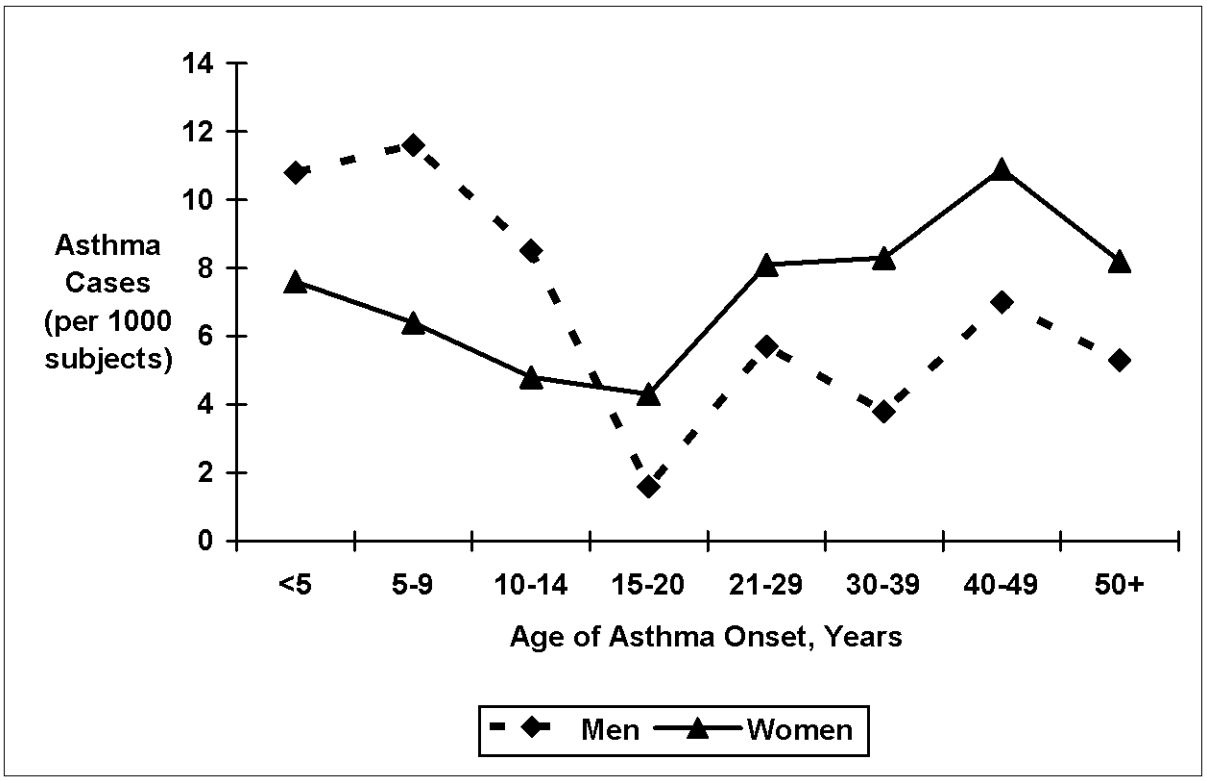

Figure 1.
Self-reported asthma age of onset among men and women.

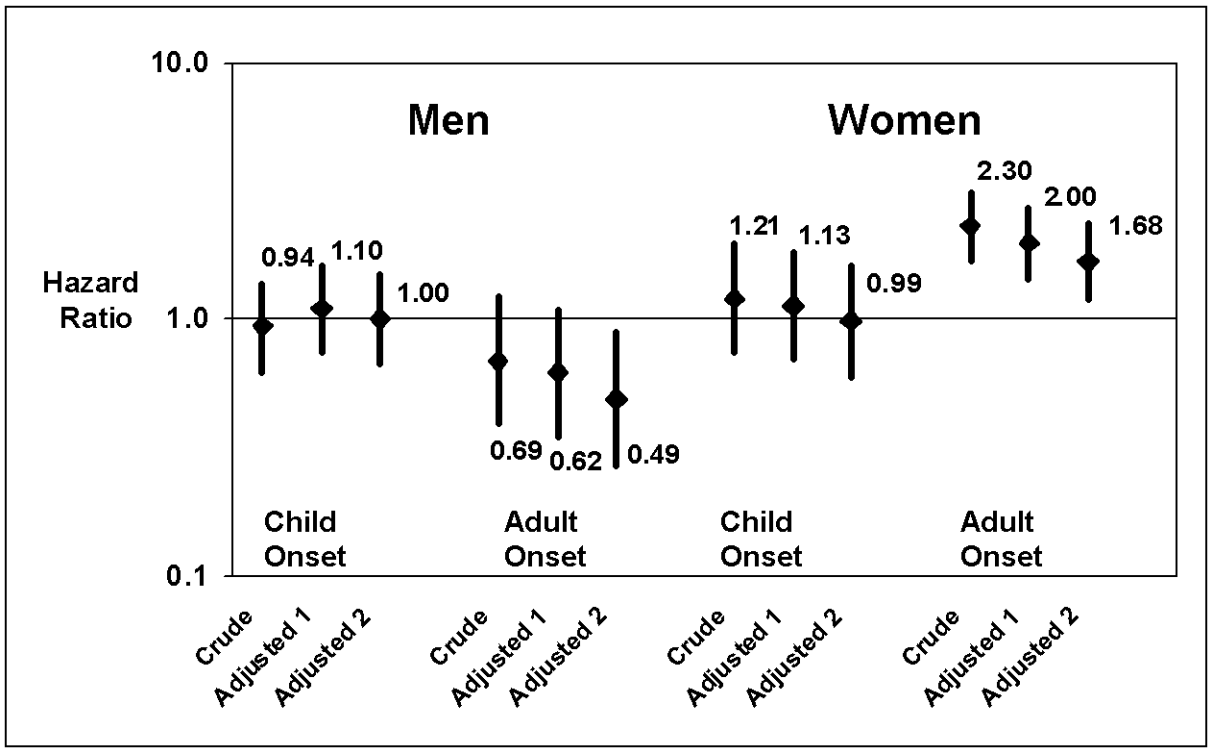

Figure 2.

Hazard ratios for incident coronary heart disease or stroke according to asthma age of onset and gender. *Adjusted 1* model includes age, body mass index, black race, smoking status, diabetes mellitus, hypertension, education level, LDL and HDL cholesterol, and physical activity; *Adjusted 2* model includes model 1 covariates plus forced expiratory volume in 1 second, chronic bronchitis, emphysema, and use of glucocorticoid or beta adrenergic medicines.

Table 1

Baseline comparison of men and women according to self-reported asthma history

	Men			Women		
Variable	**No Asthma (n=5931)**	**Child Onset Asthma* (n=210)**	**Adult Onset Asthma* (n=131)**	**No Asthma (n=7809)**	**Child Onset Asthma* (n=203)**	**Adult Onset Asthma* (n=283)**
Age (years)	54.3	53.3†	55.4†	53.7	52.9†	54.3
Black Race	23.3%	19.1%	15.3%†	29.6%	30.1%	33.2%
High School Graduate	77.5%	82.3%	65.7%†	77.2%	76.4%	69.3%†
Body Mass Index (kg/m^2)	27.4	27.2	27.3	27.8	28.3	28.9†
Diabetes Mellitus	10.5%	10.6%	14.5%	10.8%	17.2%†	17.8%†
Hypertension	32.4%	29.2%	37.4%	34.1%	33.0%	43.6%†
Chronic Bronchitis	4.0%	15.1%†	27.9%†	9.2%	39.6%†	43.1%†
Emphysema	1.9%	4.3%†	8.4%†	0.9%	3.9%†	5.3%†
Current Smoker	27.6%	22.4%	21.4%	24.6%	22.8%	29.0%
Pack Years	21.7	20.1	24.3	10.0	11.2	13.8†
Leisure Physical Activity Index	2.34	2.35	2.35	2.38	2.33	2.29†
One Second Forced Expiratory Volume (liters)	3.37	3.11†	2.74†	2.44	2.20†	2.05†
One Second Forced Expiratory Volume (% predicted)	91.4%	83.2%†	74.6%†	97.1%	86. 5%†	83.3%†
One Second Forced Expiratory Volume / Forced Expiratory Vital Capacity	73.5	68.3†	63.5†	75.9	71.1†	70.3†
Low Density Lipoprotein Cholesterol (mg/dL)	139	135	139	136	133	134
High Density Lipoprotein Cholesterol (mg/dL)	45	45	47†	58	58	58
Albumin (mg/dL)	3.92	3.96	3.91	3.83	3.78†	3.81
Fibrinogen (mg/dL)	295	294	306	307	315	316†
Current Hormone Replacement Therapy	-	-	-	19.2%	22.6%	15.7%
Post-Menopausal or Hysterectomy	-	-	-	67.1%	58.9%†	75.9%†
Beta Adrenergic Asthma Medication Use	0.6%	6.2%†	29.0%†	0.4%	13.3%†	22.6%†
Oral Glucocorticoid Asthma Medication Use	0.5%	2.9%†	12.2%†	1.0%	3.5%†	9.2%†

*Child onset = age < 21 years; adult onset = age ≥ 21 years;

†p<0.05 comparing subjects within asthma subtype to subjects reporting no history of asthma within each gender

Table 2

Incident coronary heart disease rates and hazard ratios among men and women according to asthma history

	Males			Females		
	No History of Asthma	Childhood Onset Asthma	Adult-Onset Asthma	No History of Asthma	Childhood Onset Asthma	Adult-Onset Asthma
Crude Rate* (Cases / Person-Years)	7.85 (565 / 72006)	8.52 (22 / 2582)	6.22 (10 / 1607)	3.52 (348 / 98963)	3.49 (9 / 2580)	7.34 (25 / 3407)
Crude Hazard Ratio (95% Confidence Interval)	1.0 (Ref)	1.08 (0.71, 1.66)	0.80 (0.43, 1.49)	1.0 (Ref)	0.99 (0.51, 1.93)	2.10 (1.40, 3.16)
Multivariate Adjusted† Hazard Ratio (95% Confidence Interval)	1.0 (Ref)	1.25 (0.82, 1.92)	0.71 (0.38, 1.32)	1.0 (Ref)	0.95 (0.49, 1.83)	1.78 (1.18, 2.67)

*Per 1000 person years

†Adjusted for age, body mass index, black race, diabetes mellitus, hypertension, education level, low and high density lipoprotein cholesterol levels, and physical activity

Table 3

Incident stroke rates and hazard ratios among men and women according to asthma history

	Males			Females		
	No History of Asthma	**Childhood Onset Asthma**	**Adult-Onset Asthma**	**No History of Asthma**	**Childhood Onset Asthma**	**Adult-Onset Asthma**
Crude Rate* (Cases / Person-Years)	3.50 (257 / 73489)	2.27 (6 / 2639)	1.22 (2 / 1634)	2.39 (238 / 99443)	3.51 (9 / 2565)	5.57 (19 / 3411)
Crude Hazard Ratio (95% Confidence Interval)	1.0 (Ref)	0.65 (0.29, 1.45)	0.35 (0.09, 1.41)	1.0 (Ref)	1.47 (0.76, 2.87)	2.36 (1.48, 3.76)
Multivariate Adjusted† Hazard Ratio (95% Confidence Interval)	1.0 (Ref)	-	-	1.0 (Ref)	1.25 (0.64, 2.44)	2.08 (1.30, 3.32)

*Per 1000 person years

†Adjusted for age, body mass index, black race, diabetes mellitus, hypertension, education level, low and high density lipoprotein cholesterol levels, and physical activity

Table 4

Never-smokers only - Incident combined coronary heart disease or stroke event rates and hazard ratios among men and women according to asthma history

	Males			Females		
	No History of Asthma	Childhood Onset Asthma	Adult-Onset Asthma	No History of Asthma	Childhood Onset Asthma	Adult-Onset Asthma
Crude Rate* (Cases / Person-Years)	8.31 (181 / 21757)	5.49 (5 / 910)	10.69 (5 / 468)	4.75 (251 / 52868)	5.40 (7 / 1296)	10.59 (18 / 1699)
Crude Hazard Ratio (95% Confidence Interval)	1.0 (Ref)	0.65 (0.27, 1.58)	1.31 (0.54, 3.18)	1.0 (Ref)	1.14 (0.51, 2.43)	2.24 (1.39, 3.62)
Multivariate Adjusted† Hazard Ratio (95% Confidence Interval)	1.0 (Ref)	0.74 (0.30, 1.80)	1.04 (0.43, 2.53)	1.0 (Ref)	1.10 (0.52, 2.33)	2.05 (1.28, 3.31)

*Per 1000 person years

†Adjusted for age, body mass index, black race, diabetes mellitus, hypertension, education level, low and high density lipoprotein cholesterol levels, and physical activity