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Asthma Status and Risk of Incident Myocardial Infarction: A population-based case-control study

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Abstract

Background—The role of asthma status and characteristics of asthma in the risk of myocardial infarction (MI) are poorly understood.

Objective—We determined whether asthma and its characteristics are associated with risk of MI.

Methods—The study was designed as a population-based retrospective case-control study, which included all eligible incident MI cases between November 1, 2002, and May 31, 2006, and their matched controls. Asthma was ascertained using predetermined criteria. Active (current) asthma was defined as the occurrence of asthma-related episodes (asthma symptoms, use of asthma medications, unscheduled medical or emergency department visit, or hospitalization for asthma) within one year prior to MI index date.

Results—There were 543 eligible incident MI cases during the study period. Of the 543 MI cases, 81 (15%) had a history of asthma prior to index date of MI whereas 52 of 543 controls

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Disclosures

The study investigators have nothing to disclose that poses a conflict of interest

(10%) had such a history (adjusted odds ratio [OR]: 1.68; 95% CI: 1.06–2.66) adjusting for risk factors for MI and comorbid conditions (excluding chronic obstructive lung disease). While inactive asthma did not increase the risk of MI, individuals with active asthma had a higher odds of MI, compared to those without asthma (adjusted OR: 3.18; 95% CI: 1.57–6.44) without controlling for COPD. After adjusting for COPD, although asthma overall was no longer statistically significant (adjusted OR: 1.34, 95% CI: 0.84–2.15), active asthma still was associated (adjusted OR: 2.33, 95% CI: 1.12–4.82).

Conclusion—Active asthma is an unrecognized risk factor for MI. Further studies are needed to assess the role of asthma control and medications in the risk of MI.

Keywords

Asthma; myocardial infarction; risk factors; epidemiology; inflammation; systemic

Introduction

Cardiovascular disease (CVD) is the most common cause of death among adults in the United States, accounting for 500,000–700,000 deaths per year.[1] Myocardial infarction (MI) affects nearly 15 million people annually in the United States, with an annual incidence rate of 1–10 per 1,000 depending on age, gender, and race.[2] Inflammation, particularly increased T-helper 1-proinflammatory activity (e.g., intracellular IFN-γ expression), plays an important role in the development of atherosclerosis and myocardial infarction.[3–6]

Because asthma is a Th2-predominant inflammatory condition and one of the five most burdensome diseases in the US, [7] affecting 7.7–10.1% of adults in the US, [8, 9] a potential association between asthma and the risk of CVD including coronary heart disease (CHD) or MI has been considered. [10–15] Although the Th1 vs Th2 hypothesis may have suggested an inverse relationship between asthma and CVD,[16, 17] most previous studies have suggested that asthma is associated with an increased risk of atherosclerosis, CHD, or MI, although some studies have disputed the association.[10–15, 18, 19]

In addressing the association between asthma and the risk of CHD or MI, previous studies were limited due to lack of recognizing the heterogeneity of asthma,[20, 21] inconsistent or heterogeneous definitions of CVD as an outcome event, and inadequate control of risk factors. This made it difficult to examine the effect of asthma on the risk of MI or CHD and assess the influence of characteristics of asthma on the risk of MI or CHD. To date, there are few population-based studies based on prospectively identified incident cases of MI and predetermined criteria for asthma. Also, little is known about the role of clinically pertinent characteristics of asthma in relation to the risk of MI.

Discerning the relationship between asthma and the risk of CHD or MI has clinical significance. Asthma and MI cause major morbidity in adults. Attributing excess cardiovascular risk to asthma treatments such as short-acting bronchodilators, if inaccurate, could lead to unnecessary undertreatment of bronchospasm in patients experiencing asthma exacerbation.[13, 22] Also, defining the nature of the association between asthma and the risk of MI could potentially provide important scientific insights into relatively under-recognized

systemic effects of asthma on common chronic inflammatory diseases such as CHD or MI. Therefore, to clarify the association between asthma and the risk of MI while addressing the limitations of previous studies, we conducted a population-based case-control study based on prospectively identified incident cases of MI and predetermined criteria for asthma in Olmsted County, Minnesota.

Methods

This study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center. This study was designed as a population-based, retrospective case-control study.

Study population and setting

Olmsted County, Minnesota, is an excellent setting to conduct a population-based epidemiologic study such as this because medical care is virtually self-contained within the community. The population characteristics of Olmsted County residents are similar to those of the State of Minnesota and of the Upper Midwest.[23] All clinical diagnoses are electronically indexed and information from every episode of care is contained within detailed patient-based medical records; essentially all medical care settings and providers are linked under the auspices of the Rochester Epidemiology Project (REP).

Study subjects

MI case ascertainment

The present study utilized study subjects of the original population-based, prospective cohort study that assessed the effect of the new definition of MI on case ascertainment, conducted in Olmsted County, Minnesota, between November 1, 2002, and May 31, 2006. Details of the study subjects (MI cases) and enrollment procedures have been described previously.[24, 25] Briefly, the original study enrolled a total of 693 incident MI cases during the study period. All subjects who presented to Mayo Clinic Hospital (Rochester, Minnesota) with a cardiac troponin T level over 0.03 ng/mL were prospectively identified within 12 hours of the blood draw. The validation of MI relied on: 1) chest pain, 2) electrocardiographic data using Minnesota coding, and 3) cardiac enzyme levels (cutoff value of cardiac troponin T used at Mayo Clinic; ≥ 0.03 ng/mL). Only new incident MI cases were enrolled in this study.

Selection of MI control subjects

A list of potential control subjects who had no history of MI and met the matching criteria were generated and randomly selected from the REP database for medical review and data collection. One control per case was randomly selected at the end of the study period. The matching criteria included: 1) gender, 2) birth date (within one year), 3) the same clinic registration year as matched case (within one year), and 4) closest clinic visit to index date of matched case within one year. The index date for control subjects was defined as the closest (within one year) clinic visit date to index date of MI for their corresponding matched case.

Exposure ascertainment (asthma status)

For determining a history of asthma, we conducted comprehensive medical record reviews to apply predetermined criteria for asthma delineated in Table 1. These criteria have been extensively used in research for asthma epidemiology[10, 26] and were found to have high reliability.[27, 28] We included both definite and probable asthma according to the criteria prior to the index date of MI cases because most probable asthmatics become definite over time.[28] We also obtained asthma status based on symptoms, health care services, and treatments within one year prior to index date.[29] Active (or current asthma at the time of index date) asthma was defined as the occurrence of any asthma-related episodes including asthma symptoms (cough with wheezing, shortness of breath, and chest tightness), use of asthma medications, unscheduled office visits for asthma, emergency department (ED) visits for asthma, urgent care visits for asthma, or hospitalization for asthma within one year prior to index date of myocardial infarction. Inactive asthma was defined as the absence of asthma-related events described above within 1 year prior to index date. To assess the impact of asthma medications on MI risk, we collected information on asthma medication use, including short-acting beta agonists (SABA) or long-acting beta agonists (LABA), inhaled corticosteroid (ICS), and systemic corticosteroid (SCS) therapy at index date of MI (within 3 months of index date[29]).

We collected atopic conditions other than asthma such as allergic rhinitis and atopic dermatitis based on a physician diagnosis documented in medical records to examine whether coexistence of allergic rhinitis and/or atopic dermatitis with asthma further increased the risk of MI, compared to asthma alone. Based on the asthma incidence dates, we categorized asthma onset into adult (≥18 years) vs child-onset asthma (<18).

Other variables

Demographics and clinical characteristics such as risk factors for MI (hypertension, hyperlipidemia, diabetes, smoking history, and BMI) and comorbidity within three months prior to index date were collected through comprehensive review of medical charts and REP. Hypertension, hyperlipidemia, and diabetes mellitus were defined by a diagnosis documented in medical charts or taking medications for clinical conditions. Smoking status was categorized into current and non-current smoking. Comorbidity (eg, COPD) was collected based on a physician diagnosis.

Statistical analysis

Baseline characteristics were summarized using frequencies for categorical variables and mean (SD) for continuous variables, and were tested for an association with MI in univariate models using conditional logistic regression taking into account matching. We fit multivariable models adjusting for 1) risk factors of MI and 2) both risk factors and other comorbid conditions (with and without chronic obstructive pulmonary disease, COPD). Similar analyses were performed stratifying on gender.

To examine the possibility of a differential effect across asthma characteristics, we analyzed asthma status (active vs inactive) as a nominal predictor in the regression modeling with

non-asthmatics specified as the reference group. Similar analysis was done for assessing the association of age of onset (child vs adult-onset asthma) with the risk of MI. Impact of coexistence of allergic rhinitis and/or atopic dermatitis was examined as an interaction with asthma by adding their product term to the model and testing its coefficient for significance. Also, among the subgroup of active asthmatics, the proportion treated with asthma medications (within 3 months prior to index date between for the risk of MI) was compared between unmatched MI cases and controls (patients without MI) using conventional logistic regression. Statistical significance was tested at a two-sided alpha error of 0.05. Statistical analyses were performed using SAS software package, version 9.3 (SAS Institute, Cary, NC).

Results

Subject Characteristics

Among 597 incident MI cases residing in Olmsted County, there were 543 eligible cases for this study after excluding 54 subjects due to the following reasons: no research authorization (n=15) and clinical conditions making asthma ascertainment difficult (n=39). The baseline characteristics of MI cases and their controls are summarized in Table 2.

Asthma and Risk of MI

Of the 543 cases, 81 (15%) were asthmatics whereas 52 (10%) of 543 controls had asthma (matched OR, 1.71; 95% CI, 1.16–2.51). After adjusting for the MI risk factors and all comorbid conditions mentioned above except for COPD, the association between a history of asthma and the risk of MI was significant (adjusted OR, 1.68; 95% CI, 1.06–2.66) (Model 2 without COPD in Table 3). However, as expected, the association between asthma and MI was attenuated by adding COPD as an additional adjusting covariate in the model (adjusted OR: 1.34; 95%CI: 0.84–2.15) (Model 3 with COPD in Table 3).

We examined asthma status by categorizing inactive vs active (current at the time of index date) asthma as defined in the Methods section. Controlling for the known risk factors for MI and other comorbid conditions except for COPD, odds of MI were not increased in those with inactive asthma (adjusted OR, 0.99, 95%CI: 0.54–1.83) but were approximately threefold higher in subjects with active asthma (adjusted OR, 3.18; 95% CI, 1.57–6.44) compared to those without a history of asthma. The results are summarized in Table 3. After adjusting for COPD in the model, while the effect size for active asthma was reduced, active asthma was still associated with an increased risk of MI (adj. OR: 2.33, 95%CI: 1.12–4.82) as shown in model 3 of Table 3. When we repeated these analyses stratifying subjects by gender, the results were consistent across gender.

We examined the role of asthma medications in the risk of MI based on subgroup analyses of patients with active asthma (Table 4). We found that there were no significant differences in the risk of MI between active asthmatic patients with any asthma medications and those with no medications within 3 months prior to index date ($p= 0.09$). Individual asthma medications were not associated with the risk of MI among patients with active asthma ($p\geq0.22$).

Other Asthma-related Factors and Risk of MI

Atopic dermatitis (unadjusted OR: 0.81, 95%CI: 0.54–1.21) and allergic rhinitis (unadjusted OR: 1.00, 95%CI: 0.74–1.36) were not significantly associated with the risk of MI. We also found that coexistence of other atopic conditions with asthma did not change the association (p-value for interaction = 0.48). While those with child-onset asthma did not show an increased risk of MI compared to patients without asthma (unadjusted OR: 0.68, 95%CI: 0.22–2.11), the number of such asthmatics was very low (n=13) in assessing the association. However, adult-onset asthma appears to be associated with an increased risk of MI (unadjusted OR: 1.90, 95%CI: 1.26–2.86) in comparison to those without asthma.

Discussion

We found that while inactive asthma does not increase the risk of MI, active asthma does increase the risk of MI. Asthma medications were not associated with the risk of MI among patients with active asthma.

While some studies dispute an association between asthma and the risk of CVD, other studies suggest that there is an association between asthma and the increased risks of angina, atherosclerosis, CHD, MI, congestive heart failure, or stroke.[10–15, 18, 19] Asthma-related clinical variables (poor lung function,[30] IgE level,[31] allergic sensitization,[32] airborne pollen concentration,[33] and other atopic conditions[34]) have been reported to be associated with the increased risks of similar CVD outcomes. However, previous studies were based on the broad and heterogeneous definitions of CVD and asthma and did not assess characteristics (heterogeneity) of asthma in relation to risk of MI. In this respect, our population-based study addressed these limitations as it was based on prospectively identified incident MI cases, predetermined criteria for asthma as an exposure and assessed characteristics of asthma in relation to the risk of MI.

The age- and gender-adjusted MI incidence in our study setting between 2002–2007 (14–15/1,000 among patients aged 56–80 years)[35] appears to be in a lower range of the reported MI incidence in the US, considering the incidence of MI between 1987 and 2004 in the US (10–103/1,000 among population ages 45–74 years depending on age, gender, and race).[2] Asthma prevalence in controls in our study was 10%, which is within a range of asthma prevalence between 2001–2010 among elderly adults in the US (7.7–10.1%).[8, 9, 36] Our study results confirmed the known risk factors for MI. We believe that susceptibility bias (e.g., covariate imbalance) is unlikely to account for the findings of this study given the full adjustment for pertinent covariates and potential confounders. Given that a MI is a life-threatening condition, a differential detection of MI depending on asthma status is unlikely (i.e., detection bias). Since detection of asthma might depend on follow-up duration from registration to index date of MI, we designed our study to ensure that follow-up duration was similar between cases and controls.

In our study while inactive asthma, defined by the absence of asthma-related episodes within 1 year prior to MI, did not increase the risk of MI, active asthma significantly increased the risk of MI. As asthma medications, particularly SABA, can be a potential mediator for the association between asthma and the risk of MI,[22, 29] we analyzed the role of individual

asthma medications in the risk of MI among patients with active asthma who were on asthma medications within three months of index date of MI. The results did not reveal that asthma medications were associated with an increased the risk of MI among patients with active asthma. Though statistically insignificant, use of asthma medications including SABA among individuals with active asthma had consistently lower risks of MI, compared to those without asthma medications (Table 4). This finding could be due to a transfer (survivorship) bias (the deceased asthmatic patients due to asthma medications could have been missed if it was out-of hospital mortality). However, if asthma medications truly increased the risk of MI, it is still likely for one to observe such trends among survived MI patients. While a previous study based on self-report for asthma and MI or angina reported that SABA use might account for the association between asthma and the risk of MI,[13] this finding was not fully replicated by large population-based studies.[22, 29] Suissa et al reported that while use of theophylline or nebulized or orally taken SABA increased the risk of acute cardiac death, SABA administered by metered-dose inhaler was not associated with acute cardiac death.[22] However, in their follow-up study in 2003, they could not replicate such association of asthma medications with the risk of MI.[29] Therefore, taken together, active asthma is associated with the increased risk of MI among patients with asthma.

Apart from active asthma status and asthma medications, co-existence of asthma with other atopic conditions did not additionally increase the risk of MI, and this finding is consistent with the literature.[11, 13] While child-onset asthma did not increase the risk of MI, adult-onset asthma seems to be more responsible for the risk of MI, which is consistent with the literature[12, 37] potentially suggesting age might be more important than the duration of asthma. However, the small number of child-onset asthma subjects limited analysis which was probably due to low incidence of asthma and/or underdetection of asthma during the 1940s and 1950s.[38] The results were consistent across gender. Given the known increased risk of MI among patients with COPD and some overlap between asthma and COPD (e.g., Asthma-COPD Overlap Syndrome),[39] reduction of the impact of asthma on the risk of MI after adjusting for COPD might be an expected finding. We excluded study subjects with FEV1<50% and thus, patients with severe COPD (e.g., GOLD COPD stage III) were likely to be excluded from our study. Our criteria for asthma specifically defined variability of asthma as the presence of a complete symptom-free period between asthma episodes. However, the currently available criteria including ours are unlikely to avoid misclassification of COPD to asthma completely. It is difficult to determine such possibility in retrospective studies such as this.

While the potential mechanisms underlying the association between asthma and the risk of MI are yet to be identified, we postulate the potential mechanisms. First, certain epidemiological and behavioral risk factors for MI are risk factors for asthma such as female,[40] non-Hispanic African Americans,[41, 42] low socioeconomic status,[43, 44] or smoking exposure [45] suggesting these factors as are confounders. Other factors such as physical inactivity or obesity[46, 47] as a result of active asthma might be plausible and, in turn, might increase the risk of MI. However, these factors are unlikely to account for the association between asthma and the risk of MI as our study results were adjusted for these factors. Alternatively, for the role of infection, our group has demonstrated significantly increased susceptibility to various microbial infections to virus and bacteria among patients with

asthma.[26] Another group showed an association of chlamydia and mycoplasma with asthma.[48] Given the potential role of infections in the development of CHD or MI,[49, 50] asthma might increase susceptibility to microbial infections, which, in turn, increases the risk of MI. This hypothesis needs to be tested in prospective studies. Alternatively, our study results raise the possibility that asthma-triggered inflammatory reactions such as platelet-activating factor (PAF) or specific eicosanoid mediators (e.g., cysteinyl leukotrienes) could potentially augment MI risk. PAF has been considered a crucial inflammatory mediator responsible for airway hyperresponsiveness and airway inflammation through eosinophilic recruitment into the lung in asthma[51, 52] and dysregulated inflammation and thrombosis underlying CHD.[53, 54] PAF and cysteinyl leukotrienes (inflammatory mediators associated with MI[55, 56]) mutually stimulate each pathway.[57, 58]

Our study has inherent limitations as a retrospective study design. Despite the specific nature of our asthma criteria, there may have still been some potential misclassification of COPD as asthma that might account for some of the findings of asthma. Although incident MI cases were identified prospectively, silent myocardial infarctions or sudden cardiac deaths might not be captured in our study. The study subjects were predominantly a Caucasian population, which might limit generalizability of our results to other ethnic groups or study settings. Lab data were not available for characterizing asthma such as allergic skin test and inflammatory markers. Another limitation was that we did not assess adherence to asthma medications due to the retrospective study design. The main strength of the study is a population-based study design based on prospectively identified incident MI cases, which minimized ascertainment or misclassification bias. Also, we used predetermined criteria for asthma (instead of self-report or ICD codes), which was used for our previous epidemiologic investigations for asthma and the risk of CHD and confirmed the association.[10]

In conclusion, active asthma is an unrecognized risk factor for MI and the impact of asthma goes beyond airway-related morbidity. Clinicians and patients with asthma should optimally control asthma using the preventive and therapeutic interventions. The underlying mechanisms for this association should be studied.

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Abbreviations

MI	myocardial infarction
REP	Rochester Epidemiology Project
OR	odds ratio

95%CI	95 % confidence interval
PAR	Population Attributable Risk
COPD	chronic obstructive pulmonary disease
PAF	platelet-activating factor
SABA	short-acting beta agonists

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1. What is already known about this topic?

Asthma has been reported to be associated with risks of a broad range of cardiovascular diseases (CVD) but the nature of the association between asthma and risks of CVD has been poorly understood.

2. What does this article add to our knowledge?

Active asthma is an unrecognized risk factor for incident myocardial infarction. The impact of asthma may go beyond airway-related morbidity and pose systemic inflammatory risks.

3. How does this study impact current management guidelines?

Clinicians caring for patients with active asthma should have a higher index of suspicion of myocardial infarction if their patient presents with suggestive symptoms. Further studies are needed to assess the role of asthma control status and medications in the risk of myocardial infarction.

Table 1

Definition of asthma

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following three conditions were present, and they were considered to have *probable* asthma if only the first two conditions were present:

1 History of cough with wheezing, and/or dyspnea, OR history of cough and/or dyspnea plus wheezing on examination,

2 Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and

3 Two or more of the following:

- Sleep disturbance by nocturnal cough and wheeze
- Nonsmoker
- Nasal polyps
- Blood eosinophilia higher than 300/uL
- Positive wheal and flare skin tests OR elevated serum IgE
- History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
- Pulmonary function tests showing one FEV_1 or FVC less than 70% predicted and another with at least 20% improvement to an FEV_1 of higher 70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV_1
- Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions were present:

- Pulmonary function tests that showed FEV_1 to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG less than 20 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications
- Bullous emphysema or pulmonary fibrosis on chest radiograph
- PiZZ $alpha_1$-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

FVC forced vital capacity; FEV1, forced expiratory volume in 1 sec

Table 2

Sociodemographic and clinical characteristics of study subjects and association with the risk of MI

Variables	Case (n=543)	Control (n=543)	Odds ratio (95% CI)*	P-value*
Sociodemographic variables				
Female gender	240 (44%)	240 (44%)	-	
Age at index date (years)	67.5±15.1	67.4±15.0	-	
Lead-up time (years)	38.9±18.4	38.9±18.3	-	
Caucasian (missing=7)	516 (95%)	512 (95%)	1.10 (0.60, 2.02)	0.76
Education status (missing=36)				0.78
High school unfinished	72 (14%)	79 (15%)	1.0 (referent)	
High school completion	179 (34%)	172 (33%)	1.11 (0.75, 1.64)	
Some college or associate degree	129 (25%)	120 (23%)	1.20 (0.79, 1.84)	
College completion	86 (16%)	80 (15%)	1.21 (0.77, 1.90)	
Graduate education	60 (11%)	73 (14%)	0.96 (0.58, 1.61)	
Risk factors for MI				
BMI (missing=40)	28.9±6.0	28.3±5.8	1.02 (1.00, 1.04)	0.12
Diabetes	113 (21%)	65 (12%)	1.98 (1.40, 2.79)	<0.001
Hypertension	373 (69%)	271 (50%)	2.59 (1.94, 3.46)	<0.001
Hyperlipidemia	330 (61%)	201 (37%)	2.74 (2.10, 3.58)	<0.001
Smoking status (missing=13)				<0.001
No	244 (45%)	288 (54%)	1.0 (referent)	
Current	107 (20%)	57 (11%)	2.30 (1.58, 3.35)	
Former	192 (35%)	185 (35%)	1.21 (0.93, 1.57)	
Comorbid conditions				
Autoimmune disease	17 (3%)	7 (1%)	2.43 (1.01, 5.86)	0.05
Cancer	12 (2%)	9 (2%)	1.33 (0.56, 3.16)	0.51
Chronic renal failure	54 (10%)	11 (2%)	4.91 (2.57, 9.39)	<0.001
Congestive heart failure	43 (8%)	7 (1%)	10.00 (3.58, 27.95)	<0.001
Coronary artery disease	107 (20%)	60 (11%)	2.12 (1.47, 3.06)	<0.001
Depression	66 (12%)	67 (12%)	0.98 (0.68, 1.42)	0.93
Estrogen therapy	14 (3%)	13 (2%)	1.08 (0.49, 2.37)	0.84
Metabolic syndrome (missing=86)	245 (47%)	172 (36%)	1.52 (1.16, 1.98)	0.002
Stroke	61 (11%)	48 (9%)	1.32 (0.88, 2.00)	0.18
COPD	60 (11%)	13 (2%)	5.27 (2.77, 10.05)	<0.001
Immobilization hemi/para-plegia	5 (1%)	8 (1%)	0.63 (0.20, 1.91)	0.41
Alcohol abuse	20 (4%)	8 (1%)	2.71 (1.14, 6.46)	0.02

*odds ratios and p-values for testing the association of each characteristic with risk of MI, derived from univariate models using conditional logistic regression; MI ; myocardial infarction; COPD: chronic obstructive pulmonary disease; BMI: body mass index

Table 3

The association of a history of asthma and asthma status with the risk of MI and gender-specific results

Group	Cases n=543	Controls n=543	Unadjusted OR and 95%CI	Model 1*	Model 2** (not adjusting for COPD)	Model 3** (adjusting for COPD)
Asthma:			[p=0.007]	[p=0.03] †	[p=0.03] †	[p=0.22] †
Yes	81 (15%)	52 (10%)	1.71 (1.16, 2.51)	1.62 (1.05, 2.50)	1.68 (1.06, 2.66)	1.34 (0.84, 2.15)
No	462 (85%)	491 (90%)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Asthma status:			[p=0.003]	[p=0.009]	[p=0.006]	[p=0.07]
Active ††	46 (8%)	19 (3%)	2.83 (1.57, 5.10)	2.79 (1.45, 5.36)	3.18 (1.57, 6.44)	2.33 (1.12, 4.82)
Inactive	35 (6%)	33 (6%)	1.14 (0.69, 1.88)	1.02 (0.58, 1.82)	0.99 (0.54, 1.83)	0.88 (0.47, 1.63)
No asthma	462 (85%)	491 (90%)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Analysis stratified by gender						
			Female (n=480)			
Asthma:			[p=0.03]	[p=0.11] †	[p=0.08] †	[p=0.40] †
Yes	40 (17%)	24 (10%)	1.84 (1.05, 3.22)	1.71 (0.89, 3.27)	1.92 (0.93, 3.99)	1.39 (0.64, 3.04)
No	200 (83%)	216 (90%)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Asthma status:			p=0.06	[p=0.11] †	[p=0.11] †	[p=0.51] †
Active ††	25 (10%)	12 (5%)	2.47 (1.14, 5.36)	2.66 (1.07, 6.61)	3.14 (1.07, 9.22)	1.99 (0.62, 6.41)
Inactive	15 (6%)	12 (5%)	1.32 (0.60, 2.92)	1.02 (0.40, 2.63)	1.20 (0.43, 3.31)	1.06 (0.39, 2.91)
No asthma	200 (83%)	216 (90%)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
			Male (n=606)			
Asthma:			[p=0.09]	[p=0.13] †	[p=0.20] †	[p=0.41] †
Yes	41 (14%)	28 (9%)	1.59 (0.93, 2.71)	1.59 (0.88, 2.88)	1.52 (0.81, 2.86)	1.31 (0.69, 2.51)
No	262 (86%)	275 (91%)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Asthma status:			[p=0.04]	[p=0.08] †	[p=0.09] †	[p=0.19] †
Active ††	21 (7%)	7 (2%)	3.35 (1.34, 8.36)	3.09 (1.15, 8.31)	3.30 (1.12, 9.70)	2.78 (0.89, 8.70)
Inactive	20 (7%)	21 (7%)	1.03 (0.54, 1.99)	1.08 (0.52, 2.24)	0.99 (0.46, 2.15)	0.87 (0.39, 1.96)
No asthma	262 (86%)	275 (91%)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)

[*] Model 1: Adjusted for risk factors for MI;

[**] Model 2 and 3: Adjusted for the known risk factors for MI and other comorbid conditions (alcohol abuse, autoimmune disease, cancer, chronic rental failure, congestive heart failure, coronary heart disease, depression, estrogen therapy, metabolic syndrome, stroke, chronic obstructive lung disease, and immobilization);

[†] p-value for overall comparison;

[††] Active or current asthma was defined as the occurrence of asthma-related events including asthma symptoms, or use of asthma medications, and outpatient/emergency department/hospitalization for asthma within one year prior to index date of myocardial infarction; Inactive asthma was defined as the absence of asthma-related events described above within 1 year prior to index date.

Table 4

Association of asthma medications with the risk of MI among active asthmatic patients

Medication	MI (n=46)	No MI (n=19)	Odds ratios (95%CI)	P-values*
Any treatment:				
Yes	34 (65%)	18 (35%)	0.16 (0.02, 1.31)	p=0.09
No	12 (92%)	1 (8%)	1.0 (referent)	
ICS treatment:				
Yes	22 (65%)	12 (35%)	0.53 (0.18, 1.60)	p=0.26
No	24 (77%)	7 (23%)	1.0 (referent)	
SCS treatment:				
Yes	2 (100%)	0 (0%)	-**	-**
No	44 (70%)	19 (30%)		
SABA treatment:				
Yes	29 (66%)	15 (34%)	0.45 (0.13, 1.60)	p=0.22
No	17 (81%)	4 (19%)	1.0 (referent)	
LABA treatment:				
Yes	12 (67%)	6 (33%)	0.76 (0.24, 2.46)	p=0.65
No	34 (72%)	13 (28%)	1.0 (referent)	

* p-values for comparison of active asthmatics with and without use of asthma medications (within 3 months prior to the index date of MI) derived from univariate (unmatched) logistic regression modeling;

** model estimates for testing the association between SCS treatment and MI risk were not presented due to small number of subjects with SCS treatment. MI: myocardial infarction; ICS: inhaled corticosteroid; SCS: systematic corticosteroid; SABA: short acting beta agonist; LABA: long acting beta agonist