Are patients with asthma at increased risk of coronary heart disease?

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Background Inflammation plays a role in the pathogenesis of athero-thrombosis. Because of the chronic, inflammatory nature of asthma, we hypothesized a possible link asthma and prospective risk of coronary heart disease (CHD).

Methods We performed a cohort study among 70 047 men and 81 573 women, 18–85 years old, enrolled in a large managed care organization in Northern California. Asthma was ascertained by self-report at baseline in 1964–1973 and/or interim hospitalization for asthma during follow-up. The primary endpoint was combined non-fatal or fatal CHD.

Results After a median follow-up time of 27 years, and adjusting for age, race/ethnicity, education level, smoking status, alcohol consumption, body mass index, serum total cholesterol, white blood cell count, hypertension, diabetes, and history of occupational exposures, asthma was associated with a 1.22-fold (95% CI: 1.14, 1.31) increased hazard of CHD among women. This association was seen both in never and in ever smoking women, and in younger and older women. By contrast, asthma was not associated with CHD among men (multivariate-adjusted hazard ratio = 0.99; 95% CI: 0.93, 1.05).

Conclusions Asthma was independently associated with a modest but statistically significant increased hazard of CHD among women. Further studies are warranted to confirm or refute these preliminary epidemiological findings.

Keywords Asthma, coronary heart disease, inflammation

It is now widely recognized that inflammation plays a crucial role in the pathogenesis of athero-thrombosis.1–3 Because of the chronic, inflammatory nature of asthma,4 we hypothesized a possible link asthma and coronary heart disease (CHD).

In agreement with this hypothesis, prior studies have found excess cardiovascular mortality among severe asthmatic patients5,6 and increased risk of CHD in relation to occupational asthma.7 Furthermore, bronchial asthma has been associated with cardiovascular risk factors such as elevated body mass index (BMI),8–10 high fibrinogen levels,11 and high levels of tumour necrosis factor-α (TNF-α).12,13 Finally, eosinophilia (a prominent feature of asthma) has been shown to predict cardiovascular mortality,14 and poor pulmonary function has been shown to predict cardiovascular death.15

The purpose of this paper is to examine the sex-specific prospective association between asthma and subsequent combined non-fatal and fatal CHD in a large population-based cohort of men and women. Because of the known influence of smoking on both asthma and CHD, we also performed sex-specific, stratified analysis in never and ever smokers.

Methods

Study design and procedures

A retrospective cohort design was used. The cohort was a subset of a larger population of 206 973 Northern California Kaiser Permanente members who took multiphasic health checkups at least once between 1964 and 1973 in San Francisco or Oakland and were between the ages of 15 and 92 years. Of those, the following participants were sequentially excluded: 304 because

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of missing asthma status at baseline, 6478 because of missing smoking status at baseline, 191 because of unreliable demographic information at the Multiphasic Health Checkup (age, gender, and/or name could not be confirmed against our main member demographics database), 5354 because age was either <18 or >85 years (this was done because we wanted to focus on adult asthma and because the oldest old did not contribute much to follow-up time), 4744 because of prior self-reported history of heart attack, and 38 282 who did not have any information on membership status, inpatient utilization, or mortality. These exclusions left 151 620 participants, 81 573 women and 70 047 men.

Kaiser Permanente is a large, pre-paid health plan based on group practice, and its membership is ethnically and socioeconomically representative of the local population, with the exception of extremes of the income scale.16 The multiphasic health checkup, a voluntary comprehensive medical examination, collected information on demographic factors (age, gender, race/ethnicity, educational attainment), lifestyle (cigarette smoking history and alcohol consumption in the past year), physiological factors (body weight, height, systolic and diastolic blood pressure, total cholesterol level and white blood cell count), medical comorbidities (including physician-diagnosed asthma and prior history of heart attack), exposure to eight common occupational hazards (prior to or during the past year) and parental history of major health conditions using written questionnaires and clinic procedures previously described.17 Body mass index (BMI) was computed as weight (kg) divided by height squared (m²). No information was available at baseline on prior episodes of angina pectoris or on silent myocardial infarction. We classified cohort members according to responses to the smoking questionnaire into: never smokers of any tobacco product, former cigarette smokers, current cigarette smokers, and never cigarette smokers reporting former or current use of cigars or pipe. The eight occupational exposures included: (1) chemicals, cleaning fluids, or solvents; (2) insect or plant sprays; (3) plastics or resin fumes; (4) asbestos, cement, or grain dusts; (5) silica, sandblasting, grinding/drilling dust; (6) X-rays or radioactivity; (7) ultraviolet radiation; and (8) lead or metal fumes. No data were available on habitual diet, physical activity, or on age parents were diagnosed with or died from CHD. Asthma, the main predictor variable was defined as self-reported physician-diagnosed asthma at baseline and/or inpatient admission for asthma after the multiphasic health checkup but predating the CHD event among participants who were hospitalized or died of CHD.

Statistical analysis
The primary outcome of the study was combined fatal and non-fatal CHD during prospective follow-up. Non-fatal CHD was ascertained as primary hospital discharge diagnosis coded 410–414 using the International Classification of Diseases Eighth Revision (ICD-8) from 1971 to 1979 and the Ninth Revision (ICD-9) thereafter. Age-adjusted, sex-specific CHD rates and associated 95% CI were estimated, according to asthma and smoking status, using Poisson regression. The proportional hazards model approach was used to model the sex-specific relationship of asthma with the hazard of CHD while adjusting for age and for additional covariables.18 These included: age, race/ethnicity (African-American, Asian, and a combined category of other, mixed or unknown, relative to white), education level (partial college, completed college or higher, relative to no college education), smoking status (former cigarette smokers, current cigarette smokers, never cigarette smokers reporting former or current use of cigars or pipe, relative to never smokers of any tobacco product), alcohol consumption (never, ≥3 drinks/day, unknown, relative to 1 or 2 drinks/day), BMI, total cholesterol, white cell blood count, diabetes, hypertension, parental history of CHD, and exposure to any of the eight different occupational hazards (relative to none, as a single indicator variable). To assess whether the association between asthma and CHD differed significantly by sex, age, and smoking status, we tested the significance of cross-product interaction terms in multivariate models. Only the interaction between asthma and sex was statistically significant (P = 0.005), but we present the analysis stratifying by smoking status for completeness of results. Follow-up for each person ended at the date of hospitalization with primary discharge diagnosis of CHD, death from any cause, termination of health plan membership, or 31 December 2000, which ever came first. Deaths from baseline (1964–1973) through 31 December 2000 were ascertained using the California Automated Mortality Linkage System, which has a sensitivity of 97% compared with the National Death Index.19 About 43% of study participants were followed until the closing date and the median follow-up time was 26.6 years (range: <1–36.4 years). The research protocol was approved by the Kaiser Foundation Research Institute Institutional Review Board, and all study participants gave written informed consent for the use of their multiphasic health checkup data for research purposes. All statistical analyses were conducted using SAS 8.2 (Cary, NC).

Results
The baseline cohort characteristics, according to sex and asthma status, are given in Table 1. About 9% of men and 8% of women self-reported asthma or were hospitalized for asthma during follow-up. Five per cent of men with asthma (n = 279) were incident asthma cases (i.e. hospital admissions with primary discharge diagnosis of asthma); 9% of the women with asthma (n = 589) were incident cases. Men with asthma, compared with male counterparts with no asthma, tended to be slightly younger, more educated, less likely to be diabetic, and were more likely to have a positive history of occupational exposures. In turn, women with asthma, compared with female counterparts with no asthma, tended to be slightly older, were more likely to be current smokers, had a higher BMI, and higher prevalence of hypertension, parental history of CHD, and occupational exposures. No important differences between asthma groups were noted for race/ethnicity, alcohol consumption, serum total cholesterol level, or white blood cell count.

Table 2 shows the results of the survival analysis of combined non-fatal and fatal CHD, separately in men and women. In men, the age-adjusted CHD rate was lower in those with asthma than in those with no asthma. However, there was no statically significant association between asthma and CHD in men. By contrast, in women, the age-adjusted CHD rate was higher in those with asthma than in those without asthma; in age-adjusted Cox regression, asthma was associated with
a 1.24-fold increased hazard of CHD (95% CI: 1.15, 1.33). Adjustment for multiple potential confounders including age, race/ethnicity, education level, smoking status, alcohol consumption, BMI, serum total cholesterol, white blood cell count, hypertension, diabetes, and occupational exposures changed this hazard ratio (HR) very little. Because the age range (at baseline) of participants was quite wide (18–85 years), we tested, in multivariate analysis, whether the asthma–CHD association held in younger (<50 years old) and in older (≥50 years old) women. Asthma was associated with the hazard of CHD in both younger (HR = 1.24; 95% CI: 1.11, 1.38) and in older women (HR = 1.19; 95% CI: 1.07, 1.32). Likewise, because the follow-up time was quite long (median = 26.6 and up to 36.4 years), we ascertained whether the HR was constant over time.
time. In analysis among women, asthma was not significantly associated with CHD in the first 10 years of follow-up (HR = 1.08; 95% CI: 0.89, 1.32), but it was associated in analysis of CHD events that occurred 10 years after baseline (HR = 1.19; 95% CI: 1.10, 1.29).

Sex-specific analysis of the asthma–CHD relation, stratifying by smoking status, is summarized in Table 3. No significant associations between asthma and CHD were present in never smoking or in ever smoking men. On the contrary, statistically significant associations between asthma and

### Table 2


<table>
<thead>
<tr>
<th>Men (n = 70,047)</th>
<th>Women (n = 81,573)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No asthma</td>
<td>Asthma</td>
</tr>
<tr>
<td>No. of events/people</td>
<td>12,232/63,898</td>
</tr>
<tr>
<td>Per cent rate (%)</td>
<td>19.1</td>
</tr>
<tr>
<td>No. of person-years</td>
<td>1,433,801</td>
</tr>
<tr>
<td>Age-adjusted rate per 10^6 person-years (95% CI)</td>
<td>63 (62, 68)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### Table 3

Age-adjusted incidence and hazard of coronary heart disease hospitalization or death (through the end of 2000) in relation to asthma status, by gender and smoking status. Northern California Kaiser Permanente Multiphasic Health Checkup, 1964–1973

<table>
<thead>
<tr>
<th></th>
<th>Never smokers (n = 16,430)</th>
<th>Ever smokers (n = 53,617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No asthma</td>
<td>Asthma</td>
<td>P</td>
</tr>
<tr>
<td>No. of events/people</td>
<td>2,438/14,915</td>
<td>215/15,151</td>
</tr>
<tr>
<td>Crude per cent rate (%)</td>
<td>16.3</td>
<td>14.2</td>
</tr>
<tr>
<td>No. of person-years</td>
<td>345,203</td>
<td>35,309</td>
</tr>
<tr>
<td>Age-adjusted rate per 10^4 person-years (95% CI)</td>
<td>56 (52, 59)</td>
<td>55 (48, 63)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.01</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
<td>1.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Women (n = 36,308)</th>
<th>Ever smokers (n = 45,265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No asthma</td>
<td>Asthma</td>
</tr>
<tr>
<td>No. of events/people</td>
<td>3,774/33,634</td>
</tr>
<tr>
<td>Per cent rate (%)</td>
<td>11.2</td>
</tr>
<tr>
<td>No. of person-years</td>
<td>815,101</td>
</tr>
<tr>
<td>Age-adjusted rate per 10^4 person-years (95% CI)</td>
<td>30 (28, 32)</td>
</tr>
<tr>
<td>Age-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### Notes

A Ever smokers include current and former cigarette smokers, and never cigarette smokers reporting former or current cigar or pipe use.

B Age, race/ethnicity, education level, alcohol consumption, body mass index, serum total cholesterol, white blood cell count, hypertension, diabetes, parental history of coronary heart disease, and occupational exposures.
CHD were seen in both never smoking and ever smoking women.

Discussion
The central finding of this study among a large cohort of men and women was a statistically significant association between asthma and CHD in women, which became apparent and statistically significant after 10 years of follow-up. This association was seen in both younger and older women, and in never and ever smoking women. On the other hand, no association between asthma and the hazard of CHD was found in men.

The significant interaction between sex and asthma as predictors of CHD is intriguing and deserves further testing in other populations and settings. Three non-causal explanations are possible: first, we did not adjust for several relevant confounders such as diet or physical activity, thus residual confounding may remain. Second, asthma was related to known cardiovascular risk factors (namely BMI and hypertension) in women but not in men, but this indirect explanation is unlikely because we adjusted for these factors in the analysis. Third, bronchial asthma may simulate angina pectoris. However, we ruled out this possibility by supplemental analysis excluding angina codes in our CHD outcome ascertainment (ICD-8 and ICD-9 codes 413.x), and results were unchanged (data not shown). An untested and speculative alternative is, however, that women may have a greater biological susceptibility to the inflammatory milieu of asthma, or greater susceptibility to the cardiotoxic effects of certain asthma medications. For example, beta-adenoreceptor agonists have been associated with cardiac dysrhythmias, particularly long QT syndrome and with incident myocardial infarction and unstable angina. In addition, long-term treatment with oral glucocorticoids has been associated with weight gain, visceral obesity, insulin resistance, and lipid abnormalities.

The positive association between asthma and BMI in women but not in men is consistent with findings in the Coronary Artery Risk Development in Young Adults study (CARDIA) and the Tucson Epidemiologic Study of Airways Obstructive Diseases. However, the directionality of this association remains to be elucidated.

Four prior studies have reported associations between asthma and cardiovascular outcomes. In a Swedish sample of severe asthma patients with a daily treatment of oral steroids for more than one year, there was an excess mortality from ischaemic heart disease which was, in agreement with our results, more marked among women. In a cohort of hospitalized patients discharged with a diagnosis of asthma in Western Australia, there was a significant increase in deaths attributable to ischaemic heart disease. The third study found that occupational asthma in a cohort of Canadian workers was associated with increased risk of hospital admission for CHD. Finally, in a cohort of 2242 subjects aged 16–64 years admitted for asthma, compared with a random sample of age-matched controls, failure to prescribe inhaled steroids on discharge was associated with subsequent death by asthma, and prescription of ipratropium was predictive of deaths from asthma, chronic obstructive pulmonary disease (COPD), and cardiovascular disease.

Ventilatory function impairment, particularly rapid decline, has been shown to be an independent risk factor for both cardiovascular mortality and fatal myocardial infarction. In the Cardiovascular Health Study, forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were reduced in elderly people with hypertension, ischaemic heart disease, higher left ventricular mass, and congestive heart failure.

Pro-inflammation is now considered a common denominator or initiator of many pathophysiological disease processes, and a downstream product of the immune response. Inflammation involves complex pathways that are beneficial in the short term to overcome stress or infections, but they may be detrimental if maintained over prolonged periods of time. The immune response encompasses two different arms of activity. The first arm is the type 1 response, associated with type 1 helper T (Th1) cells which produce interferon-γ, TNF-α, granulocyte macrophage colony stimulating factor (GM-CSF), and interleukins (IL) 1, 2 and 8, and activate macrophages and cytotoxic T cells. The second arm is the type 2 response, associated with type 2 helper T cells (Th2) which secrete IL 3, 4, 5, 6, 10, and 13 that promote allergic inflammation, eosinophil proliferation, and B cell production of IgE. These two arms interact with each other: the type 1 response modulates the type 2 response, but the type 2 reaction is also able to block the type 1 arm. Although asthma is a predominantly Th2 phenomenon, there is evidence that levels of TNF-α are also elevated in asthmatic patients and are associated with bronchial hyperreactivity.

Two pro-inflammatory cytokines found to be elevated is asthma, IL-6 and TNF-α, play key roles in the pathogenesis of atherosclerosis. IL-6 has been found in human atherosclerotic plaque and is a major inducer of acute phase reactants like C-reactive protein. In addition, IL-6 can activate platelets and mitogenic activity for smooth muscle cells. TNF-α, originally described by its anti-tumour activity, has also been detected in human atherosclerotic plaques and is implicated in the regulation of fibrinogen and factor VIII, and in insulin resistance.

Our study has several limitations. Asthma status was assessed by written self-report, which could have resulted in misclassification. However, all subjects in the present study reported a diagnosis of physician-diagnosed asthma, which may have decreased the likelihood of misclassification. Second, no information was available on severity, symptoms, and specific asthma medications, thus we were unable to assess their specific effects on CHD risk. Third, we relied on self-reported smoking status is thus possible that some subjects may have misrepresented their smoking history. Fourth, no data was available on lung function, airway responsiveness, presence or absence of allergy (i.e. skin tests or IgE status), or inflammatory mediators.

The strengths of the present study include its large sample size and long follow-up period, the availability of traditional CHD risk factors and occupational exposures, and the low likelihood of selection bias since the sample was derived from a population with equal access to health care.

In conclusion, our study provides preliminary evidence that asthma may be associated with a modest increase of CHD risk among women. Further studies are warranted to confirm or refute these findings and to elucidate sex-specific factors in asthma physiology or management potentially leading to athero-thrombotic disease.
References


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