Asthma predicts cardiovascular disease events
The Multi-Ethnic Study of Atherosclerosis

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Objectives—To identify and characterize an association between persistent asthma and cardiovascular disease (CVD) risk in the Multi-Ethnic Study of Atherosclerosis (MESA).

Approach and Results—MESA is a longitudinal prospective study of an ethnically diverse cohort of individuals free of known CVD at its inception. The presence and severity of asthma were assessed in the MESA at examination 1. Persistent asthma was defined as asthmatics using controller medications (inhaled corticosteroids, leukotriene inhibitors, and oral corticosteroids) and intermittent asthma as asthmatics not using controller medications. Participants were followed up for a mean (SD) of 9.1 (2.8) years for development of incident CVD (coronary death, myocardial infarction, angina, stroke, and CVD death). Multivariable Cox regression models were used to assess associations of asthma and CVD. The 6792 participants were 62.2 (SD, 10.2) years old: 47% men (28% black, 22% Hispanic, and 12% Chinese). Persistent asthmatics (n=156), compared with intermittent (n=511) and nonasthmatics (n=6125), respectively, had higher C-reactive protein (1.2 [1.2] versus 0.9 [1.2] versus 0.6 [1.2] mg/L) and fibrinogen (379 [88] versus 356 [80] versus 345 [73] mg/dL) levels. Persistent asthmatics had the lowest unadjusted CVD-free survival rate of 84.1%, 95% confidence interval (78.9%–90.3%) compared with intermittent asthmatics 91.1% (88.5%–93.8%) and nonasthmatics 90.2% (89.4%–91%). Persistent asthmatics had greater risk of CVD events than nonasthmatics (hazard ratio [95% confidence interval], 1.6 [1.01–2.5]; P=0.040), even after adjustment for age, sex, race, CVD risk factors, and antihypertensive and lipid medication use.

Conclusions—In this large multiethnic cohort, persistent asthmatics had a higher CVD event rate than nonasthmatics. (Arterioscler Thromb Vasc Biol. 2015;35:1520-1525. DOI: 10.1161/ATVBAHA.115.305452.)

Key Words: asthma ■ atherosclerosis ■ epidemiology ■ risk factors

Asthma is an inflammatory disorder that afflicts >25 million individuals in the United States. The increasing prevalence of asthma during the past decade poses a significant public health burden. Current pharmacotherapeutic management of asthma targets the underlying inflammatory mechanism of the disease. Cardiovascular disease (CVD) is the leading cause of death among adults in the United States. Similar to asthma, inflammation mediates the initiation and progression of atherosclerosis and is intricately involved in plaque rupture and acute CVD events. Individuals with other chronic inflammatory diseases, such as human immunodeficiency virus infection and rheumatoid arthritis, are at increased CVD risk because they are with higher levels of subclinical systemic inflammation. Animal models suggest that increased leukotriene production may cause an overlap between the inflammatory pathogenesis of asthma and CVD. Leukotrienes are potent proinflammatory substances found in excess in asthmatic bronchioles; emerging data indicate that leukotrienes may also be active in atherosclerotic plaques. Despite the shared inflammatory pathophysiology of asthma and CVD, few studies have investigated a potential association between asthma and CVD. To our knowledge, our study represents the largest contemporary, multiethnic, long-term, prospective cohort study of asthma and CVD.
to analyze the association of asthma and CVD. We hypothesized that persistent asthma is associated with higher CVD risk in the Multi-Ethnic Study of Atherosclerosis (MESA).

Materials and Methods
Materials and Methods are available in the online-only Data Supplement.

Results
Descriptive Characteristics
The 6792 MESA participants were followed up for a mean (SD) 9.1 (2.8) years for development of CVD. At baseline, participants were 62.2 (10.3) years old, and 47.1% were men, 38.4% were whites, 27.8% blacks, 22.0% Hispanic, and 11.8% Chinese (Table 1). The 156 participants with persistent asthma and the 511 participants with intermittent asthma were compared with the 6125 participants without asthma. The distribution of risk factors between those with persistent asthma and those with intermittent asthma differed slightly compared with those without asthma (Table 1). Those with asthma were more likely to be women (64% versus 52%) and on antihypertensive medications (41% versus 37%).

Asthma and Cardiovascular Events
A total of 642 CVD events (249 hard end point coronary heart disease events, 188 angina, 167 stroke, 3 stroke deaths, and 35 CVD deaths) occurred during the observation period. The incidence rate for CVD was higher in those with persistent asthma. The 10-year CVD-free survival rates were 89.5% (95% confidence interval [CI], 87.0%–91.9%) for those with asthma and 90.2% (89.4%–91.0%) for those who did not report a diagnosis of asthma. Among those with asthma, the 10-year CVD-free survival rates were 84.1% (78.4%–90.3%) for those with persistent asthma and 91.1% (88.5%–93.8%) for those with intermittent asthma. In multivariate models adjusted for potential confounders, having persistent asthma was associated with a significantly higher risk of CVD events. In models adjusted for age, race, and sex (Table 2, model 1), participants with persistent asthma had a higher risk of CVD events (hazard ratio [HR; 95% CI], 1.72 [1.14–2.59]; P=0.01; Figure). This association persisted in models fully adjusted for potential confounders (HR [95% CI], 1.59 [1.01–2.5]; P=0.04; Table 2, model 4). Participants with intermittent asthma, however, had no difference in CVD events compared

Table 1. Baseline and Follow-Up Descriptive Statistics

<table>
<thead>
<tr>
<th>Variables</th>
<th>No Asthma, n=6125</th>
<th>Intermittent Asthma, n=511</th>
<th>Persistent Asthma, n=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.3 (10.2)</td>
<td>59.7 (10.1)*</td>
<td>63.6 (10.1)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.1 (5.3)</td>
<td>30.0 (6.4)*</td>
<td>30.4 (7.0)*</td>
</tr>
<tr>
<td>Male, sex, n (%)</td>
<td>2962 (48.4)</td>
<td>194 (38.0)*</td>
<td>46 (29.5)*</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td>2354 (38.4)</td>
<td>187 (36.6)</td>
<td>68 (43.6)</td>
</tr>
<tr>
<td>Whites</td>
<td>2354 (38.4)</td>
<td>187 (36.6)</td>
<td>68 (43.6)</td>
</tr>
<tr>
<td>Chinese</td>
<td>755 (12.3)</td>
<td>40 (7.8)*</td>
<td>8 (5.1)*</td>
</tr>
<tr>
<td>Blacks</td>
<td>1671 (27.3)</td>
<td>161 (31.5)*</td>
<td>55 (35.3)*</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1345 (22.0)</td>
<td>123 (24.1)</td>
<td>25 (16.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>3085 (50.5)</td>
<td>251 (49.4)</td>
<td>73 (47.4)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>2226 (36.4)</td>
<td>189 (37.2)</td>
<td>63 (40.9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>797 (13.0)</td>
<td>68 (13.9)</td>
<td>18 (11.7)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>193.98 (35.3)</td>
<td>195.2 (39.4)</td>
<td>196.87 (38.0)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dL</td>
<td>50.8 (14.9)</td>
<td>51.2 (14.4)</td>
<td>56.12 (14.6)*</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>126.62 (21.5)</td>
<td>125.6 (21.9)</td>
<td>129.1 (20.4)</td>
</tr>
<tr>
<td>Family history of coronary heart disease, n (%)</td>
<td>2437 (42.4)</td>
<td>217 (44.7)</td>
<td>70 (49.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>756 (12.4)</td>
<td>76 (14.9)*</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>In income, &gt;$35,000/y, n (%)</td>
<td>3235 (55.1)</td>
<td>287 (58.0)</td>
<td>88 (57.9)</td>
</tr>
<tr>
<td>Antihypertension medication use, n (%)</td>
<td>2255 (36.8)</td>
<td>193 (37.8)*</td>
<td>78 (50.0)*</td>
</tr>
<tr>
<td>Lipid-lowering medication use, n (%)</td>
<td>978 (16.0)</td>
<td>81 (15.9)</td>
<td>36 (23.1)*</td>
</tr>
<tr>
<td>Oral corticosteroid medication use, n (%)</td>
<td>72 (1.2)</td>
<td>0 (0)</td>
<td>32 (20.5)</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist medication use, n (%)</td>
<td>7 (0.1)</td>
<td>0 (0)</td>
<td>45 (28.9)</td>
</tr>
<tr>
<td>Inhaled corticosteroid medication use, n (%)</td>
<td>28 (0.5)</td>
<td>0 (0)</td>
<td>118 (75.6)</td>
</tr>
</tbody>
</table>

*Age adjusted P<0.05, no asthma group as reference.
with those without asthma in unadjusted (HR [95% CI], 1.13 [0.83–1.50]; \( P = 0.45 \)) and fully adjusted models (HR [95% CI], 1.10 [0.78–1.48]; \( P = 0.66 \)). We found no sex or race interactions with asthma and CVD outcomes (data not shown). Associations of asthma with stroke and all-cause mortality are available in Table I in the online-only Data Supplement.

Asthma and Inflammatory Biomarkers

Inflammatory markers were analyzed to assess the burden of systemic inflammation between the groups with persistent asthma, intermittent asthma, and those without asthma. Those with persistent asthma had the highest levels of systemic inflammatory markers (Table 3). Persistent asthmatics, compared with intermittent asthmatics and nonasthmatics, respectively, had higher age-adjusted levels of C-reactive protein (CRP: 1.2 [1.2] versus 0.9 [1.2] versus 0.6 [1.2] mg/L) and fibrinogen (379 [88] versus 356 [80] versus 345 [73] mg/dL) mean differences were significant using Tukey criteria. Interleukin-6 levels were the highest in persistent asthmatics 0.44 (0.61) compared with intermittent asthmatics 0.25 (0.67) and no asthma 0.20 (0.66; Table 3). When CRP and \( \beta \)-dimer were added to the a priori fully adjusted model, they were not statistically significant predictors of CVD outcomes and did not attenuate the asthma effect. When added to these models, interleukin-6 and fibrinogen were statistically significant predictors of CVD outcomes but did not notably attenuate the asthma effect (the HR was 1.55–1.59 in all models).

Discussion

After a decade of prospective observation, persistent asthmatics had a 1.6-fold higher risk of CVD events than nonasthmatics in models fully adjusted for potential confounders. Despite being treated for their asthma, persistent asthmatics on controller medications had the highest burden of systemic inflammation. To our knowledge, our study represents the largest contemporary, multiethnic, long-term, prospective cohort to analyze the association of asthma and CVD. Previous studies investigating the association between asthma and CVD have been limited by case–control and cross-sectional designs, studied retrospective insurance claims, or contained a homogenous group of individuals with older asthma treatments.\(^\text{11–18}\) Furthermore, some studies noted no association between asthma and CVD or described limited associations of women only or associations only with stroke.\(^\text{12,15,17}\) Two previous reports from the population-based Atherosclerosis Risk in Communities (ARIC) study cohort investigated the association of asthma with incident CVD. In the first report, there was an association of stroke with asthma with a higher risk in women but no association with coronary heart disease.\(^\text{12}\) In the second, there was an association of coronary heart disease and stroke among women with adult-onset asthma but not men.\(^\text{18}\) We observed an association of persistent asthmatics, but not intermittent asthmatics, with CVD events.

Our study results and design differ from the previous studies in several ways. First, we did not observe effect modification by female sex.\(^\text{11,14,18}\) The 3 investigations that observed effect modification by sex had more participants, but 2 used insurance claims databases and the other, a report from the ARIC study, was discussed above. Our study may not have had enough
 poses, they are prone to upcoding to more severe conditions, ing. Because these codes are primarily used for billing pur-

ers, such as using International Classification of Diseases, Ninth Revision codes to identify CVD events, all claims databases do not have patient-level laboratory, physical data. Also, we found associations between hs-CRP, airway hyper-responsive-

ness, and forced expiratory volume in 1 s among individuals free of CVD, suggesting that systemic inflammation also effects lung function. High-sensitivity CRP levels also have been used as a surrogate marker of disease control in asthmas, with lower levels indicating better disease control.24

In MESA, participants with persistent asthma had the high-
est level of systemic inflammatory markers. Furthermore, there was a graded relationship between those without asthma having the lowest levels of inflammation, those with inter-
nitant asthma having intermediate levels, and those with persistent asthma having the highest levels of inflammatory markers. Previous studies have demonstrated that treatment of asthma with anti-inflammatory medications, such as inhaled corticosteroids, results in lower levels of markers of systemic inflammation.25,26 The identification of elevated inflammatory markers among participants with persistent asthma in our study is hypothesis-generating; however, we note that
their addition to the models did not attenuate the relationship between persistent asthma and CVD events; so, we cannot imply a mediated effect. This may be because of partial treatment of inflammation by controller medications. It is also possible that asthma medications have adverse CVD effects via their effects on glucocorticoid metabolism, lipid metabolism, or in the case of long-acting β-antagonists, sympathetic activation. The elevated levels of systemic inflammatory markers observed among persistent asthmatics may have contributed to the increased CVD risk in this group; however, further studies are needed to elucidate this mechanism.

**Limitations**

Despite the numerous strengths of this study, there are some limitations. As an observational study, the described associations do not confirm causation. Asthma was defined by self-report and may be prone to misclassification bias, although we classified participants by use or nonuse of controller medications to improve the specificity of the diagnosis. We did not have lung function parameters at the baseline examination, and given the heterogeneous nature of asthma severity, according to current guidelines, we defined the use of controller medications as an indicator of more severe disease. The graded levels of inflammatory markers among the asthma classifications in this report support our approach, as those using controller medications had more systemic inflammation, and if anything, misclassification should lead to a null bias. The primary hypothesis of this study was to investigate the association between persistent asthma and CVD events. Given the design of MESA, this study cannot delineate the mechanism that led to higher CVD rates. Although we treated the use of controller medications as a marker of more severe asthma and that supposition was supported by our biomarker data, we cannot exclude the possibility that controller or other asthma medications increased CVD risk. Certain classes of controller medications have been associated with CVD risk, especially among individuals with chronic obstructive pulmonary disease; however, these associations have been inconsistent and a few studies have noted a reduction in CVD events with the use of inhaled corticosteroids. Regression models were adjusted for measured risk factors and sociodemographic variables; however, unmeasured lifestyle exposures and risk factors that may be specific to each ethnicity cannot be accounted for. MESA is a United States cohort; so, the generalizability of these findings to populations outside the United States may be limited. The small number of CVD events limited our power to detect potential effect modification by sex or race. Finally, asthma is a heterogeneous disease that has complex genetic and environmental factors; thus, generalizability to all subtypes is uncertain. To disentangle the limitations of observational studies, such as MESA, it would be useful if the large, randomized clinical trials of asthma medications had longer durations, measured inflammatory biomarkers, and formally adjudicated CVD events.

**Conclusions**

Persistent asthmatics taking daily controller medications were at increased risk of CVD events. Persistent asthmatics demonstrated higher levels of systemic inflammation than nonasthmatics or intermittent asthmatics. Given the increasing public health burden of asthma and the pathophysiological overlap of asthma and CVD, further investigations into this association are needed.

**Acknowledgments**

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**Disclosures**

None.

**References**


Asthma is a significant public health burden afflicting >25 million individuals in the United States. Asthma and cardiovascular disease share common inflammatory pathophysiology; however, an association of asthma and cardiovascular disease has not been identified in a contemporary, multiethnic cohort. In this study, we found that persistent asthmatics compared with nonasthmatics had a higher risk of a cardiovascular disease event over almost a decade of observation. Despite treatment with controller medications, persistent asthmatics also had higher levels of systemic inflammatory markers compared with mild asthmatics and nonasthmatics. These findings support the need for cardiovascular disease prevention and awareness of traditional risk factors and risk factor reduction in asthmatics.
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Materials and Methods

Participants
MESA is a prospective cohort study of 6,814 participants free of known CVD at baseline. The aim of MESA is to investigate risk factors and subclinical CVD progression in an ethnically diverse population. MESA enrolled participants from six different field centers located in Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota. Details of MESA’s design have been published previously. The study was approved by the institutional review boards of all the MESA field centers, the University of Washington Data Coordinating Center, and the University of Wisconsin School of Medicine and Public Health. All participants provided informed consent. Our analysis included the 6,792 participants without missing data at baseline.

Asthma Definition
Consistent with other studies, in the absence of pulmonary function testing, the best method to define asthma is self-reported physician-diagnosed asthma. The examiner asked the participant “Has a doctor ever told you that you have [asthma]?” Self-reported physician-diagnosed asthma questions have been found to have the highest specificity of any other questions for asthma diagnosis. Asthma was defined as a self-reported physician-diagnosed history of asthma at baseline (exam 1). Because asthma is a heterogeneous condition with a broad spectrum of severity, we further stratified asthma into two subgroups: persistent asthma (defined as those with asthma on controller medications) and intermittent asthma (those with asthma not taking controller medications). Consistent with current asthma treatment guidelines, persistent asthmatics were those treated with step 2-6 therapies such as daily use of inhaled corticosteroids, oral corticosteroids, and/or leukotriene inhibitors to modify disease activity. Participants brought medication used in the past two weeks to the exam for verification.

Cardiovascular Disease Event Assessment
The outcome measure was occurrence of a CVD event during the study follow-up period. CVD events were defined as the occurrence of definite and probable myocardial infarction, resuscitated cardiac arrest, angina, stroke as well as atherosclerotic coronary heart disease death, stroke death and other cardiovascular disease death. Because of potential symptom overlap between asthma and congestive heart failure and potential for misclassification bias, congestive heart failure was not used as an endpoint. Events were identified through regularly scheduled telephone follow up calls with participants in intervals of 9-12 months, participant notification at subsequent MESA exam visits, or through the National Death Index search. Once an event was identified, death certificates and medical records including outpatient and hospitalization records were requested and reviewed by the adjudication committee. Two independent physician adjudicators blinded to participant study data reviewed each event record for classification. Event criteria for MESA were adopted from the Atherosclerosis Risk in Communities Study, the Cardiovascular Health Study, and the Women's Health Initiative. Methods of adjudicating MESA CVD events have been published previously. Complete details of event coding and protocols in MESA can be found at: http://www.mesa-nhlbi.org.

Risk Factors
Baseline laboratory samples were collected following a 12 hour fast. All laboratory analyses were performed at a central lab (University of Minnesota for lipids and University of Vermont for other laboratory measurements) using methods that have been previously reported. Total and high-density lipoprotein cholesterol were measured in EDTA plasma using
a cholesterol oxidase method (Roche Diagnostics, Indianapolis, IN 46250) on a Roche COBAS FARA centrifugal analyzer. The coefficients of variation (CV for these methods were 1.6% and 2.9%, respectively. Serum glucose was measured by rate reflectance spectrophotometry using thin film adaptation of the glucose oxidase method on the Vitros analyzer (Johnson and Johnson Clinical Diagnostics, Inc, Rochester, NY 14650), with a CV of 1.1%. Interleukin-6 (IL-6) was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN) with a CV of 6.3%. C-reactive protein (CRP) and fibrinogen were measured on the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL). For CRP, a particle-enhanced immunonephelometric assay was used, for fibrinogen quantification followed an immunochemical reaction. The intra-assay and inter-assay CVs for CRP ranged from 2.3%-4.4% and 2.1-5.7%. For fibrinogen the intra-assay and inter-assay CVs were 2.7% and 2.6%, respectively. D-dimer was measured using an immunoturbidimetric assay (Liatest D-DI; Diagnostica Stago, Parsippany, NJ) on the Sta-R analyzer (Diagnostica Stago, Parsippany, NJ). Diabetes mellitus was defined according to the American Diabetes Association. Antihypertensive and statin medication use were verified during each exam visit. Systolic blood pressure was measured after the participant had been at rest for 5 minutes in the right arm using a Dinamap Monitor Pro 100® automated oscillometric sphygmomanometer (Critikon). Three readings were obtained and the average of the last two readings was used for analysis.

**Statistical Methods**

Baseline descriptive statistics are reported as means (standard deviations) for continuous and percentages for categorical variables. Unadjusted CVD-free survival rates comparing participants with persistent asthma, intermittent asthma, and those without asthma were calculated using the Kaplan-Meier method. Unadjusted incident CVD rates were calculated for those with persistent asthma with intermittent asthma, and those without asthma. Cox proportional hazard models were utilized to compare the survival distribution of the three groups while adjusting for potential confounders. The proportional hazards assumption was evaluated using Schoenfield's test. A series of models were created by adding potential known biological confounders into each model. Model 1 adjusted for age, race, and sex. Model 2 adjusted additionally for total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking history, and diabetes mellitus. Model 3 included the confounders in model 3 and baseline use of lipid lowering and/or anti-hypertensive medications. Model 4, the primary pre-specified analysis, included the covariates in model 3 and body-mass index, family history and income. Sensitivity analyses were performed evaluating effect modification by gender. Statistical significance was set at a two-sided p<0.05. Analyses were performed in SAS (Version 9.2, Cary, NC: SAS. Institute Inc.).
REFERENCES


### Table I. Association of Asthma with Stroke and all-cause mortality

<table>
<thead>
<tr>
<th></th>
<th>Persistent Asthma *</th>
<th></th>
<th>Intermittent Asthma *</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P value</td>
<td>Hazard Ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.64 (0.77-3.51)</td>
<td>0.199</td>
<td>1.05 (0.58-1.89)</td>
<td>0.876</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.85 (0.87-3.97)</td>
<td>0.112</td>
<td>1.01 (0.56-1.83)</td>
<td>0.962</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.79 (0.84-3.84)</td>
<td>0.134</td>
<td>1.03 (0.57-1.86)</td>
<td>0.924</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.64 (0.72-3.75)</td>
<td>0.241</td>
<td>1.06 (0.59-1.93)</td>
<td>0.838</td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.55 (1.05-2.30)</td>
<td><strong>0.029</strong></td>
<td>0.99 (0.73-1.35)</td>
<td>0.971</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.62 (1.10-2.41)</td>
<td><strong>0.016</strong></td>
<td>1.00 (0.73-1.35)</td>
<td>0.979</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.62 (1.09-2.40)</td>
<td><strong>0.017</strong></td>
<td>1.01 (0.74-1.37)</td>
<td>0.944</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.52 (0.98-2.35)</td>
<td>0.064</td>
<td>0.99 (0.72-1.37)</td>
<td>0.958</td>
</tr>
</tbody>
</table>

*No asthma group as reference
CI = confidence interval
Model 1: Adjusted for age, race, sex
Model 2: Model 1 + total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking, diabetes mellitus
Model 3: Model 2 + anti-hypertensive and lipid-lowering medication use at baseline
Model 4: Model 3 + body-mass index, family history of cardiovascular disease, income