ASTHMA

Asthma and incident cardiovascular disease: the Atherosclerosis Risk in Communities Study

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Background: A possible association between asthma and cardiovascular disease has been described in several exploratory studies.
Methods: The association of self-reported, doctor diagnosed asthma and incident cardiovascular disease was examined in a biracial cohort of 45–64 year old adults (N = 13501) followed over 14 years.
Results: Compared with never having asthma, the multivariate adjusted hazard ratio (HR) of stroke (n = 438) was 1.50 (95% CI 1.04 to 2.15) for a baseline report of ever having asthma (prevalence 5.2%) and 1.55 (95% CI 0.95 to 2.52) for current asthma (prevalence 2.7%). The relative risk of stroke was 1.43 (95% CI 1.03 to 1.98) using a time dependent analysis incorporating follow up reports of asthma. Participants reporting wheeze attacks with shortness of breath also had greater risk for stroke (HR = 1.56, 95% CI 1.18 to 2.06) than participants without these symptoms. The multivariate adjusted relative risk of coronary heart disease (n = 1349) was 0.87 (95% CI 0.66 to 1.14) for ever having asthma, 0.69 (95% CI 0.46 to 1.05) for current asthma at baseline, and 0.88 (95% CI 0.69 to 1.11) using the time dependent analysis.
Conclusions: Asthma may be an independent risk factor for incident stroke but not coronary heart disease in middle aged adults. This finding warrants replication and may motivate a search for possible mechanisms that link asthma and stroke.

Relatively little research has been done investigating the potential consequences of asthma for cardiovascular disease (CVD) morbidity and mortality. Approximately 10 million adults in the US are estimated to have asthma,[1] emphasising the potential public health importance of any effect of asthma on the occurrence of CVD. Iribarren *et al*[2] recently reported a risk ratio (RR) of 1.22 (95% CI 1.14 to 1.31) for coronary heart disease (CHD) related death or hospitalisation in asthmatic women compared with non-asthmatic women after adjusting for demographic and CVD risk factors; there was no association in men.

A study of individuals with severe asthma who had been treated regularly with oral corticosteroids found an overall standardised CHD mortality ratio (SMR) of 1.9 (95% CI 1.4 to 2.4) compared with the general population. The SMR was 1.4 (95% CI 0.8 to 2.0) for men and 2.5 (95% CI 1.7 to 3.3) for women.[3] An excess CHD SMR was also found in an Australian study of people with asthma who required admission to hospital for treatment. Men were 33% more likely and women 28% more likely to have died from CHD than people from the general population. The excess mortality was found in all age groups 45–49 years and older.[4] Similarly, in a retrospective cohort study of mortality among World War II veterans hospitalised with bronchial asthma between 1945 and 1947, a RR of 1.46 was found for CHD and 1.51 for cerebrovascular disease compared with men hospitalised for acute nasopharygitis during the same time period.[5] Most studies, however, did not allow for recognised CVD risk factors especially smoking, thus limiting the inferences regarding the possibility of a causal link.

Chronic inflammation, a hallmark characteristic of asthma, may affect levels of CVD risk factors and causally associate asthma and incident CVD. For example, Enright *et al*[6] found cross sectional positive associations between a diagnosis of asthma and fibrinogen and high density lipoprotein (HDL) cholesterol levels but not with prevalent CVD, after controlling for demographic factors, smoking status, and diagnosis of chronic bronchitis and emphysema.

The inflammation of lung tissue encountered in asthma is characterised by eosinophilic infiltration. In a study of participants with forced expiratory volume in 1 second (FEV_1) less than 100% of predicted values, peripheral blood eosinophilia was predictive of death from CHD (RR = 1.7, 95% CI 1.2 to 2.2) and cerebrovascular disease (RR = 2.3, 95% CI 1.4 to 3.8) compared with the absence of eosinophilia.[7]

The long term airway remodelling from the inflammatory response and subsequent repair in asthma can produce irreversible airway obstruction and contribute to a decline in pulmonary function over time.[8–12] Decreased pulmonary function has been linked to an increase in CVD risk[13–17] and might explain any excess CVD mortality among subjects with asthma.

Based on the above literature review, we hypothesised that asthma would be associated with an increased incidence of CHD. As only one relevant study has shown an association between asthma and stroke,[5] we explored this possible association without a set hypothesis in a large, multicentre, prospective study, the Atherosclerosis Risk In Communities (ARIC) study.

METHODS

Study population

The ARIC study is a multicentre prospective study of atherosclerotic diseases. The study design and methods have been described previously.[18] Briefly, from 1987 to the end of 1989, driver's licence lists or residential sampling were used to recruit a mainly biracial population based cohort aged

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazards ratio; RR, risk ratio; SMR, standardised mortality ratio

45–64 years from Forsyth County, North Carolina; Jackson, Mississippi (blacks only); the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland.

Approximately 46% of eligible individuals in Jackson and 65% in the other three communities completed a home interview and clinic examination, giving a total of 15 792 participants. A previous report described non-participants and their characteristics;[19] 93% of those still living returned for re-examination in 1990–2; 86% returned in 1993–5; and 80% returned in 1996–8. The entire cohort is continuously monitored for incident CVD events via annual telephone calls and hospital and death certificate surveillance.

Baseline measurements

The ARIC study assessed the presence of cough, phlegm production, chest wheeze and whistle, breathlessness, and other respiratory symptoms using the American Thoracic Society (ATS) questionnaire.[20] Chronic bronchitis was defined as the presence of chronic cough and phlegm production for more than 3 months a year for 2 consecutive years. Pulmonary function at baseline was measured using digitally recorded forced vital capacity (FVC) and timed expiratory volumes following ATS guidelines.[21] Participants with an FEV_1 less than 80% of predicted value and an FEV_1/FVC ratio of less than 0.7 were classified as having low lung function, borrowing a definition used in the analysis of data from the National Health and Nutrition Examination Survey.[22] Self-reported doctor diagnoses of asthma, emphysema, and bronchitis prior to baseline were recorded. Asthma status (never, former, and current) was determined from the questions: ''Have you ever had asthma?'' ''Was it confirmed by a doctor?'' and ''Do you still have it?'' The question ''Has a doctor ever said you have asthma?'' was also asked at each ARIC visit and most annual follow up telephone calls to determine ''incident asthma'' after baseline for time dependent analysis.

Fasting blood was drawn from an antecubital vein into vacuum tubes containing EDTA (lipids) or a serum separator gel (glucose) by trained technicians. The tubes were centrifuged at 3000 *g* for 10 minutes at 4℃ and the aliquots frozen at −70℃ until analysis within a few weeks. Total cholesterol[23] and HDL cholesterol[24] were measured and low density lipoprotein (LDL) cholesterol was calculated.[25]

Blood pressure was measured three times using a random zero sphygmomanometer and the mean of the last two measurements was used for analysis. Hypertension was defined as systolic pressure ⩾140 mm Hg, diastolic pressure ⩾90 mm Hg, or the use of antihypertensive agents. Waist/hip ratio (W/H ratio) was derived from measurements of the waist at the umbilical level and hips at maximal protrusion rounded to the nearest centimetre. Participants were asked to bring all medications used during the 2 weeks before the baseline visit. The names of the medications were transcribed and later coded into therapeutic classes. Diabetes was identified as a fasting glucose level ⩾126 mg/dl, non-fasting glucose level ⩾200 mg/dl, and/or a history of or treatment for diabetes. Cigarette pack-years were defined as the mean number of cigarettes usually smoked times the number of years smoked. Baseline smoking status was labelled as never, former, or current. Physical activity was assessed using the sports score developed by Baecke *et al*.[26]

Prevalent CHD was defined at baseline, for exclusion, as a history of angina pectoris by the Rose Questionnaire,[27] a self-reported history of a physician diagnosed heart attack, evidence of a prior myocardial infarction by electrocardiogram, or a report of prior cardiovascular surgery or coronary angioplasty. Prevalent stroke was defined at baseline, for exclusion, as a self-reported doctor diagnosed stroke.

Ascertainment of incident events

The incidence of CHD and stroke was ascertained through 2000 by various ongoing surveillance methods and standardised criteria that have been previously described.[28 29] The incidence of CHD for this report was defined as a definite or probable hospital admission for myocardial infarction (MI), definite fatal CHD, coronary revascularisation procedure, or silent MI by electrocardiogram. Stroke was defined by rapid onset of a focal neurological deficit lasting ⩾24 hours or until death, in the absence of a non-stroke cause. A nurse abstracted medical records of potential stroke cases for symptoms, signs, and neuroimaging results. Cases were then classified by a computer algorithm and by a physician as no stroke or as a definite or probable subarachnoid haemorrhage, intracerebral haemorrhage, thrombotic brain infarction, or embolic brain infarction. Differences in classifications were adjudicated by a second physician. Definite stroke required neuroimaging, necroscopic, surgical, or spinal fluid evidence of stroke. End points were classified blind to asthma diagnosis.

Data analysis

Of the 15 792 participants in the ARIC study, 13 501 had no prevalent chronic bronchitis, stroke, or CHD at baseline and were included in this analysis. For descriptive purposes, CVD risk factors, FEV_1, FVC, and the FEV_1/FVC ratio were contrasted for participants reporting current, former and never asthma at ARIC visit 1. The prevalence of wheezing symptoms, cough, breathlessness, and asthma medication use at visit 1 were also described. Race was categorised as black and non-black (the latter group was 99% white).

Follow up time started at the baseline visit and continued until the earliest of the following: an incident CVD event, death, loss to follow up, or 31 December 2000. Hazard ratios (HRs) and 95% confidence intervals (CIs) of CVD were computed based on ever, former, and current versus never asthma using Cox's proportional hazards regression.[30] Lifetime asthma duration at baseline was estimated using age and questions regarding onset and remission of asthma; HRs were calculated among those with less than or more than 20 years of lifetime asthma versus never asthma. In addition, incident asthma was treated as a time dependent variable in which an asthma-free time was calculated for each participant from visit 1 to the end of the follow up period. If participants denied ever having asthma and were asthma-free throughout the follow up period, or if their asthma-free time was greater than their disease follow up time (for example, they had incident stroke or CHD before reporting asthma), they were categorised as non-asthmatic. Adjusted HRs were determined using Cox proportional hazards regression. Finally, asthma was defined among participants who reported having had a wheezing attack that caused shortness of breath from the ATS questionnaire. For each of the above four measures of asthma, analyses were performed using two models—model 1 adjusted for age, race/centre, and sex; and model 2 which included major cardiovascular risk factors. All analyses were completed with SAS version 8.02 statistical software (SAS, Cary, NC, USA).

RESULTS

After excluding those with prevalent chronic bronchitis, stroke and CHD at baseline, 2.7% of participants (2.9% of women, 2.4% of men) at baseline reported current asthma diagnosed by a doctor and 2.5% of participants reported former asthma, giving a prevalence of 5.2% for ever asthma (table 1). Among men, whites had a higher prevalence of asthma than blacks, but race was not associated with asthma diagnosis in women. In both men and women a diagnosis of asthma was significantly associated ($p<0.05$) with greater

Table 1 Sex specific mean (SD) or n (%)* of risk factors according to current, former, or never asthma diagnosis: ARIC baseline, 1987–9

	Women			Men		
Variable	**Current asthma (N = 227)**	**Former asthma (N = 186)**	**Never asthma (N = 7287)**	**Current asthma (N = 139)**	**Former asthma (N = 157)**	**Never asthma (N = 5505)**
Age (years)	54 (6)	54 (6)	54 (5.8)	54 (6.0)	54 (6.1)	54 (6)
Cigarettes (pack years)	11.3 (17.1)	11.7 (17.3)	9.5 (15.9)	20.9 (25.7)	19.0 (21.7)	21.0 (23.7)
BMI (kg/m^2)	29.0 (6.4)	28.1 (6.3)	27.8 (6.1)	27.4 (4.3)	27.0 (3.5)	27.5 (4.2)
W/H ratio	0.91 (0.08)	0.90 (0.08)	0.89 (0.08)	0.97 (0.07)	0.96 (0.06)	0.96 (0.05)
LDL cholesterol (mg/dl)	130 (41)	136 (38)	135 (41)	136 (41)	136 (32)	139 (37)
HDL cholesterol (mg/dl)	59 (18)	58 (16)	58 (17)	46 (12)	45 (13)	45 (14)
Fibrinogen (mg/dl)	314 (66)	312 (71)	306 (64)	306 (67)	287 (57)	294 (63)
Systolic BP (mm Hg)	123 (20)	121 (19)	120 (19)	123 (17)	122 (15)	122 (18)
Sport score	2.27 (0.72)	2.37 (0.72)	2.32 (0.75)	2.58 (0.89)	2.65 (0.91)	2.58 (0.81)
FEV_1 (l)	2.01 (0.61)	2.31 (0.52)	2.45 (0.48)	2.84 (0.89)	3.25 (0.74)	3.38 (0.72)
FVC (l)	2.89 (0.70)	3.13 (0.63)	3.22 (0.61)	4.36 (0.91)	4.59 (0.92)	4.59 (0.85)
FEV_1/FVC	69.0 (10.8)	73.6 (7.6)	76.0 (7.1)	64.1 (12.1)	70.7 (9.0)	73.8 (8.1)
Low lung function*†	71 (31)	23 (12)	476 (7)	56 (40)	31 (20)	714 (13)
Race*						
Black	86 (38)	53 (29)	2222 (31)	23 (17)	32 (20)	1317 (24)
White	141 (62)	133 (72)	5065 (70)	116 (84)	125 (80)	4188 (76)
Smoking status*						
Never	115 (51)	100 (54)	3918 (54)	47 (34)	50 (32)	1661 (30)
Former	60 (26)	42 (23)	1643 (23)	68 (49)	75 (48)	2417 (44)
Current	52 (23)	44 (24)	1719 (24)	24 (17)	32 (20)	1425 (26)
Diabetes*	48 (21)	22 (12)	775 (11)	15 (10)	15 (10)	566 (10)
Hypertension medication*	84 (37)	54 (29)	1838 (25)	39 (28)	35 (23)	1125 (21)
Less than high school education*	62 (27)	51 (27)	1635 (22)	65 (47)	67 (43)	2296 (42)

BMI, body mass index; W/H ratio, waist to hip ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
†Low lung function defined as FEV_1 <80% of predicted values and an FEV_1/FVC ratio <0.7.

antihypertensive medication use and fibrinogen, and lower lung function. In women asthma was also related to a higher body mass index (BMI) and diabetes prevalence while, in men, it was associated with smoking status and greater W/H ratio. Asthma was not significantly associated with the sports score, age, pack years, HDL cholesterol, LDL cholesterol, or systolic blood pressure in men or women.

In the ARIC study recurrent wheeze, cough, and shortness of breath varied little with sex so comparisons were made between all participants with respect to asthma category (table 2). Participants reporting current asthma were far more likely to report wheeze associated with shortness of breath or recurrent wheeze, were nearly three times more likely to report cough, and about twice as likely to have shortness of breath with exertion as participants without asthma. Approximately 46% of participants with current asthma brought asthma medications to visit 1. Participants with former asthma reported intermediate levels of these variables.

Compared with never having had asthma, neither ever (model 2 HR = 0.87, 95% CI 0.66 to 1.14), former (HR = 1.04, 95% CI 0.73 to 1.49), nor current asthma (HR = 0.69, 95% CI 0.46 to 1.05) were associated with the incidence of CHD in the ARIC study (table 3). In men, current asthma was found to be associated with a lower incidence of CHD after multivariate adjustment for major cardiovascular risk factors (model 2 HR = 0.52, 95% CI 0.29 to 0.95). This association was not seen in women (HR = 0.92, 95% CI 0.52 to 1.76) or in black (HR = 0.59, 95% CI 0.24 to 1.45) or white subjects (HR = 0.73, 95% CI 0.47 to 1.16). Duration of asthma was also not associated with CHD. Treating asthma status as a time dependent covariate, asthma at baseline or follow up was found not to be related to the incidence of CHD (model 2 HR = 0.88, 95% CI 0.69 to 1.11). When asthma was defined as a wheeze attack that caused shortness of breath, it was not associated with the incidence of CHD (model 2 HR = 1.02, 95% CI 0.84 to 1.24).

The data in table 4 show that, compared with never having had asthma, ever having asthma was associated with an increased incidence of stroke in both model 1 (HR = 1.65, 95% CI 1.17 to 2.33) and after risk factor adjustment in model 2 (HR = 1.50, 95% CI 1.04 to 2.15). Participants with current

Table 2 Prevalence of pulmonary symptoms and asthma medication use according to current asthma diagnosis: ARIC baseline, 1987–9

	Current asthma (N = 366)	**Former asthma (N = 343)**	**Never asthma (N = 13088)**
Does your chest ever sound wheezy or whistling apart from colds?	63%	18%	7%
Does your chest sound wheezy or whistling most days or nights?*	32%	15%	16%
Have you ever had an attack of wheezing that made you feel short of breath?	84%	58%	7%
Have you had two or more such episodes?*	93%	79%	59%
Do you usually have a cough?	24%	10%	8%
Are you troubled by shortness of breath when hurrying on the level or walking up a slight hill?	50%	29%	27%
Brought asthma medication to visit 1	46%	3%	<1%

*These questions were asked only of participants with an affirmative answer to the preceding question.

Table 3 Incidence rates and adjusted hazard ratios (HRs) of CHD in relation to asthma variables: ARIC, 1987–2000

Asthma definition	No of events	Incidence rate*	Model 1 HR†	95% CI	Model 2 HR‡	95% CI
Never	1185	8.12	1.0	–	1.0	–
Ever	64	7.81	0.95	0.74 to 1.23	0.87	0.66 to 1.14
Former	35	8.85	1.04	0.75 to 1.46	1.04	0.73 to 1.49
Current	28	6.81	0.86	0.59 to 1.26	0.69	0.46 to 1.05
Asthma duration						
Never	1185	8.12	1.0	–	1.0	–
Current or former						
⩽20 years	44	8.74	1.06	0.78 to 1.44	1.03	0.75 to 1.42
>20 years	16	6.22	0.79	0.48 to 1.29	0.50	0.34 to 1.06
Time dependent						
No asthma	1164	8.38	1.0	–	1.0	–
Asthma	85	5.51	0.93	0.74 to 1.15	0.88	0.69 to 1.11
Wheeze attack						
No wheeze attack with shortness of breath	1124	8.09	1.0	–	1.0	–
Wheeze attack with shortness of breath	126	8.16	1.07	0.89 to 1.26	1.02	0.84 to 1.24

Maximum number of person-years was 154 315 and maximum number of events was 1250. Some subgroups have less because of missing data.
*Crude (per 1000 person-years).
†Model 1 adjusted for age, sex, and race/centre.
‡Model 2 adjusted for age, sex, race/centre, HDL cholesterol, LDL cholesterol, systolic blood pressure, hypertension medication use, smoking status, pack years, W/H ratio, diabetes diagnosis, and sport score.

asthma also had significantly higher rates of stroke than those without asthma using model 1 (HR = 1.93, 95% CI 1.23 to 3.02), but this was not statistically significant in model 2 (HR = 1.55, 95% CI 0.95 to 2.52). In model 2, black subjects with current asthma experienced significantly higher rates of stroke than those without asthma (HR = 1.95, 95% CI 1.02 to 3.76). This association was not observed among white subjects (HR = 1.11, 95% CI 0.52 to 2.36). Similarly, women with current asthma were found to have higher risk for stroke (HR = 2.20, 95% CI 1.25 to 3.90) but this was not the case for men (HR = 0.72, 95% CI 0.26 to 1.95). However, when multiplicative interaction terms of asthma by race and sex were added stepwise to the models, none proved statistically significant. Asthma was associated with a twofold higher rate of stroke in model 1 among patients with asthma of 20 years or more, but not in model 2 (table 3). In the time dependent analysis, asthma was associated with stroke in both models 1 and 2 (HR = 1.43, 95% CI 1.03 to 1.98). Asthma defined as wheezing attack with shortness of breath was also associated with an increased incidence of stroke (HR = 1.56, 95% CI 1.18 to 2.06) in model 2. Ever having asthma was not individually associated with ischaemic stroke (model 2 HR = 1.37, 95% CI 0.91 to 2.06) or haemorrhagic stroke (model 2 HR = 2.03, 95% CI 0.72 to 5.78).

In a supplemental analysis, predicted FEV_1 was entered into model 2 to determine whether airflow limitation might explain the association between asthma and the incidence of stroke. The addition of FEV_1 somewhat attenuated the association between ever having asthma and the incidence of stroke (HR = 1.42, 95% CI 0.94 to 2.14 compared with HR of 1.50 in table 4). In another supplemental analysis the education level and plasma fibrinogen were entered into model 2 for CHD and stroke and the results in table 4 were somewhat attenuated with the HR of stroke for ever having asthma falling to 1.38 (95% CI 0.95 to 2.01).

Although the main analysis of this study attempted to control for the effects of smoking by using regression techniques and excluding participants with symptoms of chronic bronchitis, analyses were also performed excluding former and current smokers. Using model 2, ever having asthma in never smokers was not associated with CHD (397

Table 4 Incidence rates and adjusted hazard ratios (HRs) of stroke in relation to asthma variables: ARIC, 1987–2000

Asthma definition	No of events	Incidence rate*	Model 1 HR†	95% CI	Model 2 HR‡	95% CI
Never	403	2.69	1.0	–	1.0	–
Ever	35	4.22	1.65	1.17 to 2.33	1.50	1.04 to 2.15
Former	14	3.50	1.38	0.81 to 2.35	1.44	0.84 to 2.46
Current	20	4.80	1.93	1.23 to 3.02	1.55	0.95 to 2.52
Asthma duration						
Never	403	2.69	1.0	–	1.0	–
Current or former						
⩽20 years	17	3.33	1.38	0.85 to 2.24	1.40	0.86 to 2.28
>20 years	13	5.02	2.07	1.16 to 3.49	1.53	0.81 to 2.87
Time dependent						
No asthma	394	2.77	1.0	–	1.0	–
Asthma	44	2.79	1.44	1.06 to 1.97	1.43	1.03 to 1.98
Wheeze attack						
No wheeze attack with shortness of breath	374	2.62	1.00	–	1.00	–
Wheeze attack with shortness of breath	64	4.09	1.57	1.21 to 2.06	1.56	1.18 to 2.06

Maximum number of person-years was 13 522 and maximum number of events was 438. Some subgroups have less because of missing data.
*Crude (per 1000 person-years).
†Model 1 adjusted for age, sex, race/centre.
‡Model 2 adjusted for age, sex, race/centre, HDL cholesterol, LDL cholesterol, systolic blood pressure, hypertension medication use, smoking status, pack years, W/H ratio, diabetes diagnosis, and sport score.

events, HR = 1.05, 95% CI 0.68 to 1.62) or stroke (173 events, HR = 1.26, 95% CI 0.68 to 2.33).

DISCUSSION

The results of this population based prospective study show that, contrary to our hypothesis, self-reported doctor diagnosed asthma was not associated with the incidence of CHD. Asthma was positively (but modestly) associated with the 14 year incidence of stroke in middle aged women and men. Subgroup analysis showed that this association was somewhat stronger in black subjects and women, although these possible interactions were not statistically significant. The association between asthma and stroke was stronger for the overall sample and largely absent among never smokers, so the asthma-stroke association may in part be due to residual confounding by smoking. To our knowledge, only one other study[5] found a positive association between asthma and stroke, although other studies have linked conditions related to asthma—such as greater eosinophilia[7] and low lung function[14 15]—with an increased risk of stroke. For the most part, the positive association between asthma and the incidence of stroke was not affected by the addition of low lung function variables into the regression models. This suggests that asthma may be associated with a greater stroke risk independent of basal lung function.

There are several other plausible mechanisms for an increased risk of stroke among asthmatic subjects. Blood pressure is known to increase during and after acute asthma attacks, which may also increase the risk of stroke.[31] Asthmatic subjects sometime lose consciousness during a severe exacerbation, probably due to cerebral hypoxia. In rare near fatal asthma exacerbations, the hypoxic episode may be long and severe enough to damage cerebral tissue; stroke-like symptoms have been reported after severe asthma attacks.[32 33] The hypoxia that occurs during severe asthma exacerbations may differentially affect stroke and CHD; emergency room studies of coronary function during exacerbations have shown a lack of life threatening arrhythmias.[34] However, information from asthma related emergency hospital admissions is not available in the ARIC study. Chronic airflow limitation as opposed to severe hypoxic episodes may also affect stroke morbidity, and reduced FEV_1 has been associated with subclinical cerebral abnormalities in the ARIC study.[16] In our analysis, adjusting for FEV_1 somewhat attenuated the association between asthma and stroke, suggesting that impaired airflow may contribute. The inflammation sensitive plasma protein fibrinogen has been associated with an increased incidence of stroke,[35] but adjustment for fibrinogen had no effect on our results. Other possible mechanisms by which asthma might increase the risk of stroke are via pulmonary hypertension, atrial fibrillation, or the effects of asthma medication. However, pulmonary hypertension and atrial fibrillation were rare in this cohort, as was use of individual asthma mediations, thus precluding meaningful analysis.

Our findings, which largely show no association between asthma and CHD, contrast with some previous studies and with our expectation. Previous investigations included persons discharged from hospital with a diagnosis of asthma[2] or asthmatics treated with oral corticosteroids,[3] probably indicating greater average asthma severity than found in the ARIC population. Although previous studies controlled less well for confounding variables, the addition of these variables did not alter the general conclusions about associations between asthma and CHD or stroke in ARIC participants. In our subgroup analysis by sex, men with current asthma appeared to have half the CHD risk of men without asthma. However, we perceive no biological reason why this might be so for men and not for women. This is probably a chance subgroup finding, arising in part from multiple testing.

It is unclear why asthma might increase the risk of stroke but not of CHD. If the association with stroke was spuriously caused by some unadjusted confounding factor, it would have to be specific for stroke and not CHD. One such potential confounder might be childhood socioeconomic position which may be more strongly related to stroke than CHD.[36] If the asthma association with stroke is causal, then it implies a causal pathway that would not be operating for CHD.

One concern of our analysis is the validity of self-reported physician diagnosed asthma in a middle aged population. Asthma is diagnosed clinically on the basis of respiratory symptoms and typically would be more accurately classified in a younger cohort. Those reporting asthma in the ARIC study on average also reported much more wheeze, cough, breathlessness, and asthma medication use. This suggests reasonable validity for our asthma classification.

Some people with asthma may be undiagnosed or they might confuse other chronic lung conditions with what they reported as asthma. To enhance the specificity of our asthma classification we excluded subjects with symptoms of chronic bronchitis. This may have excluded subjects with the hypersecretory phenotype of asthma, so our findings may be generalisable to ''non-secretory'' asthma only. On the other hand, many people reporting asthma, and included in the analysis, may have asthma combined with other lung diseases. If these other lung diseases also result in an increased stroke risk, our reported risk estimates for stroke could be inaccurate. On the other hand, a variety of definitions of asthma were used and the results were largely consistent, suggesting the association was robust. Nonetheless, random misclassification of asthma would tend to have attenuated our estimate of association between asthma and CVD.

A second major concern of our study was the relatively low statistical power for subgroup analysis for both stroke and CHD. The small number of stroke events and wide confidence intervals also mean that type I error could perhaps account for our findings for stroke.

In conclusion, this study provides new evidence for an association between asthma and incident stroke, but not CHD, after multivariate adjustment for major CVD risk factors. If this observed association is causal and not due to residual confounding, it adds to the significant burden that is imposed by asthma, a highly prevalent condition in the general population. The prevalence of persistent neurological changes in asthmatic patients who lose consciousness and require emergency intubation merits greater investigation. The biological mechanisms by which subjects with asthma may have an excess risk of stroke require further study.

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